35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Hierarchical Individualization of a Recruitment Model with a Viscoelastic Component for ARDS Patients

Christoph Schranz, Jörn Kretschmer, Knut Möller

Abstract— **Patient-specific mathematical models of respiratory mechanics enable substantial insight into patient state and pulmonary dynamics that are not directly measurable. Thus they offer potential e.g. to predict the outcome of ventilator settings for Acute Respiratory Distress Syndrome (ARDS) patients. In this work, an existing static recruitment model is extended by viscoelastic components allowing model simulations in various ventilation scenarios. A hierarchical approach is used to identify the model with measured data of 12 ARDS patients under static and dynamic conditions. Identified parameter values were physiologically plausible and reproduced the measured pressure responses with a median Coefficient of Determination (CD) of 0.972 in the dynamic and 0.992 in the static maneuver. Overall, the model presented incorporates physiological mechanisms, captures ARDS dynamics and viscoelastic tissue properties and is valid under various ventilation patterns.**

I. Introduction

Mathematical models of respiratory mechanics can be used to predict the effects of various ventilator settings and thus identify patient-specific lung protective settings in case of Acute Respiratory Distress Syndrome (ARDS) patients [1]. Optimal predictions at the bedside in real-time require computational efficient models. Hence, the applied model must be as simple as possible while capturing all relevant dynamics.

In case of ARDS, relevant dynamics includes primary alveolar recruitment effects increasing lung compliance by opening up new alveolar units [2]. Secondly, alveolar distension effects at higher pressure have to be considered indicating over-inflation. The combination of these effects were considered in a previously developed pressure dependent recruitment model (PRM), that was able to reproduce Low-Flow (LF) responses of ARDS patients with high accuracy [3]. However, individualized PRMs lead to significant prediction errors when simulating more dynamic ventilation scenarios of ARDS patients [4]. In contrast, models of higher order (e.g. Viskoelastic Models – VEM) were able to reproduce the observed dynamics in LF and dynamic situations but didn't consider recruitment effects [4].

To capture pressure and dynamic effects in both situations, the PRM and the VEM are combined to a pressure dependent recruitment model with a viscoelastic component (VEPRM). In this paper, the VEPRM is individualized using clinical data of 12 ARDS patients and tested in various ventilation scenarios.

*Research supported by the Deutsche Forschungsgemeinschaft DFG under Grant MO 579/1-2 PAR.

C. Schranz, J. Kretschmer and K. Möller are with the Institute of Technical Medicine (ITeM), Furtwangen University, 78054 Villingen-Schwenningen, Germany (phone: 0049 7720 307 4395, fax: 0049 7720 4210; e-mail: krj@hs-furtwangen.de).

II. Materials & Methods

A. Data

Measurements of 12 mechanically ventilated patients were selected from a previous ARDS study, where standardized ventilation maneuvers were performed using an Evita4Lab-System (Dräger Medical, Lübeck, Germany). The measurements consisted of flow rate ($\dot{V}$) and airway pressure (p_{aw}) signals sampled at 125 Hz. The study was approved by the local ethics committees of the participating university hospitals. Informed consent was signed by patients or their legally authorized representative. Please refer to [5] for a detailed description of the experimental setup.

Low-Flow (LF) Maneuver: The lung is inflated by a low constant gas flow of 33 mL/s and a Positive End-Expiratory Pressure (PEEP) of 0 cmH_2O until the airway opening pressure reaches 45 cmH_2O, enabling a quasi-static pressure/volume relationship.

Dynamic-Slice (DS) Maneuver: Five consecutive respiratory cycles with a flow rate of 600 mL/s and an inspiration time of 2 s are initiated during baseline ventilation. Inspiration data of the first breathing cycle is analyzed in the following investigation.

Static Compliance Automated Single Step (SCASS) Maneuver: After reaching a randomized tidal volume, the airway is occluded for 5 s to obtain a quasi-static pressure/volume relationship.

B. Models

The following models are individualized using clinical data of flow rate as model input and airway pressure as model output.

Linear 1st Order Model (FOM): The FOM consists of a serial arrangement of a resistance R representing the airway resistances and resistive tissue contributions, and a compliance C, which is a measure for the elasticity of the respiratory system (lung and chest wall). Thus, the patient-specific parameters of the FOM are $P = [R, C]$.

