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Online Estimation of Respiratory Mechanics in Non-Invasive Pressure Support Ventilation: a Bench Model Study

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***Abstract*—An online algorithm for determining respiratory mechanics in patients using non-invasive ventilation (NIV) in pressure support mode was developed and embedded in a ventilator system. Based on multiple linear regression (MLR) of respiratory data, the algorithm was tested on a patient bench model under conditions with and without leak and simulating a variety of mechanics. Bland-Altman analysis indicates reliable measures of compliance across the clinical range of interest (±11-18% limits of agreement). Resistance measures showed large quantitative errors (30-50%), however, it was still possible to qualitatively distinguish between normal and obstructive resistances. This outcome provides clinically significant information for ventilator titration and patient management.**

I. Introduction

IN spontaneously breathing patients suffering from respiratory insufficiency, respiratory system (RS) mechanics - namely resistance and compliance - provide important information about the type, severity, and progression of disease. This information assists in clinical decision-making, particularly titrating ventilator settings. In practice, the clinician makes inferences about RS mechanics from the patient's statistics, pathology, and by inspection of the pressure and flow waveforms. Little has been done to make quantitative information available on a ventilator system for the convenience of the clinician or as a control reference for automated therapy.

Measuring mechanical parameters of the RS in spontaneously breathing patients using non-invasive ventilation (NIV) on pressure support presents major challenges and a sound method is yet to be established for such systems.

Approaches with the most potential to achieve this are the forced oscillation technique (FOT) [1], and applying multiple linear regression (MLR) of sampled data to a model [2, 3]. The latter approach has superior clinical advantage in that it does not necessitate system excitation or maneuvers which impose additional hardware requirements, and possibly interrupt the continuity of therapy. Furthermore, it derives a meaningful set of parameters pertinent to breathing frequency that facilitates better clinical understanding for practitioners.

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This paper is dedicated to the validation of an adaptive MLR algorithm designed to estimate respiratory parameters in non-invasively ventilated patients. The implementation is embedded in a real-time environment in a ventilator system and tested with a spontaneously breathing patient bench model.

II. Methods

A. Bench model setup and data acquisition

The algorithm (described in section II.*D*) was embedded using C++ in a bi-level ventilator (VPAP research prototype, ResMed) where analogue pressure and flow signals are converted to digital, filtered and calibrated. The system was tested on a patient bench model using pressure support ventilation, as described below. A range of patient mechanics and ventilator settings was configured and data were collected via a serial link to a computer.

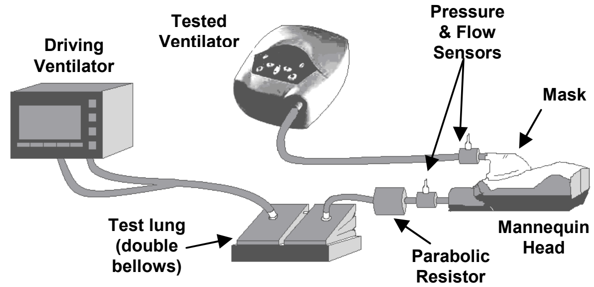

Fig. 1: Schematic of patient bench model connected to test ventilator.

A paired bellows system was used to model the lungs (Metron QA-VT Dual adult ventilator tester) in series with a mannequin head (Bill I, VBM Medizintechnik GmbH, Sulz, Germany) to simulate a spontaneously breathing patient under NIV conditions (Fig. 1). The driving ventilator used was an ICU ventilator (Evita 4, Drägerwerk AG, Lübeck, Germany) in pressure control mode. The compliance of the patient bellows (C_{sys}) was adjusted manually. The patient bellows was connected in series with the head, equipped with upper airways and trachea, via an adjustable parabolic resistor analogous to the lower airways resistance (R_p). The test ventilator was connected to the head via a medium size oro-nasal vented mask (Ultra Mirage Full Face, ResMed).

A pneumotachograph and pressure transducer (Biopac Systems, Goleta, CA, USA) was inserted between the ventilator tubing and the mask, and a second set was inserted between the trachea and patient lung compartment to determine flow and pressure at the 'mouth' and 'alveoli'. To generate leak, a three-way stopcock with a constant orifice (2 mm) was inserted in the circuit,

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between the mouth transducer set and the mask. The following variables were recorded (MP100, Biopac Systems, Goleta, CA), sampled at 200 Hz: pressure at the mouth, P_{aw}; pressure in the lung, P_{alv}; flow at the mouth, $\dot{V}_{aw}$; and, flow at the lung, $\dot{V}_{alv}$. Parameters internal to the ventilator were sampled at 100 Hz. These included: flow with leak compensation, $\dot{V}_{pat}$; delivered pressure measured at the mask, P_v; estimated resistance, R_{est}; estimated compliance, C_{est}; estimated positive end-expiratory pressure (PEEP), $PEEP_{est}$; and, mean expired tidal volume, V_t.

