Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnline CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 53-2 (2020) 16221–16226

Virtual Patient Modeling and Prediction Validation for Pressure Controlled Mechanical Ventilation

Sophie E Morton*, Jennifer L Knopp*, Merryn H Tawhai, Paul Docherty*, Knut Moeller***, Serge J Heines****, Dennis C Bergmans****, J. Geoffrey Chase***

*University of Canterbury, Centre for Bioengineering, Private Bag 4800, Christchurch, NZ (Geoff.Chase@canterbury.ac.nz).

**University of Auckland, Auckland Bioengineering Institute, Auckland, NZ (e-mail: m.tawhai@auckland.ac.nz)

*** Furtwangen University, Institute for Technische Medizin, Villingen-Schwenningen, Germany, (e-mail: Knut.Moeller@furtwangen.de) ***

**** Maastricht University, School of Medicine, Dept of Intensive Care, Maastricht, Netherlands,

Abstract: Respiratory failure patients in the intensive care unit (ICU) require mechanical ventilation (MV) to support breathing and tissue oxygenation. Optimizing MV care is problematic. Significant patient variability confounds optimal MV settings and increase the risk of lung damage due to excessive pressure or volume delivery, which in turn can increase length of stay and cost, as well as mortality. Model-based care using in silico virtual patients can significantly affect ICU care, personalizing delivery and optimising care. This research presents a virtual patient model for pressure-controlled MV, an increasingly common mode of MV delivery, based on prior work applied to volume-controlled MV. This change necessitates predictions of flow and thus volume, instead of pressure, as the unspecified variable. A model is developed and validated using clinical data from five patients (N=5) during a series of PEEP (positive end expiratory pressure) changes in a recruitment maneuver (RM), creating a total of 242 predictions. Peak inspiratory volume, a measure of risk of lung damage, errors were 56 [26-95]mL (10.6 [5.3-19.1]%) for predictions of PEEP changes from 2-16cmH2O. Model fitting errors were all lower than 5%. Accurate predictions validate the model, and its potential to both personalise and optimise care.

Keywords: Include a list of 5-10 keywords, preferably taken from the IFAC keyword list.

1. INTRODUCTION

Mechanical ventilation (MV) is a core therapy for intensive care patients suffering from respiratory failure (Slutsky, 1993, Slutsky and Tremblay, 1998). A clinician set pressure and flow is delivered to the lungs, opening the alveoli and allowing for gas exchange. However, determining optimal ventilator settings to maximise oxygenation while minimising the risk of further damage through ventilator induced lung injury (VILI) (Amato et al., 1998, Ricard et al., 2003) is difficult.

Staircase titration of PEEP (positive end expiratory pressure) to find the PEEP level with minimum elastance recruits new alveoli and ensures open alveoli do not collapse at the end expiration, preventing repetitive damage (Amato et al., 1998, Suarez-Sipmann et al., 2007, Suter et al., 1978). However, increasing pressures increases the risk of barotrauma and increasing volumes increases the risk of volutrauma (Briel et al., 2010), a balance between patient care and risk.

The problem is one of risk balancing between low and high PEEP, and thus low and high pressure and volume settings. In addition, there is predictive risk when changing settings, where the ability to know if a change would lead to further damage, or no added recruitment value, would be useful before making it. There is thus a need for methods to provide better insight into optimal ventilator settings, predictive of changes in patient lung response to changes in care (Morton et al., 2019a).

Model-based methods give clinicians real-time information on patient-specific lung condition to balance these risks, while ensuring adequate oxygenation and care. Recently, such models have shown accurate prediction of patient-specific response to changes in care to help guarantee safety from barotrauma in volume-controlled MV (Morton et al., 2018, Morton et al., 2019b). However, current medical practice prefers pressure controlled ventilation (PCV) in many ICUs (Major et al., 2018), and volutrauma in PCV is an equally damaging form of VILI.