Viscoelastic Model (VEM): The VEM is an extension of the FOM. It assumes that the tissue comprising the walls of the alveolar compartment are viscoelastic, rather than simply elastic. The analogous electrical circuit for the VEM is shown in Fig. 1. R_1 denotes the airway resistances and C_1 the

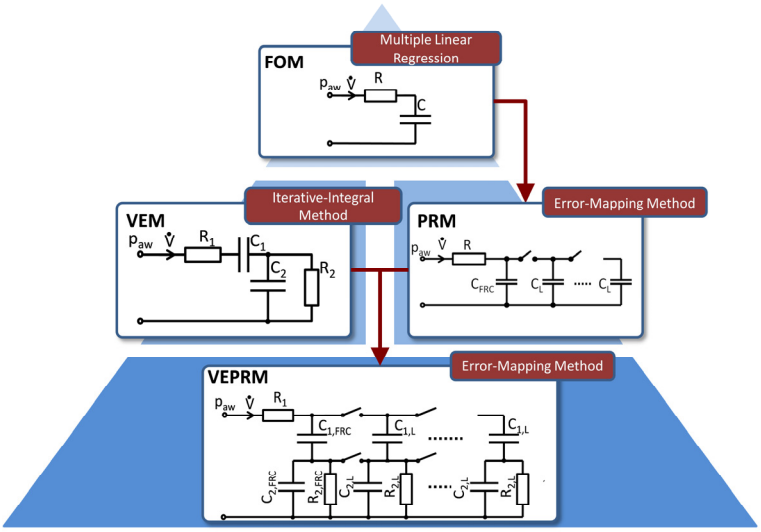


Figure 1. Models and pathways for hierarchical model individualization of the viscoelastic pressure dependent recruitment model (VEPRM) with model-specific individualization methods. Involved models: FOM – 1st Order Model, VEM – Viscoelastic Model, PRM – Pressure Dependent Recruitment Model;

static compliance of the respiratory system. R_2 and C_2 are the resistance and compliance of the viscoelastic component [6]. The patient-specific parameters of the VEM to be identified are $P = [R_1, C_1, R_2, C_2]$.

Pressure Dependent Recruitment Model (PRM): The PRM is based on the alveolar recruitment mechanism as proposed by Hickling [7]: The lung is divided into 30 layers consisting of an evenly distributed amount of alveolar units. Each layer can be represented by a compliant element (C_L). C_{FRC} denotes the compliance of the initially open alveoli forming the residual capacity. Alveolar recruitment is controlled by the Threshold Opening Pressure (*TOP*), which has to be exceeded to open up and to stabilize alveolar units. Recruitment is simulated by closing the switches in the electrical analogous (Fig. 1 – PRM). Secondly, alveolar distension effects are assigned to each compliant element [8] leading to pressure dependent compliances (C_{FRC} and C_L). The overall compliance $\hat{C}$ is defined as the sum of C_{FRC} and the number of "recruited" layers (C_L). This nonlinear compliance function replaces the constant compliance of the FOM yielding the PRM [3]. The patient-specific parameters of the PRM are defined as $P = [R, C, \Theta, K, TOP]$. With R being the airway resistance, K the exponential coefficient of the over-distension function [3], C representing the maximal compliance of a completely recruited lung:

$$C = C_{FRC} + 30 \cdot C_L \tag{1}$$

and Θ being the portion of C_{FRC} of the maximal compliance:

$$\Theta = \frac{C_{FRC}}{C} \tag{2}$$

Viscoelastic Pressure Dependent Recruitment Model (VEPRM): To additionally consider dynamic effects in the recruitment model, viscoelastic elements are assigned to each layer in the PRM. According to the electrical analogues in Fig. 1, the combination yields a complex model where the static compliance of the VEM is replaced by a pressure dependent compliance consisting of an initially open compartment ($C_{1,FRC}$) and recruitable compartments ($C_{1,L}$). Each recruitment event adds a viscoelastic element ($R_{2,L}$, $C_{2,L}$) to the viscoelastic element ($R_{2,FRC}$, $C_{2,FRC}$) of the initially opened tissue. The patient-specific VEPRM are parameters are defined as $P = [R_1, C_1, R_2, C_2, \Theta, K, TOP]$. With C_1, R_2, C_2 being the overall values of a completely recruited lung.

$$\begin{aligned} C_1 &= C_{1,FRC} + 30 \cdot C_{1,L} \\ R_2^{-1} &= R_{2,FRC}^{-1} + 30 \cdot R_{2,L}^{-1} \\ C_2 &= C_{2,FRC} + 30 \cdot C_{2,L} \end{aligned} \tag{3}$$

The proportions of initially opened tissue properties on the overall properties are, according to the PRM (Eq. 3), equally distributed between the FRC- and the recruitable layers:

$$\Theta = \frac{C_{1,FRC}}{C_1} = \frac{R_2}{R_{2,FRC}} = \frac{C_{2,FRC}}{C_2} \tag{4}$$

C. Hierarchical Model Individualization

The presented models are arranged in a hierarchical structure according to their complexity. The hierarchy and the model-specific parameter identification method are presented in Fig. 1. A certain model in a hierarchical layer can always be considered as an extension or combination of the models in the layer above assuring a defined relation between the models in the hierarchy.

