Time-Varying Respiratory Elastance for Spontaneously Breathing Patients

Yeong Shiong Chiew*, Sarah F. Poole*, Daniel P. Redmond*, Erwin J. van Drunen*,
Nor Salwa Damanhuri*, Christopher Pretty*, Paul D. Docherty*, Bernard Lambermont**,
Geoffrey M. Shaw***, Thomas Desaive**, J. Geoffrey Chase*

*Department of Mechanical Engineering, University of Canterbury,
Christchurch, New Zealand (e-mail: Yeongshiong.chiew@canterbury.ac.nz).
**GIGA-Cardiovascular Sciences, Thermodynamics of Irreversible Processes, 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: Respiratory mechanics models can be used to optimise patient-specific mechanical ventilation (MV), but are limited to fully sedated MV patients who are not spontaneously breathing. This research presents a non-invasive model-based method to determine respiratory mechanics of spontaneously breathing MV patients. Patient-specific respiratory mechanics of 22 spontaneously breathing patients are described using a single compartment lung model with time-varying elastance (E_{drs}). The normalised E_{drs} trajectories and the area under the curves ($AUCE_{drs}$) are calculated using clinical data from 22 patients ventilated using pressure support (PS) and neurally adjusted ventilatory assist (NAVA). E_{drs} trajectories are also compared between ventilation modes. E_{drs} for PS ventilation were significantly higher compared to NAVA (p < 0.05). E_{drs} trajectories were more variable during NAVA than PS (p < 0.05). 20 of 22 patients had $AUCE_{drs} > 25$ cmH_2Os/l. The $AUCE_{drs}$ is a surrogate of elastance, and thus can be used as a respiratory failure severity indicator. This non-invasive model-based approach captures unique dynamic respiratory mechanics for spontaneously breathing patients during PS and NAVA. The model is fully general and is applicable to both fully controlled and partially assisted MV modes, with the resulting potential to standardise treatment for all MV patients.

1. INTRODUCTION

Application of partially assisted ventilation modes supporting the patient's work of breathing is increasingly used in intensive care. These ventilation modes promote spontaneous breathing effort, reduce the use of anaesthesia and improve weaning, resulting in better outcomes for mechanically ventilated patients (Kuhlen and Putensen, 1999, Putensen et al., 2001, Wrigge et al., 2005, Slutsky et al., 2005, Brander and Slutsky, 2006, Kogler, 2009). However, as patient disease state and response to mechanical ventilation (MV) are variable between patients and over time, there is a lack of a standard method of care by which optimal ventilator settings are selected (Villar et al., 2012, Bernstein et al., 2013).

Estimation of patient-specific respiratory mechanics has shown promising results in optimising MV on a patient-specific basis (Lucangelo et al., 2007, Brochard et al., 2012). However, for spontaneously breathing (SB) patients, additional equipment or invasive clinical manoeuvres are required to determine the patient's true respiratory mechanics (Benditt, 2005, Khirani et al., 2010). In particular, the patient's own breathing effort obscures model-based observation of the mechanics of the sedated, passive lung. Thus, estimating respiratory mechanics to guide MV is currently limited to patients who are fully sedated, and is often less reliable when the patient is semi-conscious, awake and breathing spontaneously (Iotti et al., 1995, Talmor et al., 2008, Brochard et al., 2012). This issue significantly limits

the use of model-based methods based on the estimation of respiratory dynamics, as more patients are ventilated with SB modes of MV (Kuhlen and Putensen, 1999, Putensen et al., 2001, Wrigge et al., 2005, Slutsky et al., 2005, Brander and Slutsky, 2006, Kogler, 2009).

Currently, oesophageal pressure measurements are used to eliminate the impact of the patient's own inspiratory effort on the estimated respiratory mechanics (Benditt, 2005, Talmor et al., 2008, Khirani et al., 2010), and titrate therapy. In this research, a non-invasive model-based method to estimate respiratory mechanics in SB patients using airway measurements is presented. More specifically, a conventional compartment lung model describing the respiratory system of sedated patients is extended to provide more in-depth and specific understanding of lung physiology and its mechanics for SB patients. Respiratory mechanics captured during SB potentially provide useful patient and clinical insight in guiding therapy. Such a capability, without the requirement of additional invasive measurements would improve and dramatically extend the application of respiratory mechanics to titrate MV care to all respiratory patients.