To date there are significant virtual patient development in the area of metabolic systems (e.g. (Chase et al., 2010, Evans et al., 2012, Chase et al., 2018, Dickson et al., 2018, Chase et al., 2011)). They are in clinical use for blood glucose control (Fisk et al., 2012, Stewart et al., 2016), but are emerging for cardiovascular and pulmonary systems (Chase et al., 2018, Morton et al., 2019a, Desaive et al., 2019). There is thus a

10.1016/j.ifacol.2020.12.615

growing need to extend and bring these models into clinical practice to personalise care.

This study is an initial model extension from volume-controlled MV to PCV, including proof-of-concept validation on clinical data. The goal is to provide accurate prediction of patient-specific response in pressure controlled ventilation.

2. METHODS

2.1 Data, Patients and Ethics

This analysis uses data from a single RM from N=5 PCV MV patients under a BIPAP MV mode in Maastricht in November 2017 to January 2018. Data was obtained at the start of MV, captured at 125Hz. A proof-of-concept validation set. Ethics approval and use of this data for this study was provided by the institutional review board.

2.2 Virtual Patient Model

Basis functions for volume-controlled MV virtual patient models were used to derive new formulations to predict outcome volumes, instead of pressures, for PCV input variables (Morton et al., 2018, Morton et al., 2019b). Its underlying structure is based on the well-known single compartment model (Bates, 2009b, Bates, 2009a), which has been well used and validated with clinical data (Chiew et al., 2011, Chiew et al., 2015b, Chiew et al., 2015a, van Drunen et al., 2013a, van Drunen et al., 2013b, van Drunen et al., 2014), assuring a proven foundation model.

The initial model used in (Morton et al., 2018, Morton et al., 2019b) is defined:

$$P(t) = \left(\underbrace{E_1 (V - V_m)^2}_{\substack{recruitment \\ elastance}} + \underbrace{E_2 \frac{P(t)}{60}}_{\substack{distension \\ elastance}} \right) V(t) + \left(\underbrace{R_1 + R_2 |Q(t)|}_{Rohrer\ resistance} \right) Q(t) + PEEP \quad (1)$$

where $P(t)$ is the airway pressure delivered by the ventilator (cmH_2O), $PEEP$ is the positive end-expiratory pressure (cmH_2O), $V(t)$ is integral of the flow delivered, $Q(t)$ (L/s), from time, t=0, for each breath, and V_m = 1L.

The recruitment elastance basis function term $(V\text{-}V_m)^2$ is set to zero for $V > V_m$ and is piecewise parabolic with respect to V at a given PEEP. The recruitment and distension elastances, E_1 and E_2 (cmH_2O/L), and flow resistances, R_1 and R_2 (cmH_2O*s/L), are found from measured data and linear least squares regression.

The goal is to use measured pressure data, $P(t)$, to identify flow ($Q(t)$) in PCV, the opposite of the approach in (Morton et al., 2018, Morton et al., 2019b). Identification yielded $R_2 \sim 0$ because most MV flows are laminar (Morton et al., 2019b), and was thus removed from analysis.

2.3 System Identification Method

Data is identified breath to breath, beginning at the first flow $Q > 0$L/s, and ending when $Q = 0$L/s, covering inspiration and expiration. $PEEP$ is the minimum measured pressure, which can differ from the ventilator set value. A median breath was developed from all breath data available at each PEEP level of the staircase recruitment maneuver.

E_1, E_2, R_1 are identified using linear least squares regression for the median breath at each PEEP, from:

$$P(t) = \left(E_1 (V - V_m)^2 + E_2 \frac{P(t)}{60} \right) V(t) + R_1 Q(t) + PEEP \quad (2)$$

Since $PEEP$, $P(t)$, $Q(t)$, and thus $V(t)$ integrated from the known input $Q(t)$ are known, the variables can be identified using least squares and Equation (2).

However, in specific, data for each breath analysed was truncated to 60 points to provide equal weighting to both inspiration and expiration data (30 points each), where inspiration had (median [IQR]) 27 [23 – 30] data points. Hence, the value of 30 splits the data into approximately equal sections. It also minimises near-zero flow data at the end of expiration, which ensures a more robust least squares problem. There are thus 60 equations and 3 unknowns.