Parameter identification of more complex models is commonly performed by error-mapping methods (e.g. Levenberg-Marquardt Algorithm). These algorithms are supposed to approach the global minimum value on a multi-dimensional error surface starting from defined initial values for every parameter. With increasing model complexity, error-mapping methods tend to converge to local minima leading to parameter values that have no relation to the patient's properties. Hence, initial values should be ideally set within the attractor region of the global minimum. This information is usually not *a-priori* available. Therefore a hierarchical approach is applied to support the derivation of

appropriate initial values. The individualization of a model within the hierarchy in level L_n with error-mapping methods requires previous identification of the inheriting model layer above L_{n-1}. Those resulting parameters are incorporated in the derivation of initial values to identify the selected model. If the identification of the upper layer model requires again initial values, prior identification of the inheriting model in the next higher level L_{n-2} is required [9].

The hierarchical approach to identify the VEPRM is depicted in Fig. 1. The identification of the VEPRM with error-mapping methods requires preceding identification of the VEM and the PRM.

The VEM identification was performed by the Iterative Integral Method [10], enabling robust parameter identification of linear higher order models without initial values. The viscoelastic effects can be uncovered and captured by the VEM in SCASS maneuvers as airway occlusions evoke exponential pressure drops, that can be assigned to viscoelastic tissue properties (Fig. 3a,b).

The PRM identification was performed by an error-mapping method using LF-Data that provide quasi-static conditions, where mainly pure pressure effects are present. The initial values for the PRM identification were partly derived via prior identification of the FOM. The FOM as basic linear model can be identified without initial values using a multiple linear regression method. Identified FOM values of R and C lead to convenient initial values for PRM identification [3].

This sequential approach to identify the VEPRM leads to pathways highlighting the approach for deriving convenient initial values (Fig. 1). As the PRVEM combines pressure-dependent and dynamic effects, the identification incorporates LF and DS – Data simultaneously. The Sum of Squared Error (SSE) for VEPRM is minimized according to:

$$SSE = SSE_{LF} + SSE_{DS} \tag{5}$$

with

$$SSE_{LF} = \frac{1}{N_{LF}} \sum_{1}^{N_{LF}} \left(p_{aw,LF} - p_{aw,VEPRM,LF}(P)\right)^2 \tag{6}$$

$$SSE_{DS} = \frac{1}{N_{DS}} \sum_{1}^{N_{DS}} \left(p_{aw,DS} - p_{aw,VEPRM,DS}(P)\right)^2 \tag{7}$$

Where $p_{aw,LF}$ and $p_{aw,DS}$ are measured pressure responses in the LF and DS maneuver. $p_{aw,VEPRM,LF}$ and $p_{aw,VEPRM,DS}$ are the simulated pressure responses with the corresponding flow rates during the LF and DS maneuver as function of the model parameters P. N_{LF} and N_{DS} are the number of measured samples.

To quantify the fitting quality, the coefficient of determination (CD) was computed:

$$CD = 1 - \frac{SSE}{\sum \left(p_{aw,Model} - \overline{p}_{aw}\right)^2} \tag{8}$$

$p_{aw,Model}$ corresponds to the simulated response of a particular model; $\overline{p}_{aw}$ represents the mean value of the measured pressure response.

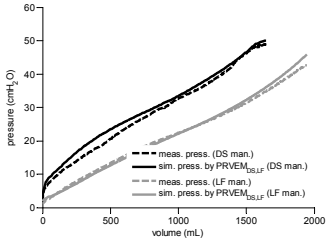
III. Results

A. Individualization

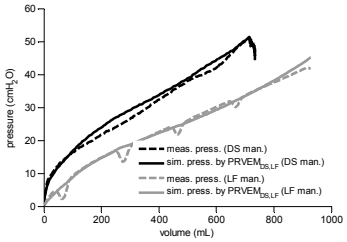
The individualization of the FOM based on LF data, being the first step of the hierarchical approach, lead to patient specific FOM_{LF} that reproduced the measured responses with a median CD value of 0.989 [IQR: 0.985 – 0.996]. Note, the index of the model (e.g.: FOM_{LF}) denotes the underlying maneuver for its individualization.