2. METHODOLOGY

2.1 Time-Varying Elastance Model

The conventional equation describing patient-specific respiratory mechanics during controlled positive pressure

ventilation (Brochard et al., 2012) without the influence of offset pressure is defined:

$$P_{aw}(t) = R_{rs} \times Q(t) + E_{rs} \times V(t) \qquad (1)$$

Where the $P_{aw}(t)$ is airway pressure, t is the time, R_{rs} is the conducting airway resistance, $Q(t)$ is the flow and E_{rs} is the respiratory elastance and $V(t)$ is the air volume entering the lung (Tidal volume). However, this model only yields reasonable parameter estimates for patients who are fully sedated and under controlled ventilation modes (Brochard et al., 2012).

During partially assisted ventilation, when patients are actively participating in breathing, Eq. (1) can be extended to capture patient-specific breathing effort. Respiratory Elastance (E_{rs}) is substituted with a time-varying elastance (E_{drs}) that comprises of 3 subcomponents: 1) the cage elastance (E_{cage}); 2) the demand elastance (E_{demand}); and 3) the lung elastance (E_{lung}), as defined (also shown in Fig. 1):

$$E_{drs}(t) = E_{cage}(t) + E_{demand}(t) + E_{lung}(t) \qquad (2)$$

$$P_{aw}(t) = (E_{cage}(t) + E_{demand}(t) + E_{lung}(t)) \times V(t) + R_{rs} \times Q(t) \quad (3)$$

$$P_{aw}(t) = P_{cage}(t) + P_{demand}(t) + P_{lung}(t) + P_{rs}(t) \qquad (4)$$

E_{lung} - A time-varying measure of the elastic properties of the lung or the collection of alveoli. E_{lung} decreases if overall alveoli recruitment outweighs the pressure build-up. E_{lung} will increase if the overall alveoli are stretched with lesser or no further recruitment (Chiew et al., 2011). Thus, E_{lung} is the representation of true mechanics that captures the patient-specific response to MV in each breathing cycle and thus provides an indication of the patient disease state.

E_{cage} - The elastic properties of the chest wall, including the rib cage, and the intercostal muscles. This elastance subcomponent can be assumed not to vary with disease-state and is thus a patient-specific constant (Chiumello et al., 2008).

E_{demand} - Represents the patient-specific inspiratory demand, which varies depending on patient-specific and breath-specific effort. This elastance is negative ($E_{demand} < 0$) as it represents the reduced apparent elastance due to the patient's inspiratory effort creating a pressure reduction by opening the lung.

P_{cage} and P_{demand} are the pressure components generated from E_{cage} and E_{demand}. Combining these pressure components will thus give information on the pleural pressure (P_{pl}), which is the pressure changes in the pleural space (chest wall). P_{lung} is the pressure in the lung during MV and P_{rs} is the pressure drop due to the conducting airway.

E_{lung} and E_{cage} describe the elastance of the patient's lungs and chest cavity. These values are always positive. However, E_{demand} represents the change in elastance due to patient-specific breathing effort and is thus negative. In particular, when trying to breathe, the diaphragm contracts and intercostal muscles move the rib cage upwards increasing the volume of the chest, creating a negative change in pressure that draws air into the lungs. During inspiration, Q is

positive, with increasing V. Thus, from Eq. (3) the negative pressure will result in 'negative' values for E_{demand} ($E_{demand} < 0$). As patient demand aids the breathing effort, the effective overall pressure, as seen at the airway, is therefore reduced. In any given breathing cycle, the time-varying E_{drs} of Eq. (2) captures all three elastance components together.
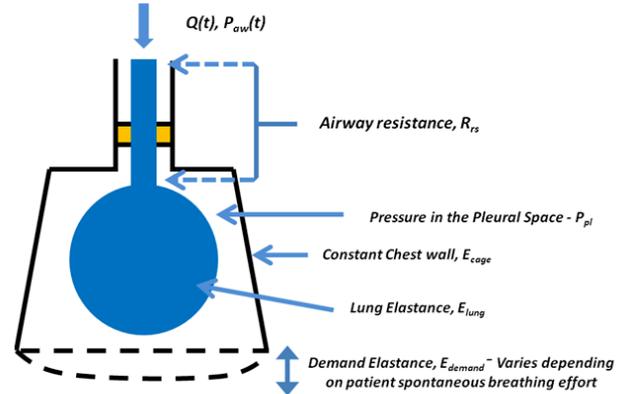

Fig. 1. The measured airway pressure consists of 4 pressure components: 1) Pressure drop due to airway resistance (P_{rs}), 2) pressure in the lung compartments (P_{lung}), 3) P_{cage} and 4) P_{demand} will form the pressure change in the pleural space ($P_{cage} + P_{demand}$).