Because flow and volume are related, forward simulation of flow from known input pressure data was performed using Newton's method. An initial guess of $Q(t)$ = 3L/s constant flow is used to start the iterative process, where this value is a typical peak value in adult ICU MV. Each iteration updated this flow to be more physically realistic, including negative expiratory flow. Since volume is the integral of flow, the process employs two equations:

$$V_{i-1}(t) = \int Q_{i-1}(t)\, dt \quad (3)$$

$$Q_i(t) = \frac{(P(t) - PEEP - (E_1 (V_{i-1}(t) - V_m)^2) V_{i-1}(t) - (E_2 \frac{P(t)}{60}) V_{i-1}(t))}{R_1} \quad (4)$$

Equations 3-4 are iterated until maximum flow converges to 0.1% or less change or a maximum of 500 iterations.

2.4 Model Prediction

Prediction validation examined the upward increasing PEEP arm of the RM, since risk arises from increasing pressure and PEEP, rather than reducing pressures. Predictions were made for all possible upward PEEP changes covering one or more steps. The number of predictions studied for each prediction interval size are shown in Table 1, where the total number of predictions is 242, which is large enough and across enough PEEP levels to ensure a robust proof-of-concept validation.

When PEEP rises, there is an increase in retained lung volume at the end of expiration, V_{frc}, due to recruitment. $V_{frc} > 0$ when PEEP rises and $V_{frc} < 0$ when it falls. The change in the value of V_{frc} for a change in PEEP is calculated iteratively with a starting estimated value of 0.05L (50mL) using a zero-flow condition from Equation (1) defined (Morton et al., 2018, Morton et al., 2019b):

$$V_{frc}^n = \frac{(PEEP_{n+1} - PEEP_n)}{E_1 (V_{frc} - V_m)^2 + E_2 PEEP_{n+1}/60} \quad (5)$$

Table 1. Number of predictions studied for each interval size of increasing PEEP (N=242 total)

Increase in PEEP	Number of Predictions
0 cmH_2O	46
2 cmH_2O	42
4 cmH_2O	37
6 cmH_2O	32
8 cmH_2O	27
10 cmH_2O	22
12 cmH_2O	17
14 cmH_2O	12
16 cmH_2O	7

2.5 Model Validation

The values are identified at a given PEEP level for E_1, E_2 and R_1, and used to predict flow, $Q(t)$, and volume, $V(t)$, at higher PEEP levels using the known pressure controlled input, $P(t)$. Fitting error assesses model validity and structure. Prediction error assesses clinical validity in using the model and methods to personalise and guide care.

Safety from volutrauma is assessed in the prediction error for peak inspiratory volume (PIV) at a new PEEP level. This predicted value includes estimated V_{frc} and any error in that value, which is directly computed from the clinical data at a PEEP change for comparison. Hence, if fitting error is low, indicating good model structure to the observed dynamics, then prediction error, independent of fitting error, assesses clinical safety and validity of the model and methods, although it is expected these errors move in tandem.

Root Mean Square (RMS) error is the average sum-squared error over the breath. Percentage RMS error normalises this value to pressure level for fair comparison across a wide range of PEEP values. PIV error is calculated as absolute value (mL) and percentage error. Finally, since flow and volume are related, peak flow is also compared. Per Table 1, predictions are made from 1-8 PEEP levels upward or forward, for ΔPEEP ranges of 6-22cmH_2O.

3. RESULTS

3.1 Model Fit

The model fit of volume assessed across all PEEP levels is shown in Table 2 noted as a prediction over PEEP change of zero (0cmH20 PEEP change). Prediction of PIV had absolute error (median [IQR]) of 8.8 [5.2 – 12.2] mL, with an RMS error of 21.2 [16.0 – 26.5]mL. The fitting RMS error was 37 [25 - 64]mL (18.3 [11.9 - 28.1]%). There was peak flow error of -1 [-0.7 - -1.2]L/s, and RMS error 11 [6-24]mL/s. Model flow error was overall larger than volume error, as slight timing offsets in modelled vs. measured flow with steep gradients magnified error, but overall area under the curve (volume) was similar.