B. Experimental protocol

The driving ventilator was set in pressure control mode with a frequency of 12 breaths min^{-1}. Leak compensation available in the therapy ventilator was used. Pressure support (PS) and C_{sys} were changed across three discrete levels. Two resistors were used, the numeric label denoting the coefficient of the parabolic pressure-flow relationship of the resistor. The tests were performed using a full face mask with and without leaks. Data were obtained with the ventilation settings and test variables given in Table I. All thirty-six (36) unique combinations of the test variables were assessed. Each condition was tested for 90 seconds.

TABLE I. VENTILATOR AND TEST VARIABLE SETTINGS

Ventilator Setting	Value
Mode	pressure support
PEEP	5 cmH2O
Trigger	0.1 L/s
Rise time	100 ms
Cycle	25% of peak inspiratory flow
Max inspiratory time	4 s
Test Variable	
R	'Rp5', 'Rp20'
C	20, 50, 100 mL/cmH2O
PS	10, 15, 20 cmH2O
Leaks	0, ~12 L/s

C. System mechanics calibration

Leak was determined by subtracting $\dot{V}_{aw}$ and $\dot{V}_{alv}$. The mean value was 12.3±5.87 Lmin^{-1}, calculated over the 90 s duration for each test.

Respiratory system compliance, C_{sys}, was taken to be the value set on the bellows.

Total respiratory system resistance included resistive components between the bellows and the mouth: the mask, head, tubing, and parabolic resistor. This was characterized by performing a series of inflation-deflation maneuvers, and fitting the pressure drop of the system to the turbulent model of flow,

$$\Delta P = P_{alv} - P_{aw} = K_1\dot{V} + K_2\dot{V}^2 , \tag{1}$$

where K_1 represents the laminar and K_2 the fluidic resistance across the system. Fig. 2 shows an example of the fitted data for the setup with R_p = 20. Derived values of K for each resistor were for R_p=5: K_1 = 3.50, K_2 = 4.24; and, for R_p=20: K_1 = 6.00, K_2 = 12.49.

A single linear resistance R_{sys}, was calculated for each of the 36 test conditions based on the range of flow values present in each data set, $\dot{V}_i$, $i = \{1:36\}$. Resistive pressure, P_{Ri}, was calculated accordingly by fitting the data to the turbulent flow model using obtained values for K. System resistance was calculated by taking the derivative with respect to flow,

$$R_{sys} = \frac{dP_{Ri}}{d\dot{V}} = K_1 + K_2\dot{V}_i , \tag{2}$$

and averaging the resulting values to arrive at an effective linear value.

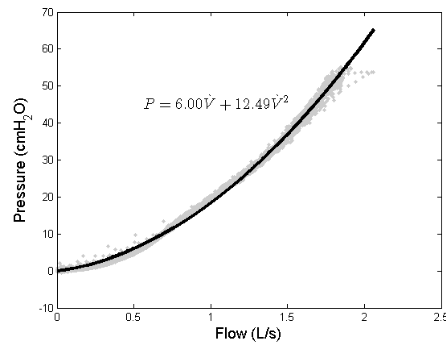

Fig. 2: Data from ten maneuvers with parabolic resistor Rp = 20 fitted to the parabolic curve yielding K_1 and K_2.

Using this method, potential for bias was caused by highly variable counts of discrete values at low flow depending on each of the tests. This was removed by taking a histogram of the data with bins of width 0.05 Ls^{-1}, and finding the average resistance in each bin. Finally, R_{sys} for the test was obtained as the mean across the bins.

D. Algorithm description

The algorithm relies on the application of multiple linear regression (MLR) of which the basic form is,

$$Y_i = \beta_0 + \beta_1 x_{i,1} + \beta_2 x_{i,2} + \cdots \beta_k x_{i,k} + \varepsilon_i , \tag{3}$$

and random errors ε_i = 1, 2,…,n, are normally distributed random variables with zero mean and constant variance σ^2.