It is important to note that E_{drs} is a combined effective elastance (Eq. 2). It is assessed as the change in pressure for a given tidal volume of flow. Thus, lower effective elastance implies less risk of lung damage (Chiew et al., 2011).

2.2 Data Analysis

In this study, time-varying E_{drs} trajectories during inspiration are estimated from retrospective clinical data from 22 patients ventilated using both pressure support (PS) and neurally adjusted ventilator assist (NAVA) mode (Piquilloud et al., 2011). In each mode, the airway pressure, flow and the electrical diaphragmatic signal ($Eadi$) were recorded. The patients were first ventilated using PS for 20 minutes before switching to NAVA for another 20 minutes. The NAVA gain was set to give the same level of pressure support as in the PS mode. The detailed clinical protocol and data acquisition procedure can be found elsewhere (Piquilloud et al., 2011, Moorhead et al., 2012).

In this study, the airway resistance (R_{rs}) is set as a constant (5 cmH_2Os/l) based on a realistic physiological range (Chiew et al., 2011). Thus, any variations of E_{drs} trajectory can be attributed to changes in E_{lung} and E_{demand} (E_{cage} is constant), while the assumed constant airway resistance allows direct comparison between different ventilation modes for one patient.

2.3 Mapping E_{drs} Trajectories

During PS or NAVA, the E_{drs} trajectory during a breath depends on patient inspiratory demand. In addition, the inspiratory time for every breathing cycle is different, and demand is patient-specific and breath-specific. To allow equal visualisation for all E_{drs} trajectories, the inspiratory time (Ti) is normalised to its maximum value for each breath

such that the data for each breath is interpolated to an arbitrary 1 second inspiratory time frame ($nTi = 1$ s). This choice of 1.0 s is arbitrary to ensure units are uniform and is interpreted only as 0~100% of the inspiratory part of the specific breath.

Arranging each breathing cycle's E_{drs} trajectory, such that it is bounded by the E_{drs} of the preceding breath and the subsequent breath, leads to a three-dimensional, time-varying, breath-specific E_{drs} surface (E_{drs} mapping). This surface allows the effect of changes in ventilator settings on E_{drs} to be visualised directly. It also clearly shows the breath-to-breath variability together with the effective elastance for each patient and MV mode, allowing them to be quantified.

2.4 Assessing E_{drs} Trajectories and $AUCE_{drs}$

For each MV mode, the 5th, 25th, 50th, 75th and 95th percentile of all E_{drs} trajectories for each patient and the $AUCE_{drs}$ is calculated. (Chiew et al., 2011). The $AUCE_{drs}$ is defined as the area under the curve of E_{drs} values between 0.3-1.0 s of normalised inspiration.

When $E_{drs} < 0$, there is effectively 'no harm' done to the patient, because any pressure or flow applied is due to the patient's initial state or demand. However, when a smaller negative E_{drs} is observed, it indicates that either weak demand or inability of the patient to create significant negative pressure. These cases are of clinical concern, so a less negative E_{drs} would merit clinical investigation and intervention.

The E_{drs} between NAVA and PS are compared per-patient, so the patient is his/ her own control. Kolmogorov-Smirnov test is used for significance testing. A value of p < 0.05 indicates that $AUCE_{drs}$ in NAVA is significantly different than PS.

3. RESULTS

The E_{drs} trajectories and trends for patients ventilated with PS are significantly different from those seen in patients ventilated using NAVA (p < 0.05 for 15/22 patients). Fig. 2 shows an example of mapping the E_{drs} trajectories for Patient 9. For the same patient, the 5th, 25th, 75th and 95th percentile of E_{drs} trajectory, airway pressure (P_{aw}), volume (V), and $Eadi$ curves during PS and NAVA is shown in Fig. 3. It should be noted in Fig. 3 that $Eadi$ is the same for PS and NAVA, but NAVA has lower and more variable E_{drs} and more variable V (Moorhead et al., 2012). The summary of $AUCE_{drs}$ for all 22 patients during PS and NAVA are shown in Table 1.