Table 2: Results for flow prediction, peak flow estimation and fitting error metrics (RMS, mean (signed) and mean (absolute) shown). Note that peak flow error is in litres/second, while other error metrics are in ml/second. These results are shown as median [IQR] for all predictions studied for a given ΔPEEP prediction that interval size.

Prediction Interval Size	Peak Flow Estimation Error (L/s)	RMS Error (mL/s)	Mean Error (signed) (mL/s)	Mean Error (absolute) (mL/s)
0 cmH_2O	-1.0[-1.2 - -0.7]	11 [6 - 24]	-7 [-16 - 6]	554 [463 - 631]
4 cmH_2O	-0.9 [-1.1 - -0.7]	24 [16 - 45]	-8 [-21 - 36]	599 [498 - 643]
8 cmH_2O	-0.8 [-1.3 - -0.6]	36 [11 - 72]	-10 [-39 - 33]	676 [579 - 773]
12 cmH_2O	-0.9 [-1.3 - -0.5]	37 [18 - 91]	-11 [-35 - 58]	795 [551 - 953]
16 cmH_2O	-0.7 [-1.2 - -0.2]	62 [9 - 95]	6 [-14 - 95]	1007 [604 - 1048]

3.2 Model Prediction of Flow

Figure 1 and Table 2 present all prediction errors (non-zero PEEP changes). For all PEEP prediction intervals studied, peak flow had (median [IQR]) absolute prediction error of 0.86 [0.65 - 1.18]L/s. The percentage absolute error was 13.9 [11.1 - 18.0]%. for each prediction interval, including zero for the fitting error case.

Differences in RMS and mean (signed) error, compared to mean (absolute) error shows the general shape of flow is captured well over the breath, but timing is not necessarily precise with peaks and troughs occurring at slightly different times. Figure 2 shows a typical prediction, where the RMS and mean (signed error) were each 0.024L, but mean (absolute) error was 0.326L. The error in maximum flow estimation was 0.590L/s.

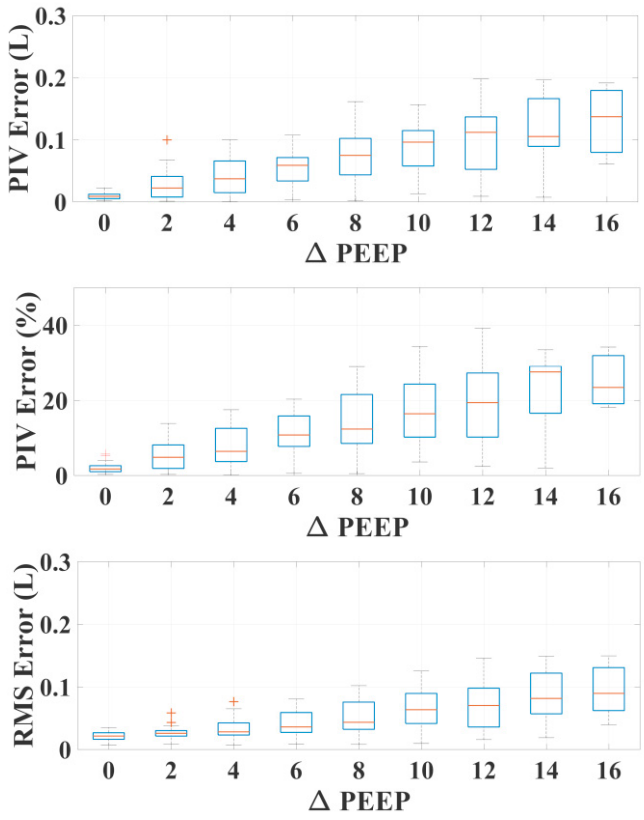

Figure 1: Specific error results for model prediction. a) Error (L) in predicting peak inspiratory volume across all PEEP interval sizes. b) Error (%) in predicting peak inspiratory volume across all PEEP interval sizes. c) RMS Error (L) in predicting lung mechanics across all PEEP interval sizes.