The patient-ventilator system can be modeled as a single compartment such that the total driving pressure is the sum of the elastic and resistive properties of the system

$$P_{tot}(t) = R\dot{V}(t) + \frac{V(t)}{C} + P_0 \tag{4}$$

where P_{tot} is the driving pressure, $\dot{V}$ is the air flow through the airways, V is the volume displaced within the lungs, R is the airway resistance to air flow, C is the compliance of the respiratory system, and P_0 is the pressure at end-expiration, which is the sum of the applied external PEEP and internal PEEP of the patient. Defining the driving pressure as the single response variable, and flow ($\dot{V}_{pat}$) and volume as the explanatory variables, MLR was applied to the measured data to estimate the parameters R_{est} and C_{est}.

Patient muscle effort is a non-random noise source that has significant implications for the accuracy of the model.

In a spontaneously breathing patient using a ventilator the driving pressure, P_{tot}, at any time is generated by both the ventilator, P_v, and the patient's respiratory muscles, P_{mus},

$$P_{tot} = P_v + P_{mus}. \tag{5}$$

Because P_{mus} cannot be measured directly without using an esophageal balloon catheter, determination of mechanical parameters non-invasively is impossible during inspiration when the diaphragm and accessory muscles contract. Fitting respiratory data during inspiration without consideration of muscle activity underestimates resistance and overestimate compliance. Thus, data used for the regression in each breath comprised the beginning of expiration up to 90% of the expired volume, V_t. In this way, the driving pressure was solely provided by the ventilator, P_v. The median values of the fitted mechanics parameters from the last 15 breaths were taken as representative of a typical expiratory breath. The coefficient of determination, R^2, was used as a criterion to eliminate poorly fitted breaths. A threshold of 0.95 was used. Differentiation between inspiration and expiration was derived from [4].

III. RESULTS

The t-test for paired observations showed no statistical difference between the two measurements for both resistance (R_{sys}: 11.8±4.1, R_{est}: 11.7±5.8, p=0.94) and compliance (C_{sys}: 56.7±33.5, C_{est}: 59.0±36.4, p=0.06). The correlation for system and estimated resistances was significant (ρ= 0.84) as was that for compliance (ρ=0.94).

Bland-Altman is commonly used to assess the degree of agreement between two clinical measures [5]. Bland-Altman difference plots for resistance (Fig. 3) and compliance (Fig. 4) show a discernable funneling pattern where larger variability in error occurs with increasing resistance values. The compliance plot also shows a descending linear trend across the range investigated. Within each of the three compliance groups, the range of averages do not deviate from C_{sys} by more than -1.5±5.2%.

Limits of agreement (LOA) are the expected limits of error of the method applied to a future measurement. They were calculated using the regression approach for non-uniform differences [5] in combination with the refinements proposed by [6].

A meta-analysis of existing studies on a cross-section of hospitalized patients (both intubated and NIV) was conducted to establish expected ranges of compliance and resistance values [2, 7, 8, 9, 10]. Respiratory mechanics measurements were obtained either by standard occlusion, pure MLR or FOT.

For normal respiratory system mechanics, resistance values do not exceed 5.7 cmH_2O/Ls^{-1} and on average range between 2.12-3.92 cmH_2O/Ls^{-1}. There exists a wider range and variability for pathologically affected lungs as to be expected, with mean values ranging between 8.8-20.34 cmH_2O/Ls^{-1}. Average resistance for chronic obstructive pulmonary disease (COPD) patients was substantially higher than that of normals at 20.562 cmH_2O/Ls^{-1}.

The range for compliance spans between 10 and 110 mL/cmH_2O for all classifications, and differentiation between normal and pathological patients is less straightforward. Restrictive lungs are attributed to having low values of compliance (<30 mL/cmH_2O). Obstructive patients occupy the higher values of the scale, and may present with either 'normal' static compliance of the respiratory system (Cst,rs ~60 mL/cmH2O) or elevated (Cst,rs > 88.5 mL/cmH_2O) [8].

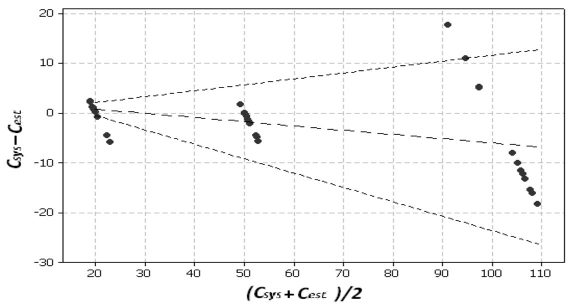

Fig. 3: Bland-Altman plot for resistance. Mean error (middle dashed line) and LOA (upper and lower dashed lines) are shown.