4. DISCUSSION

4.1 E_{drs} Trajectories and $AUCE_{drs}$: Comparing NAVA and PS

From Fig. 2, it is found that there is a significant difference in the shape of the E_{drs} mapping for PS and NAVA. During PS, it is observed that the E_{drs} mapping is more consistent and uniformly shaped in comparison to NAVA. This result indicates that different MV modes, or, more specifically, different pressure delivery techniques, will result in different E_{drs} trajectories, as might be expected. In particular, the uniformity of E_{drs} mapping observed during PS suggested

lower breath variability compared to NAVA (Piquilloud et al., 2011, Moorhead et al., 2012). Hence, these shapes and their $AUCE_{drs}$ (after 0.3 s normalised), can be monitored and modified to obtain lower, more desirable E_{drs} to optimise MV delivery. In any of these cases, higher E_{drs} may thus indicate greater lung damage and hence, greater risk for lung to overstretch (Chiew et al., 2011).
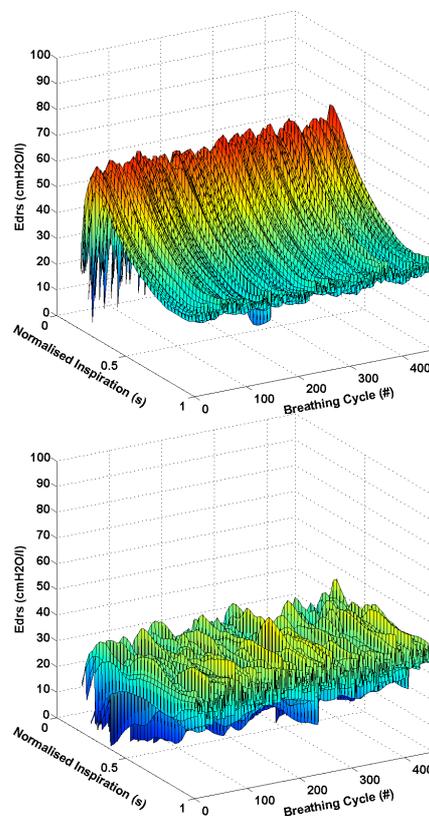

Fig. 2. Mapping of E_{drs} trajectory for Patient 9 during PS (Top) and NAVA (Bottom). E_{drs} scale is identical for direct comparison.

In Fig. 3, at the beginning of an inspiratory cycle, typical E_{drs} values for both PS and NAVA were less than zero. Negative E_{drs} occurs when the negative pressure generated inside the patient's pleural space causes air flow to enter the lung. As lung volume increases due to positive pressure ventilation, E_{drs} increases above 0, as expected clinically and from the model definition. As patient inspiratory demand is met, the magnitude of the E_{demand} component of E_{drs} reduces toward zero, as seen in E_{drs} as a surrogate, and E_{drs} becomes more positive. During PS, E_{drs} increases from a negative value to a patient-specific maximum before decreasing (Fig. 3). This result suggests that PS may potentially be a more invasive support mechanism than NAVA. As pleural pressure decreases due to the patient's inspiratory demand, the airway pressure or flow changes. When the ventilator detects this change, it provides the full, specified pressure support. This instantaneous step pressure support, known as the pressurisation slope (Piquilloud et al., 2011), stretches the lung at the start of ventilation. As the air enters the lung and distributes evenly, the value of E_{drs} drops. If a supported breath overstretches the lung, the overall E_{drs} may continue to increase until the end of a breathing cycle.