Note that timing errors in flow leading to larger flow errors are less evident in (integrated) volume values. However, it should be noted volume is the more clinically relevant metric for risk and patient safety. Thus, a model developed originally for volume-controlled ventilation translates well in accuracy to pressure-controlled ventilation based on the low volume prediction errors.

Finally, clinically important PIV error over all PEEP changes predicted across had (median [IQR]) error of 56 [26-95]mL (10.6 [5.3-19.1]%) with 95th percentile absolute error of 160mL. These errors are summarised for each ΔPEEP prediction interval in the boxplots in Figure 1.

4. DISCUSSION

Model fit yielded volume and flow results fitting measured values well over all RM steps. This outcome indicates the model structure, and thus the specific basis functions used in (Morton et al., 2018, Morton et al., 2019b), are thus more broadly validated across volume and pressure controlled MV. The results show it captures the observed physiology of elastance in recruitment and distension well. This overall result should be expected as the MV mode is not expected to significantly impact physiological mechanical properties for relatively small differences between MV modes.

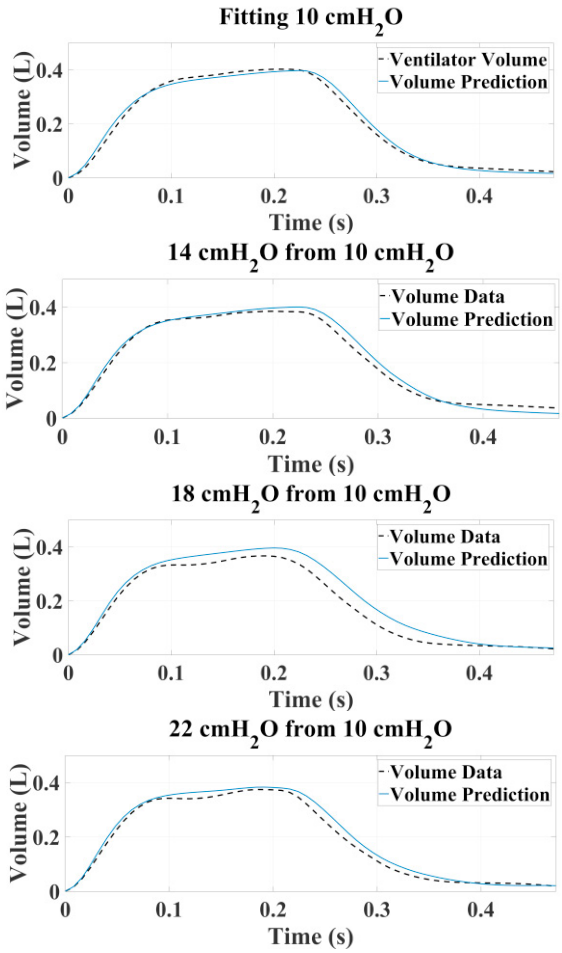

Figure 2: Specific prediction results for Patient 1, fitting the model to a PEEP of 10 cmH$_2$O and predicting lung mechanics up to a PEEP of 22 cmH$_2$O.

Peak inspiratory volume was predicted across PEEP interval increases of 4 cmH$_2$O with (median [IQR] and median error of 40 [20 - 70] mL (6.3%), increases of 8 cmH$_2$O with error of 70 [40 - 100] mL (12.3%) and increases of 12 cmH$_2$O with error of 110 [50 - 140] mL (19.3%). Importantly, prediction intervals of 12cmH2O or more are not clinically relevant or likely, as smaller steps are more typical. However, the relatively low PIV error for these large intervals provides a more robust validation of the model and its potential clinical use. Equally, the much lower error at clinically relevant PEEP change intervals validates the safety and efficacy likely to result in clinical use.

In some cases, PIV prediction and RMS fit percentage errors can be large. However, in some cases, the volume increases to be estimated are very small making these errors, which have small absolute errors in mL, seem larger than they are in clinical terms. More directly, small absolute errors have little meaning, even if the percentage error is large.