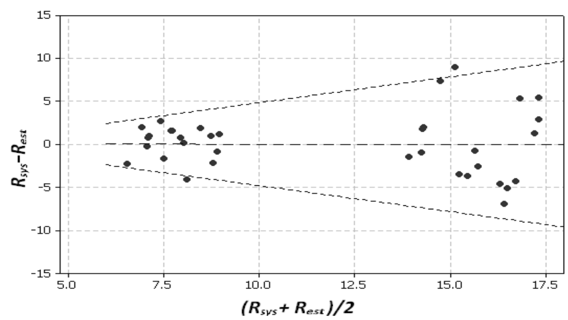

Fig. 4: Bland-Altman plot for compliance. Mean error (middle dashed line) and LOA (upper and lower dashed lines) are shown.

Table II shows the overall performance of the algorithm, giving the mean error and LOA for each mechanics variable. Resistances from the model parameters are calculated as the average of each data cluster pertaining to a physical parabolic resistor in the Bland-Altman plot. Approximate clinical values as gleaned from the meta-analysis are extrapolated for normal (chosen at the upper bound ~5 cmH_2O/Ls^{-1}) and obstructive resistances (~ 20 cmH_2O/Ls^{-1}).

TABLE II. MEAN ERROR AND LOA FOR C AND R MEASURES. INCLUDES LOA OF NORMALS VS COPD

	Mean Error	LOA upper	LOA lower	Max. Prediction	Min. Prediction
C (mL/cmH_2O)					
20	0.84	2.14	-0.46	22.14	19.54
50	-1.71	5.71	-9.13	55.71	40.87
100	-5.96	11.66	-23.58	111.66	76.42
R (cmH_2O/Ls^{-1})					
Rp5 - 7.837	0.05	3.57	-3.47	11.4	4.37
Rp20 - 15.736	0.05	8.31	-8.22	24.05	7.51
Normal - 5	0.05	1.86	-1.76	6.86	3.24
COPD - 20	0.04	10.87	-10.79	30.87	9.21

IV. DISCUSSION AND CONCLUSIONS

It was the aim of this study to validate an algorithm using MLR as its basis for fitting respiratory data to a model of the ventilated patient to derive clinically meaningful estimates for resistance and compliance. The original contribution of this work is in the application of MLR during real-time intended for spontaneously breathing patients using NIV on pressure support. Furthermore, the algorithm is embedded in a ventilator and is applied to a portion of data that excludes effects of inspiratory effort, and exploits system dynamics to best effect.

The results from the study show that the modified MLR algorithm for estimating RS mechanics works reasonably well in a bench patient model under conditions of varying pressure support, leaks and patient mechanics. For both measures good correlation was observed between the system and estimated values.

For normal and mildly obstructive resistance values (<8cmH$_2$O/Ls-1) as well as moderate to highly restrictive values (>15cmH$_2$O/Ls-1) the algorithm is able to offer only qualitative estimates of resistance with between 30-50% error. Importantly, however, limits of agreement for normal and average obstructive resistances are mutually exclusive and hence the algorithm is able to differentiate between these categories. Clinically this has important implications. The capability to monitor trends and global changes in respiratory mechanics in real-time on a ventilator, particularly in COPD, would facilitate tracking of disease progression and recovery, effects of drugs, and effectiveness of ventilation.

Restrictive patients with low compliance as well as normal and obstructive patients with a moderately compliant RS (20-60 mL/cmH$_2$O) could be identified accurately by the algorithm within ±11-18%. The greatest predicted error would be for obstructive patients with an extremely compliant RS (>90mL/cmH$_2$O), where the algorithm might underestimate compliance by up to 23.6% in the worst case, however, this would still be identifiable by clinicians as above normal compliance.

The few attempts at applying conventional MLR to spontaneously breathing ventilated patients [2, 3], have shown that patients' inspiratory effort significantly compromises the accuracy of the parameter estimation. Other novel MLR-based algorithms have been proposed [11, 12, 13], and while excellent agreement with reference values were observed, they were applied exclusively to sedated ventilated patients. Recent validation of these and/or similar algorithms was undertaken in spontaneously breathing patients without ventilation therapy [14], however trans-pulmonary pressure was invasively measured and used in the calculations in place of pressure at the airway, P_{aw}.

There are several limitations to the current study. To validate the algorithm using real patients would have been preferable but was prohibitive, due to the unreliable nature of measuring RS mechanics in spontaneously breathing patients and limited accessibility to methods which facilitate measurements during spontaneous breathing (e.g. FOT, invasive trans-pulmonary pressure measurement). Future studies would involve a comparison study with these techniques in humans. The model simplicity does not account for many non-linearities, inhomogeneities in multiple lung compartments, viscoelastic properties of tissues, and expiratory flow limitation. These influences result in poor data fitting and parameter inaccuracies, particularly with increasing degree of severity in disease. Work by Bates [9], however, argues for the case of using a linear single-compartment model in MLR in preference to higher order and multi-compartment models because the latter currently have little clinical significance. In a real-time therapy application intended for seamless and integrated use by clinicians and patients alike, such as the algorithm described herein, compromise between a perfected model and clinical usability is imperative to technology development and its adoption into practice.