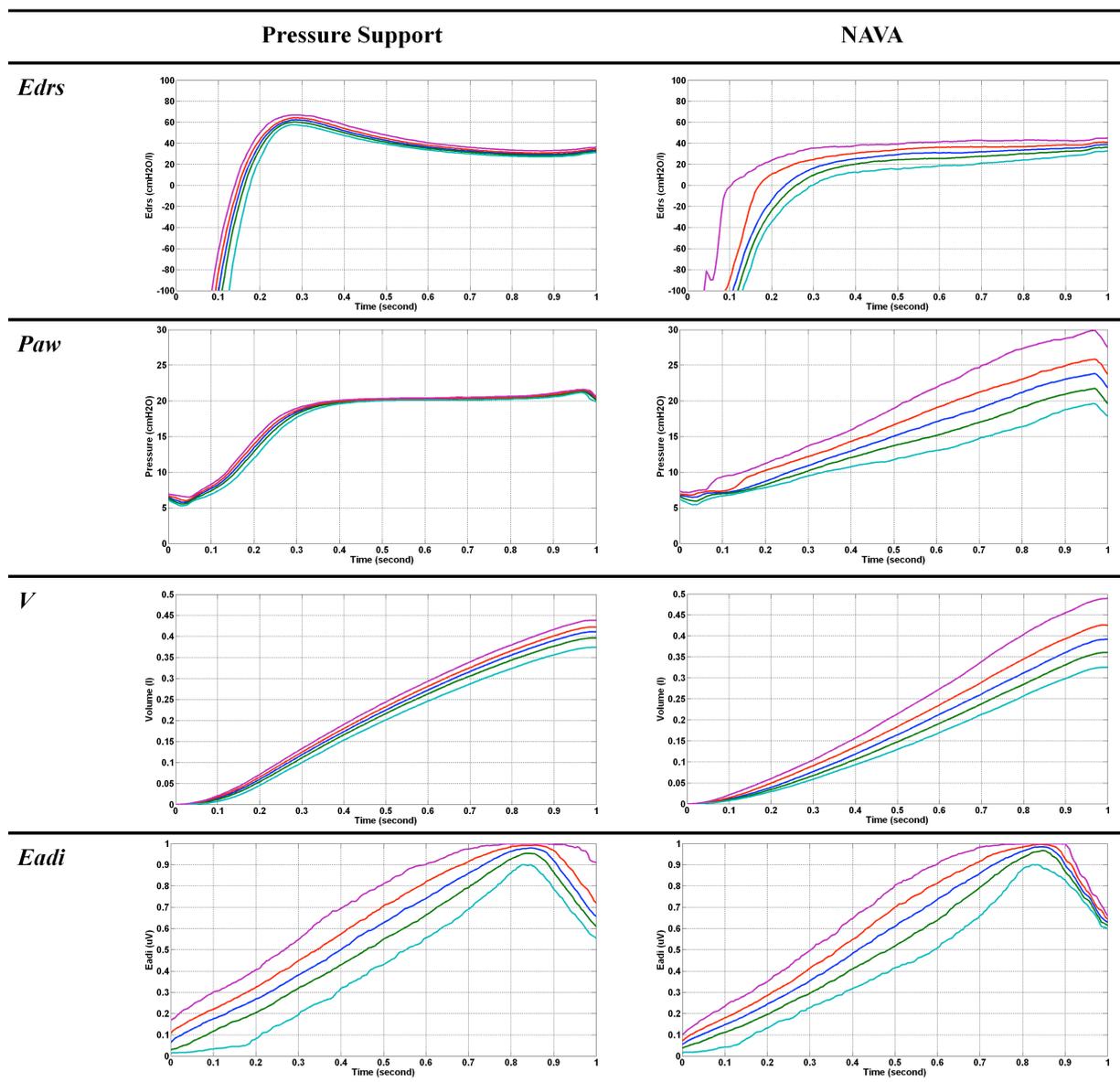|	Pressure Support	NAVA
Edrs		
Paw		
V		
Eadi		

Fig. 3. Time-varying E_{drs}, pressure, volume and electrical diaphragm activity (*Eadi)* curves for Patient 9 during PS (left) and NAVA (Right). The lines indicate the 5th (Light blue), 25th (Green) 50th (Blue), 75th (Red) and 95th (Pink) percentile of all breathing cycles.

