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Diagnosis and treatment of flow limitation with a controllable airway resistance – a software simulation

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Abstract: An easy and available manoeuvre to treat flow limitation in severe COPD (chronic obstructive pulmonary disease) is pursed lip breathing. However, in unconscious or sleeping patients or patients who can't overcome the painful and panic triggering effects of dyspnoea through blocked airways, a device to treat flow limitation would be very helpful. Based on a first order lung model enhanced by flow limitation, a simulation to analyze the influence of a controllable airway resistance on flow limitation is presented and evaluated. The effects of flow limitation can be reduced considerably.

Keywords: Trapped Air, Airway resistance, COPD, flow limitation, FOM, pursed lip breathing

1. INTRODUCTION

Simulation plays an increasing role in the evaluation of novel developments in medical instrumentation. Medical approval regulation for example demand high cost, effort and time for medical industries. Here, part of the development could be tested and evaluated in realistic scenarios at a workbench to relieve some of the costs and effort. Therefore a sophisticated patient simulator (Kretschmer et al. 2016) has been developed that is flexible and efficient (Fig. 1).

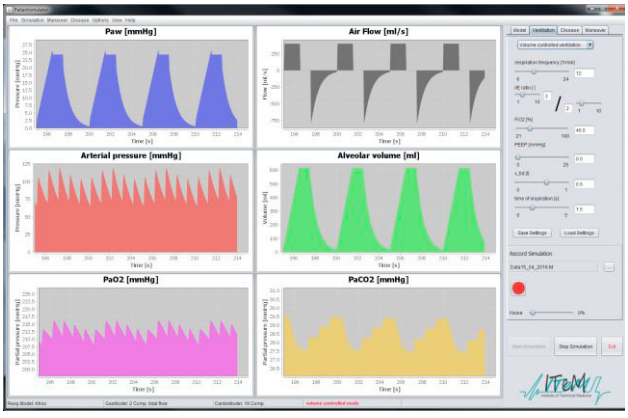

Fig. 1 The graphical user interface of a software based patient simulator that can be used to test and evaluate algorithms for automated therapy in mechanically ventilated patients

It mainly targets mechanically ventilated patients, outpatient care has not been considered up to now. That patient group however represents the majority of patients with lung diseases. Among those, obstructive lung diseases are wide spread all around the world (Loddenkemper 2003). Asthma, COPD (chronic obstructive pulmonary disease) and Emphysema are the most common and well-known amongst them. Especially in severe forms these diseases can be accompanied by a blockage or collapse of the airways, which should be modelled within the simulator to test strategies counteracting this phenomenon. While the trachea and the bigger bronchi are supported by cartilage structures embedded in their walls, smaller bronchioles are kept open by the same mechanism that keeps the alveoli open. Surfactant (surface active agent) influences the surface tension and prevents the collapse of the alveoli and small bronchioles (Andreassen et al. 2010). Thus, the smaller airways don't have the powerful assistance by cartilage and so they can collapse or can be pinched (Bowen et al. 1981). In severe COPD the totally expanded or even over expanded alveoli can generate a pressure on the small bronchioles, which are already narrowed by mucus. This pressure can constrict the bronchioles and finally blocking the airflow. This phenomenon occurs when the alveolar pressure is much higher than the airway pressure (West 2013) and is called flow limitation (Babb 2013, Ranieri et al. 1996). Flow limitation can be attended by trapped air in the lungs of the patients (Verschakelen and De Wever 2007). The limited flow handicaps the expiration of the air in the lungs and thus, not all the inspired air can be exhaled. Breath by breath more air is trapped in the lung, which in turn boosts the flow limitation. Hence these patients can breathe in but have problems to empty their filled lungs.

A manoeuvre to avoid the collapse of the bronchioles is pursed lip breathing (PLB), first mentioned in the 1950'th. Many studies about PLB showed the advantages of this method (Barach 1973, Mueller et al. 1970, Spahija et al. 2005, Spahija and Grassino 1996). Both the gas exchange is improved and the airway pressure continuously remains positive during expiration, which avoids the collapse of the bronchioles and keeps the airways open. Technically, pursed lip breathing can be seen as an additional airway resistance and to overcome this resistance, the patient has to use the expiratory muscles to exhale. Hence, a positive airway pressure (PAP) is sustained in the airways during a large part

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of the expiration phase, which supports the bronchioles and avoids their collapse.

As easy as the PLB manoeuvre is, the dependence on the collaboration of the patient is a major disadvantage and an independent control-mechanism would be very helpful. The nightmarish feeling of patients with dyspnoea, robbed of the ability to breathe by blocked airways, triggers panic while they should relax (Renfroe 1988) and concentrate on their breathing. Therefore, the global aim of this study is the construction of a device, that provides an alternative controllable airway resistance and influences the respiratory behaviour just when needed. The application of this device would be helpful for all patients, including panic-fuelled patients, spontaneous breathing but unconscious patients or potentially even ventilated patients.