More specifically, the largest tidal volume in this study was 0.82 L (median [IQR] of 0.51 [0.39 – 0.63]). However, functional residual capacity of the lung for a health adult is 1.8L to 2.4L for women and men. The tidal volumes are thus

a measurable fraction of this capacity, but changes in tidal volume between PEEP steps may be much smaller. Thus, small changes may not be predicted well, but those relatively larger errors are not clinically meaningful in absolute value.

Similarly, the results show some larger flow prediction errors, but much lower volume prediction errors. The flow errors arise primarily from small differences in timing between rapidly changing flow during a breath in the data and in the identified model prediction. The overall shapes are very close, but errors can appear large. However, these errors are effectively cancelled in integrating to get volume, indicating these errors, while appearing large, are not meaningful in difference. More specifically, low mean values for the signed errors in these cases further show any over or under prediction in flow cancels.

Prior work by Morton et al (2018; 2019a,b) showed errors in estimating V_{frc} in Equation (5) were relatively and clinically small. They thus had lesser impact on predicted pressures in those prior cases, but in proportion where smaller V_{frc} error led to smaller predicted pressure error. The same proportion and impact should hold true in this case for predicted volume. Hence, improving V_{frc} estimation should improve the errors reported here.

In context, this is the first virtual patient model with accurate prediction for any form of MV. This work extends it from volume controlled MV to the equally to more commonly used pressure controlled mode of MV. This prediction is in comparison to a wide range of models, which accurately fit data but cannot predict changes to MV settings (Schranz et al., 2011, Schranz et al., 2012a, Schranz et al., 2012b, Sundaresan et al., 2009, Sundaresan and Chase, 2011, Sundaresan et al., 2011, Morton et al., 2019a), which is critical clinically. The model and results are thus unique.

Overall, a predictive lung mechanics method has been used to forward predict volume over a recruitment maneuver. Prediction accuracies are clinically relevant with a median error or 10.6% over all predictions, and much lower error over smaller PEEP changes. Such predictions can be used to inform clinical care, as they provide insight to tidal volume, in the context of achieving recruitment and minimising volume trauma.

5. CONCLUSIONS

The results of this study show the proposed model, already validated in volume-controlled ventilation, can provide good prediction in pressure-controlled ventilation MV modes. This extension thus show the model dynamics and approach cover both major forms of ventilation. More importantly, the results show the potential, with further in depth studies, to significantly impact the personalisation and optimisation of MV care, and to reduce the risk of ventilator induced lung injury in all forms.

More specifically, low fitting errors indicate the model captures all observed dynamics of clinical importance. Accurate forward prediction of peak inspiratory volume ensures the virtual patient model can act as a safe means to predict clinically relevant values, despite slightly larger errors in flow prediction. The model presented is thus a first of its kind virtual patient for pressure-controlled ventilation with initial proof-of-concept validation. Finally, these outcomes all show the virtual patient model for volume-controlled ventilation generalises very well to pressure controlled modes, and thus is a further validation of the underlying models and methods in its generalisation here.

REFERENCES

AMATO, M. B. P., BARBAS, C. S. V., MEDEIROS, D. M., MAGALDI, R. B., SCHETTINO, G. P., LORENZI-FILHO, G., KAIRALLA, R. A., DEHEINZELIN, D., MUNOZ, C., OLIVEIRA, R., TAKAGAKI, T. Y. & CARVALHO, C. R. R. 1998. Effect of a Protective-Ventilation Strategy on Mortality in the Acute Respiratory Distress Syndrome. *N Engl J Med,* 338**,** 347-354.

BATES, J. H. T. 2009a. *The linear single-compartment model Lung Mechanics*, Cambridge University Press.

BATES, J. H. T. 2009b. *Lung Mechanics: An Inverse Modeling Approach,* United States of America, New York, Cambridge University Press.

BRIEL, M., MEADE, M., MERCAT, A., BROWER, R. G., TALMOR, D., WALTER, S. D., SLUTSKY, A. S., PULLENAYEGUM, E., ZHOU, Q., COOK, D., BROCHARD, L., RICHARD, J.-C. M., LAMONTAGNE, F., BHATNAGAR, N., STEWART, T. E. & GUYATT, G. 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,* 303**,** 865-873.