Table 1. Summary of $AUCE_{drs}$ for all 22 patients during PS and NAVA

Patients	PS					NAVA				
	5th*	25th	50th	75th	95th	5th	25th	50th	75th	95th
Median	23.9	29.5	31.9	35.2	39.1	8.0	12.6	16.2	20.5	28.4
IQR*	17.8-30.2	21.2-33.9	23.6-37.2	26.2-41.8	28.4-48.3	3.3-20.0	5.9-27.2	8.7-35.2	13.3-43.8	19.8-58.2

*th – Percentiles of the E_{drs} trajectories, IQR –Interquartile Range

During NAVA, E_{drs} begins as a negative value, again due to the negative pressure created in the pleural space due to patient inspiratory demand. However, during NAVA ventilation, E_{drs} reaches a maximum near the peak inspiratory pressure (PIP), rather than at the beginning of inspiration as seen in PS mode. The pressure delivered in NAVA mode is proportional to the measured electrical diaphragm activity (*Eadi*). The pressure delivered during NAVA reaches a maximum near the end of the inspiratory cycle, and in most cases, E_{drs} reaches its peak at peak inspiratory pressure.

In the cohort, it was found that the 5th-95th percentile range for E_{drs} was typically wider in NAVA than in PS, occurring in 18 out of 22 patients (p < 0.05). Figs. 2 and 3 clearly show more variation between breaths in NAVA mode compared to PS mode. This difference is as expected due to more variable pressure delivery in NAVA. The underlying method used by PS leads to the smooth, consistent curves seen in Figs. 2 and 3, while NAVA is dependent on the patient *Eadi*, which leads to much more variation in E_{drs} between breaths, as seen in other studies comparing the matching of patient demand

(*Eadi*) to tidal volume (*Vt*) for these patients (Piquilloud et al., 2011, Moorhead et al., 2012). Comparing $AUCE_{drs}$ between PS and NAVA patients, it was found that overall $AUCE_{drs}$ is higher in PS than in NAVA. This result suggested that, due to the variable pressure assist during NAVA, the NAVA level, as selected based on similar peak pressure during PS (Piquilloud et al., 2011, Moorhead et al., 2012), is able to avoid over assistance that may overstretch and damage the lung.

4.2 AUCE_{drs}: A severity indicator

Table 1 shows the $AUCE_{drs}$ for the 22 patients during PS and NAVA. The $AUCE_{drs}$ was normalised area under the curve and can be used to describe patient-specific disease state similar to conventional two point static elastance. The 95th percentile $AUCE_{drs}$ was above 25 cmH_2Os/l for 20 of 22 patients in PS mode, and only 15 of 22 patients in NAVA mode. Acute respiratory distress syndrome (ARDS) patients have been shown to have higher respiratory system elastance with $E_{drs} \geq 25$ cmH_2O/l (The ARDS Definition Task Force, 2012). This result shows that, in most cases, the proposed $AUCE_{drs}$ metric is able to capture mechanics similar to those observed in an ARDS patient during full sedation and MV, giving confidence of the clinical relevance of the $AUCE_{drs}$ value. The results also show differences between modes and delivery of pressure on patient-specific response and risk. $AUCE_{drs} < 25$ cmH_2Os/l suggests that the patients' lung in this SB study is more compliant than that of fully sedated ARDS patient lungs, as might be expected for SB patients.

The $AUCE_{drs}$ for SB patients is dependent on the initial pleural pressure or the magnitude of negative E_{demand}. Thus, a lower $AUCE_{drs}$ may indicate that a patient has comparatively higher individual breathing effort than others, and obviously more than a sedated patient who has none and for whom $AUCE_{drs} > 0$ is always true (Chiew et al., 2011). In general, SB patients are healthier than sedated patients who require full MV, and the $AUCE_{drs}$ metric was able to uniquely capture this information without the need for oesophageal pressure.

4.3 General Utility of Time-Varying E_{drs}

Fundamentally, this extended model is thus general over SB and sedated MV patients, and implies that negative pressure ventilation will generate $E_{drs} < 0$, while positive pressure ventilation will result in $E_{drs} > 0$. Thus, the E_{drs} can be used as a simple, real-time indicator to assess patients-specific disease state and response to MV. Equally, as E_{drs} rises it can be indication of the changes in SB patients, to investigate issues around reduced demand or oesophageal pressure.

For a fully sedated patient, the time-varying E_{drs} values were found to be positive ($E_{drs} > 0$) throughout the entire breath (Chiew et al., 2011, Zhao et al., 2012). This outcome is consistent with what we would expect for a patient who is not providing the negative thoracic pressure that facilitates spontaneous breathing. For SB patients who have their own inspiratory effort, E_{demand} will be negative, lowering the overall E_{drs} towards zero or to less than zero. More specifically, E_{drs} will be less than zero when patient breathing demand is high at the beginning of inspiration, and will

gradually decrease in magnitude as patient demand decreases during the breath.