Incorporating the FOM_{LF} parameters for PRM simulation using LF data yield patient-specific PRM_{LF} with a median CD value of 0.999 [IQR: 0.998 – 0.999].

Model individualization of the VEM using the Iterative Integral Method and SCASS data lead to individualized VEM_{SCASS} that reproduce the measured responses with a median CD value of 0.985 [IQR: 0.955 – 0.994].



a)



b)

Figure 2. Fitting quality of individualized $VEPRM_{LF,DS}$: a) Patient 1, b) Patient 2; Measured (dashed lines) and simulated pressure responses (solid lines) in the Dynamic Slice Maneuver (DS) (black lines) and in the Low-Flow Maneuver (LF) (gray lines).

By applying the patient-specific VEM and PRM parameter for VEPRM identification lead to individualized $VEPRM_{LF,DS}$ that were able to reproduce measured pressure responses with a median CD of 0.972 [IQR: 0.910 – 0.984] in DS maneuver and 0.992 [IQR: 0.989 – 0.996] in LF maneuver simultaneously. The resulting simulated pressure responses of two patients are depicted in Fig. 2 a, b.

The patient-specific $VEPRM_{LF,DS}$ parameter of the 2 patients of Fig. 2 and the cohort statistics are given in Table 1.

B. Model Simulation

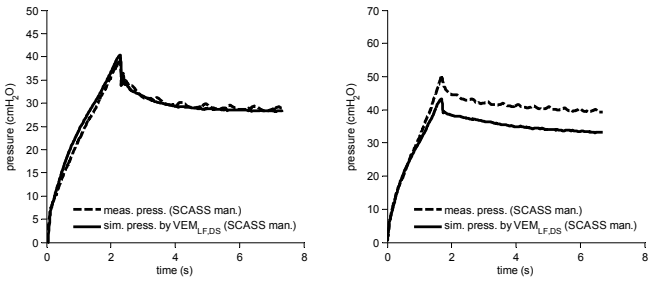
The prediction ability of the individualized $VEPRM_{LF,DS}$ were tested by model simulations in the SCASS maneuver, where CD values of 0.883 [IQR: 0.742 – 0.924] could be achieved. The relatively high inter-quartile range indicates two different groups of different simulation quality. Simulations in 6 of 12 patients were accurate with CD values in the range of 0.900 and higher (e.g. Fig. 3a), whereas the simulation results of the remaining patients lead to lower CD values (e.g. Fig. 3b). These simulations mainly

show deviations during the relaxation process as the peak pressure could not be reached.

TABLE I. RESULTING MODEL PARAMETERS VALUES OF VEPRM IDENTIFICATION OF 2 PATIENTS AND COHORT STATISTICS

Pat.	R_1	C_1	R_2	C_2	Θ	K	TOP
1	9.2	95.2	12.1	92.3	0.58	0.03	6.7
2	12.7	39.4	42.3	68.2	0.45	0.02	5.7
Q_{25}	10.1	50.0	14.6	85.6	0.37	0.01	1.8
median	13.2	75.9	16.7	93.4	0.46	0.01	5.2
Q_{75}	16.4	96.4	26.0	150.8	0.59	0.03	9.7

Units are: $cmH_2O \cdot s/L$ for resistances, mL/cmH_2O for compliances, 1 for Θ, 1/cmH2O for K, cmH_2O for TOP, Q_{25} represents the lower and Q_{75} the upper quartile of the cohort.



a) b)

Figure 3. Prediction quality of individualized $VEPRM_{LF,DS}$ in SCASS Maneuver: a) Patient 1, b) Patient 2; Measured (dashed lines) and simulated pressure responses (solid lines). Viscoelastic tissue properties are visible as pressure relaxation processes after reaching the peak pressure and can be described by an exponential pressure drop.

IV. DISCUSSION

Combining the PRM and VEM lead to the VEPRM. Individualized VEPRMs are able to reproduce the measured pressure responses in the DS and LF maneuver simultaneously. This ability is an improvement over the static FOM and PRM that are only valid in those maneuvers used for parameter identification.

The VEPRM is a nonlinear model consisting of seven patient-specific model parameters. A direct approach with gradient-based parameter identification would have been impossible since no appropriate initial values were available. In contrast, the hierarchical approach incorporates related simpler models to derive initial values and lead the identification process to physiological plausible results with improved efficiency.