CHASE, J. G., LE COMPTE, A. J., PREISER, J.-C., SHAW, G. M., PENNING, S. & DESAIVE, T. 2011. Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice? *Annals of intensive care,* 1**,** 11.

CHASE, J. G., PREISER, J. C., DICKSON, J. L., PIRONET, A., CHIEW, Y. S., PRETTY, C. G., SHAW, G. M., BENYO, B., MOELLER, K., SAFAEI, S., TAWHAI, M., HUNTER, P. & DESAIVE, T. 2018. Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them. *Biomed Eng Online,* 17**,** 24.

CHASE, J. G., SUHAIMI, F., PENNING, S., PREISER, J. C., LE COMPTE, A. J., LIN, J., PRETTY, C. G., SHAW, G. M., MOORHEAD, K. T. & DESAIVE, T. 2010. Validation of a model-based virtual trials method for tight glycemic control in intensive care. *Biomed Eng Online,* 9**,** 84.

CHIEW, Y., PRETTY, C., SHAW, G., CHIEW, Y., LAMBERMONT, B., DESAIVE, T. & CHASE, J. 2015a. Feasibility of titrating PEEP to minimum elastance for mechanically ventilated patients. *Pilot and Feasibility Studies,* 1**,** 9.

CHIEW, Y. S., CHASE, J. G., SHAW, G., SUNDARESAN, A. & DESAIVE, T. 2011. Model-based PEEP

Optimisation in Mechanical Ventilation. *BioMedical Engineering OnLine,* 10**,** 111.

CHIEW, Y. S., PRETTY, C., DOCHERTY, P. D., LAMBERMONT, B., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2015b. Time-Varying Respiratory System Elastance: A Physiological Model for Patients Who Are Spontaneously Breathing. *PLoS ONE,* 10**,** e0114847.

DESAIVE, T., HORIKAWA, O., ORTIZ, J. P. & CHASE, J. G. 2019. Model-based management of cardiovascular failure: Where medicine and control systems converge. *Annual Reviews in Control*.

DICKSON, J. L., STEWART, K. W., PRETTY, C. G., FLECHET, M., DESAIVE, T., PENNING, S., LAMBERMONT, B. C., BENYO, B., SHAW, G. M. & CHASE, J. G. 2018. Generalisability of a Virtual Trials Method for Glycaemic Control in Intensive Care. *IEEE Trans Biomed Eng,* 65**,** 1543-1553.

EVANS, A., LE COMPTE, A., TAN, C. S., WARD, L., STEEL, J., PRETTY, C. G., PENNING, S., SUHAIMI, F., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2012. Stochastic targeted (STAR) glycemic control: design, safety, and performance. *J Diabetes Sci Technol,* 6**,** 102-15.

FISK, L. M., LE COMPTE, A. J., SHAW, G. M., PENNING, S., DESAIVE, T. & CHASE, J. G. 2012. STAR Development and Protocol Comparison. *Biomedical Engineering, IEEE Transactions on,* 59**,** 3357-3364.

MAJOR, V. J., CHIEW, Y. S., SHAW, G. M. & CHASE, J. G. 2018. Biomedical engineer's guide to the clinical aspects of intensive care mechanical ventilation. *Biomedical engineering online,* 17**,** 169.

MORTON, S. E., DICKSON, J., CHASE, J. G., DOCHERTY, P., DESAIVE, T., HOWE, S. L., SHAW, G. M. & TAWHAI, M. 2018. A virtual patient model for mechanical ventilation. *Comput Methods Programs Biomed,* 165**,** 77-87.

MORTON, S. E., KNOPP, J. L., CHASE, J. G., DOCHERTY, P., HOWE, S. L., MÖLLER, K., SHAW, G. M. & TAWHAI, M. 2019a. Optimising mechanical ventilation through model-based methods and automation. *Annual Reviews in Control*.