An $E_{drs} > 0$ implies that the positive pressure ventilation contributes or adds to the patient-specific lung elastance. Therefore, $E_{drs} > 0$ is a measure of patient lung condition and response to MV. Only $E_{drs} > 0$ may be considered as a potentially 'harmful' state to the lung, depending on level and trend throughout the breath. In particular, elastance is defined as pressure response to the delivered volume. High elastance (E_{drs}) indicates more pressure per unit volume delivered, and thus greater risk for lesser volume and recruitment.

Time-varying E_{drs} is a measure of patient-specific response towards the ventilator (Chiew et al., 2011). Titrating care using this unique and physiologically relevant overall elastance parameter can potentially optimise both pneumatic settings of the ventilator (pressure and volume) simultaneously, as it incorporates both elements in its definition. It is a unique metric in capturing the relationship between pressure and (delivered) volume, compared to other approaches that try to titrate care in just one of these metrics (pressure or volume only).

Equally, the $AUCE_{drs}$ is able to capture a unique parameter that is directly relevant to respiratory mechanics of SB patients without the use of invasive oesophageal pressure measurements (Khirani et al., 2010). The application of E_{drs} can potentially be used to guide PEEP selection, optimal pressure support and NAVA level in SB patients, which is currently not available without these additional invasive manoeuvres (Talmor et al., 2008, Khirani et al., 2010). This extended model and proof of concept analysis should thus open up new options in selecting the proper SB modes, and their associated PEEP or level of pressure support, as well as being general to both SB and fully sedated MV patients.

4.4 Limitations

One of the limitations of this study is the use of a constant resistance of 5 cmH_2Os/l. As the estimation of E_{drs} is dependent on the airway resistance (R_{rs}), a constant resistance could yield incorrect E_{drs} estimation. However, during intra-patient comparisons that switch between ventilation modes, the impact of R_{rs} can be neglected in favour of trends.

Time-varying E_{drs} is not normally calculated in MV patients. It is a new concept that provides unique information to monitor the patient-specific disease state and response to MV. When applied in SB patients, negative E_{drs} values only correspond to the negative pressure generated in the pleural space to inflate the lung. Existing data on time-varying E_{drs} or compliance in fully sedated MV patients has been shown to be positive (Chiew et al., 2011, Zhao et al., 2012). $E_{drs} < 0$ is only possible for patients who are breathing spontaneously, as it requires that the patient produces inspiratory effort. The validity of the estimated negative values of E_{drs} as a measure of patient-specific demand similar to the use of oesophageal pressure in SB patients warrants further investigation and direct quantification based on these results, as this data does not present this opportunity.

5. CONCLUSIONS

An extended model that defines conventional respiratory elastance into 3 separate components is presented. The proposed model was able to capture unique dynamic respiratory mechanics for spontaneously breathing patients during PS and NAVA, which is otherwise not possible without added invasive manoeuvres that interrupt conventional care methods. The work presented here is the first of its kind to present a method and monitor time-varying E_{drs} in SB patients without additional measuring equipment or interruption of care. It is a fully general model that is applicable to all MV modes and conditions with the resulting potential to 'standardise' treatment for all sedated and non-sedated MV patients.

6. ACKNOWLEDGEMENT

The authors wish to thank Lise Piquilloud, Philippe Jolliet, Jean-Pierre Revelly, Jean Roeseler, Emilie Bialais and Thierry Sottiaux for data collection and input on results. The authors also wish to thank GIGA Cardiovascular Science in University of Liege for supporting this research.

7. CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

REFERENCES

Benditt, J. O. (2005). Esophageal and Gastric Pressure Measurements. *Respiratory Care,* volume 50**,** 68-77.

Bernstein, D., Nguyen, B., Allen, G. and Bates, J. T. (2013). Elucidating the fuzziness in physician decision making in ARDS. *Journal of Clinical Monitoring and Computing,* volume 27**,** 357-363.

Brander, L. and Slutsky, A. (2006). Assisted spontaneous breathing during early acute lung injury. *Critical Care,* volume 10**,** 102.