In conclusion, the method described for measuring respiratory system resistance and compliance gives reliable measures of compliance across the clinical range of interest, and is able to accurately distinguish between normal versus obstructive resistances. It may provide a useful tool for ventilator titration and patient management.

V. References

[1] E. Oostveen, D. MacLeod, H. Lorino, R. Farre, Z. Hantos, K. Desager, and F. Marchal, "The forced oscillation technique in clinical practice: methodology, recommendations and future developments," *Eur Respir J*, vol. 22, pp. 1026-41, 2003.

[2] R. Peslin, J. F. da Silva, F. Chabot, and C. Duvivier, "Respiratory mechanics studied by multiple linear regression in unsedated ventilated patients," *Eur Respir J*, vol. 5, pp. 871-8, 1992.

[3] G. A. Iotti, A. Braschi, J. X. Brunner, T. Smits, M. Olivei, A. Palo, and R. Veronesi, "Respiratory mechanics by least squares fitting in mechanically ventilated patients: applications during paralysis and during pressure support ventilation," *Intensive Care Med*, vol. 21, pp. 406-13, 1995.

[4] Q. Mulqueeny, S. J. Redmond, D. Tassaux, L. Vignaux, P. Jolliet, P. Ceriana, S. Nava, K. Schindhelm, and N. H. Lovell, "Automated detection of asynchrony in patient-ventilator interaction," *Conf Proc IEEE Eng Med Biol Soc*, vol. 1, pp. 5324--5327, 2009.

[5] J. M. Bland and D. G. Altman, "Measuring agreement in method comparison studies," *Stat Methods Med Res*, vol. 8, pp. 135--160, 1999.

[6] M. A. Proschan and E. S. Leifer, "Comparison of two or more measurement techniques to a standard," *Contemp Clin Trials*, vol. 27, pp. 472--482, 2006.

[7] C. A. Volta, E. Marangoni, V. Alvisi, M. Capuzzo, R. Ragazzi, L. Pavanelli, and R. Alvisi, "Respiratory mechanics by least squares fitting in mechanically ventilated patients: application on flow-limited COPD patients," *Intensive Care Med*, vol. 28, pp. 48-52, 2002.

[8] S. Nava, C. Bruschi, C. Fracchia, A. Braschi, and F. Rubini, "Patient-ventilator interaction and inspiratory effort during pressure support ventilation in patients with different pathologies," *Eur Respir J*, vol. 10, pp. 177-83, 1997.

[9] D. Georgopoulos, I. Mitrouska, K. Markopoulou, D. Patakas, and N. R. Anthonisen, "Effects of breathing patterns on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation," *Intensive Care Med*, vol. 21, pp. 880-6, 1995.

[10] A. Rossi, S. B. Gottfried, B. D. Higgs, L. Zocchi, A. Grassino, and J. Milic-Emili, "Respiratory mechanics in mechanically ventilated patients with respiratory failure," *Journal of Applied Physiology*, vol. 58, pp. 1849-58, 1985.

[11] J. H. Bates and A. M. Lauzon, "A nonstatistical approach to estimating confidence intervals about model parameters: application to respiratory mechanics," *IEEE Trans Biomed Eng*, vol. 39, pp. 94--100, 1992.

[12] G. Avanzolini, P. Barbini, A. Cappello, G. Cevenini, and L. Chiari, "A new approach for tracking respiratory mechanical parameters in real-time," *Ann Biomed Eng*, vol. 25, pp. 154-63, 1997.

[13] A. Eberhard, P. Y. Carry, J. P. Perdrix, J. M. Fargnoli, L. Biot, and P. F. Baconnier, "A program based on a 'selective' least-squares method for respiratory mechanics monitoring in ventilated patients," *Comput Methods Programs Biomed*, vol. 71, pp. 39-61, 2003.

[14] S. Khirani, G. Polese, A. Aliverti, L. Appendini, G. Nucci, A. Pedotti, M. Colledan, A. Lucianetti, P. Baconnier, and A. Rossi, "On-line monitoring of lung mechanics during spontaneous breathing: a physiological study," *Respir Med*, vol. 104, pp. 463—471, 2010.