Additionally, parameterized VEPRMs seem to be able to produce accurate model simulations in SCASS maneuvers (Fig. 3 a) in 50% of the patient cohort. Simulation errors in the remaining 50% of the patients could be caused by changes in lung physiology (mainly compliance) between or due to the ventilation maneuvers. Further investigations regarding ventilation protocols are necessary to clarify the validity of individualized VEPRMs in various maneuvers.

A. Limitations

Even though, individualized models enabled accurate model simulations indicated by high CD values, physiological interpretation of the model parameter are only valid if the underlying mechanisms are plausible. While the plausibility of the VEM was confirmed in various studies [11, 12], the true recruitment mechanisms in ARDS patients remain unclear. More studies including imaging methods are required to further validate Hickling's recruitment principle and the PRM.

B. Clinical relevance

The VEPRM models recruitment, over-distension and viscoelastic effects using physiological parameters allowing accurate model predictions under various ventilation maneuvers. This model shows potential to be implemented in an online tool providing forward simulations of potentially applicable ventilator settings. Thus, optimized patient-specific ventilator settings can be derived directly at the bedside.

ACKNOWLEDGMENT

The authors thank the McREM Study Group and Dräger Medical for providing the data.

REFERENCES

[1] S. E. Rees, C. Allerød, D. Murley, Y. Zhao, B. W. Smith, S. Kjaergaard, P. Thorgaard, and S. Andreassen, "Using physiological models and decision theory for selecting appropriate ventilator settings," *J Clin Monit Comput,* vol. 20, no. 6, pp. 421-9, Dec. 2006.

[2] L. Gattinoni, P. Caironi, M. Cressoni, D. Chiumello, V. M. Ranieri, M. Quintel, S. Russo, N. Patroniti, R. Cornejo, and G. Bugedo, "Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome," *N Engl J Med,* vol. 354, no. 17, pp. 1775-86, Apr. 2006.

[3] C. Schranz, P. D. Docherty, Y. S. Chiew, J. G. Chase, and K. Möller, "Structural identifiability and practical applicability of an alveolar recruitment model for ARDS patients," *IEEE Trans Biomed Eng.,* vol. 59, no. 12, pp. 3396-404, Dec. 2012.

[4] C. Schranz, and K. Möller, "Inverse Modeling Supports Quantification of Pressure and Time Depending Effects in ARDS Patients," in *Engineering in Medicine and Biology Society, EMBC, 2011 Annu. Internat. Conf. of the IEEE*, Boston, MA, USA, 2011, pp. 1013-1016.

[5] C. A. Stahl, K. Moller, S. Schumann, R. Kuhlen, M. Sydow, C. Putensen, and J. Guttmann, "Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome," *Crit Care Med,* vol. 34, no. 8, pp. 2090-2098, Aug. 2006.

[6] J. H. Bates, *Lung Mechanics: An Inverse Modeling Approach*, 1 ed., New York: Cambridge University Press, 2009.

[7] K. G. Hickling, "The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs," *Am J Respir Crit Care Med,* vol. 158, no. 1, pp. 194-202, Jul. 1998.

[8] E. Salazar, and J. H. Knowles, "An analysis of pressure-volume characteristics of the lungs," *J Appl Physiol,* vol. 19, pp. 97-104, Jan. 1964.

[9] C. Schranz, C. Knöbel, J. Kretschmer, Z. Zhao, and K. Möller, "Hierarchical Parameter Identification in Models of Respiratory Mechanics," *IEEE Trans Biomed Eng,* vol. 58, no. 11, pp. 3234-3241, Nov. 2011.

[10] C. Schranz, P. D. Docherty, Y. S. Chiew, K. Möller, and J. G. Chase, "Iterative Integral Parameter Identification of a Respiratory Mechanics Model," *Biomed Eng Online,* vol. 11, no. 38, 18.07. 2012.

[11] L. Beydon, C. Svantesson, K. Brauer, F. Lemaire, and B. Jonson, "Respiratory mechanics in patients ventilated for critical lung disease," *Eur Respir J,* vol. 9, no. 2, pp. 262-73, Feb. 1996.

[12] B. Jonson, L. Beydon, K. Brauer, C. Mansson, S. Valind, and H. Grytzell, "Mechanics of respiratory system in healthy anesthetized humans with emphasis on viscoelastic properties," *J Appl Physiol,* vol. 75, no. 1, pp. 132-40, Jul. 1993.