Brochard, L., Martin, G., Blanch, L., Pelosi, P., Belda, F. J., Jubran, A., Gattinoni, L., Mancebo, J., Ranieri, V. M., Richard, J.-C., Gommers, D., Vieillard-Baron, A., Pesenti, A., Jaber, S., Stenqvist, O. and Vincent, J.-L. (2012). Clinical review: Respiratory monitoring in the ICU - a consensus of 16. *Critical Care,* volume 16**,** 219.

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.

Chiumello, D., Carlesso, E., Cadringher, P., Caironi, P., Valenza, F., Polli, F., Tallarini, F., Cozzi, P., Cressoni, M., Colombo, A., Marini, J. J. and Gattinoni, L. (2008). Lung Stress and Strain during Mechanical Ventilation for Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med,* volume 178**,** 346-355.

Iotti, G. A., Braschi, A., Brunner, J. X., Smits, T., Olivei, M., Palo, A. and Veronesi, R. (1995). Respiratory mechanics by least squares fitting in mechanically ventilated patients: Applications during paralysis and during pressure support ventilation. *Intensive Care Medicine,* volume 21**,** 406-413.

Khirani, S., Polese, G., Aliverti, A., Appendini, L., Nucci, G., Pedotti, A., Colledan, M., Lucianetti, A., Baconnier, P. and Rossi, A. (2010). On-line monitoring of lung mechanics during spontaneous breathing: a physiological study. *Respiratory Medicine,* volume 104**,** 463-471.

Kogler, V. M. (2009). Advantage of spontaneous breathing in patients with respiratory failure. *SIGNA VITAE,* volume 4.

Kuhlen, R. and Putensen, C. (1999). Maintaining spontaneous breathing efforts during mechanical ventilatory support. *Intensive Care Medicine,* volume 25**,** 1203-1205.

Lucangelo, U., Bernabè, F. and Blanch, L. (2007). Lung mechanics at the bedside: make it simple. *Current Opinion in Critical Care,* volume 13**,** 64-72

Moorhead, K., Piquilloud, L., Lambermont, B., Roeseler, J., Chiew, Y. S., Chase, J. G., Revelly, J.-P., Bialais, E., Tassaux, D., Laterre, P.-F., Jolliet, P., Sottiaux, T. and Desaive, T. (2012). NAVA enhances tidal volume and diaphragmatic electro-myographic activity matching: a Range90 analysis of supply and demand. *Journal of Clinical Monitoring and Computing,* volume**,** 1-10.

Piquilloud, L., Vignaux, L., Bialais, E., Roeseler, J., Sottiaux, T., Laterre, P.-F., Jolliet, P. and Tassaux, D. (2011). Neurally adjusted ventilatory assist improves patient–ventilator interaction. *Intensive Care Medicine,* volume 37**,** 263-271.

Putensen, C., Zech, S., Wrigge, H., Zinserling, J., Stuber, F., Von Spiegel, T. and Mutz, N. (2001). Long-Term Effects of Spontaneous Breathing During Ventilatory Support in Patients with Acute Lung Injury. *Am. J. Respir. Crit. Care Med.,* volume 164**,** 43-49.

Slutsky, A. S., Brochard, L., Putensen, C., Hering, R. and Wrigge, H. 2005. Spontaneous Breathing During Ventilatory Support in Patients with ARDS. *In:* Vincent, J.-L. (ed.) *Mechanical Ventilation.* Springer Berlin Heidelberg.

Talmor, D., Sarge, T., Malhotra, A., O'donnell, C. R., Ritz, R., Lisbon, A., Novack, V. and Loring, S. H. (2008). Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury. *New England Journal of Medicine,* volume 359**,** 2095-2104.

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.

Villar, J., Zhang, H., Blanco, J. and Slutsky, A. (2012). Year in review 2011: Critical Care - respirology. *Critical Care,* volume 16**,** 243.

Wrigge, H., Zinserling, J., Neumann, P., Muders, T., Magnusson, A., Putensen, C. and Hedenstierna, G. (2005). Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: a randomized controlled computed tomography trial. *Crit Care,* volume 9**,** R780 - R789.

Zhao, Z., Guttmann, J. and Moller, K. (2012). Adaptive Slice Method: A new method to determine volume dependent dynamic respiratory system mechanics. *Physiol Meas.,* volume 33**,** 51-64.