MORTON, S. E., KNOPP, J. L., CHASE, J. G., MÖLLER, K., DOCHERTY, P., SHAW, G. M. & TAWHAI, M. 2019b. Predictive Virtual Patient Modelling of Mechanical Ventilation: Impact of Recruitment Function. *Annals of biomedical engineering,* 47**,** 1626-1641.

RICARD, J. D., DREYFUSS, D. & SAUMON, G. 2003. Ventilator-induced lung injury. *Eur Respir J,* 22**,** 2s-9.

SCHRANZ, C., DOCHERTY, P., CHIEW, Y. S., MOLLER, K. & CHASE, J. G. 2012a. Iterative Integral Parameter Identification of a Respiratory Mechanics Model. *BioMedical Engineering OnLine,* 11**,** 38.

SCHRANZ, C., DOCHERTY, P. D., CHIEW, Y. S., CHASE, J. G. & MOLLER, K. 2012b. Structural identifiability and practical applicability of an alveolar recruitment model for ARDS patients. *IEEE Trans Biomed Eng,* 59**,** 3396-404.

SCHRANZ, C., KNÖBEL, C., KRETSCHMER, J., ZHAO, Z. & MÖLLER, K. 2011. Hierarchical Parameter Identification in Models of Respiratory Mechanics. *IEEE Trans Biomed Eng.,* 58**,** 3234-41.

SLUTSKY, A. 1993. Mechanical Ventilation. American College of Chest Physicians' Consensus Conference. *Chest,* 104(6)**,** 1833-1859.

SLUTSKY, A. S. & TREMBLAY, L. N. 1998. Multiple system organ failure. Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med,* 157**,** 1721 - 1725.

STEWART, K. W., PRETTY, C. G., TOMLINSON, H., THOMAS, F. L., HOMLOK, J., NOEMI, S. N., ILLYES, A., SHAW, G. M., BENYO, B. & CHASE, J. G. 2016. Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. *Ann Intensive Care,* 6**,** 24.

SUAREZ-SIPMANN, F., BOHM, S. H., TUSMAN, G., PESCH, T., THAMM, O., REISSMANN, H., RESKE, A., MAGNUSSON, A. & HEDENSTIERNA, G. 2007. Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. *Crit Care Med,* 35**,** 214 - 221.

SUNDARESAN, A., CHASE, J., SHAW, G., CHIEW, Y. S. & DESAIVE, T. 2011. Model-based optimal PEEP in mechanically ventilated ARDS patients in the Intensive Care Unit. *BioMedical Engineering OnLine,* 10**,** 64.

SUNDARESAN, A. & CHASE, J. G. 2011. Positive end expiratory pressure in patients with acute respiratory distress syndrome - The past, present and future. *Biomed Signal Proc and Control,* 7**,** 93-103.

SUNDARESAN, A., YUTA, T., HANN, C. E., GEOFFREY CHASE, J. & SHAW, G. M. 2009. A minimal model of lung mechanics and model-based markers for optimizing ventilator treatment in ARDS patients. *Computer Methods and Programs in Biomedicine,* 95**,** 166-180.

SUTER, P. M., FAIRLEY, H. B. & ISENBERG, M. D. 1978. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. *Chest,* 73**,** 158 - 162.

VAN DRUNEN, E., CHASE, J. G., CHIEW, Y. S., SHAW, G. & DESAIVE, T. 2013a. Analysis of different model-based approaches for estimating dFRC for real-time application. *BioMedical Engineering OnLine,* 12**,** 9.

VAN DRUNEN, E., CHIEW, Y. S., CHASE, J., SHAW, G., LAMBERMONT, B., JANSSEN, N., DAMANHURI, N. & DESAIVE, T. 2013b. Expiratory model-based method to monitor ARDS disease state. *BioMedical Engineering OnLine,* 12**,** 57.

VAN DRUNEN, E., CHIEW, Y. S., PRETTY, C., SHAW, G., LAMBERMONT, B., JANSSEN, N., CHASE, J. & DESAIVE, T. 2014. Visualisation of time-varying respiratory system elastance in experimental ARDS animal models. *BMC Pulmonary Medicine,* 14**,** 33.