Common treatment of mechanical ventilated patients with flow limitation is the reduction of the tidal volume and/or the usage of PEEP (Budweiser et al. 2008) respectively CPAP (Continuous Positive Airway Pressure) (Reddy and Guntupalli 2007). However, the application of PEEP is a compromise, apart from different advantages, it increases the probability of ventilator induced lung injury (VILI), which can involve lung inflammation due to overdistension (mechanotransduction mechanism (Sutherasan et al. 2014)), circular depression, edema, or other pathophysiologic effects. Therefore, to avoid CPAP or PEEP, another treatment option would be helpful.

2. METHODS

Forward simulation is an advantageous tool, which can generate results before any measurements on critically ill patients are done. In this study we did a simulation based on an enhanced first order model (FOM_{fl}) to investigate the effects of an additional airway resistance R_c on flow limitation, which occurs in severe COPD. The FOM is a simple model to describe the behaviour of the lung (Cobelli 2008). The airway passage is symbolized by a single resistance and the tissue property of the lung and airways is described by a capacitance. The FOM equation of the expiratory phase of the breathing cycle is shown in (1) and the electrical analogy is shown in Fig. 2.

$$P = P_{aw} + R_{exp}\dot{V} = \frac{1}{C}V + (R + R_{exp})\dot{V} \qquad (1)$$

where: P is the atmospheric pressure, P_{aw} is the airway pressure, C is the respiratory system compliance, V is the volume, R is the respiratory system resistance, R_{exp} is an expiratory resistance and $\dot{V}$ is the flow.

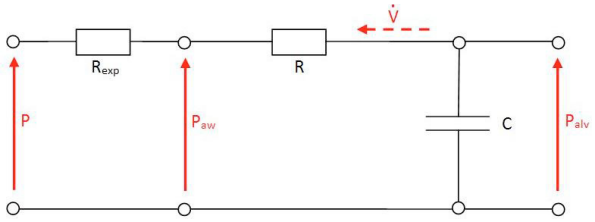

Fig. 2. The first order model (FOM) of pulmonary mechanics during expiration

To model a severe form of COPD we simulated the blockage of the bronchioles (flow limitation) by an additional airway resistance R_{fl} close to the capacitor (lung). Furthermore, the device to control flow limitation was included by a second airway resistance R_c, added to the expiratory resistance ("outside the body"). The implementation of these additional resistances can be seen in Fig. 3, (2) is the corresponding mathematical description.

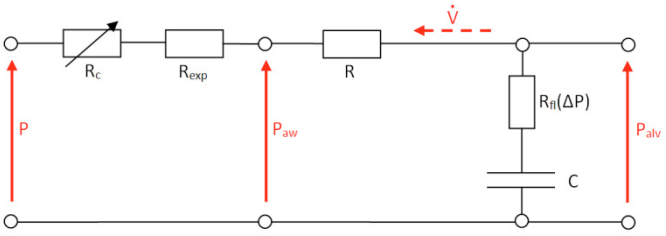

Fig. 3 First order model (FOM_{fl}) extended by an additional resistance $R_{fl}(\Delta P)$ to simulate flow limitation and a resistance R_c to avoid the flow limitation

$$P = P_{aw} + (R_{exp} + R_c)\dot{V} = \frac{1}{C}V + (R + R_{fl} + R_{exp} + R_c)\dot{V} \qquad (2)$$

where: P is the atmospheric pressure, P_{aw} is the airway pressure, C is the respiratory system compliance, V is the volume, R is the respiratory system resistance, R_{exp} is an expiratory resistance, R_{fl} is the resistance simulating the blockage of the bronchioles, R_c is the control resistance and $\dot{V}$ is the flow.

The resistance simulating the blocked bronchioles respectively the flow limitation R_{fl} is dependent on the pressure difference ΔP between the alveolar pressure P_{alv} and the airway pressure P_{aw} (v Neergaard and Wirz 1927). Usually during the total inspiration phase and additionally at the start of expiration flow limitation doesn't occur, thus the airway resistance R_{fl} was initialized with 0mmHg·sec/ml for these periods. If during further exhalation, the mentioned pressure difference ΔP reached a closing threshold (we used 15mmHg in this simulation), the resistance was set after a short delay (0.1sec) to 0.16mmHg·sec/ml. In case of the reduction of the pressure difference below an opening threshold (we used 14mmHg), it was reset back to 0mmHg·sec/ml (4).

$$\Delta P = \lfloor Palv - Paw \rfloor \qquad (3)$$

$$R_{fl}(\Delta P) = \begin{cases} 0.16 & if \quad \Delta P \geq 15mmHg \\ 0 & if \quad \Delta P < 14mmHg \end{cases} \qquad (4)$$

where the unit of R_{fl} is mmHg·sec/ml.

The control resistance R_c in the airways is to counteract the flow limitation and thus the blockage of the bronchioles was simulated according to (5). If a sudden reduction of the flow occurs, the control resistance was "activated". Hence, R_c was set to 0.04mmHg sec/ml and was reduced linearly with time (6).

$$\Delta\dot{V} = -\left|\dot{V}(t-1) - \dot{V}(t)\right| \quad (5)$$

$$R_c(\Delta\dot{V}) = \begin{cases} 0.04\left(1 - \frac{t}{t_{exp}}\right) & if \ \max(\Delta\dot{V}) \geq 500ml/sec \\ 0 & else \end{cases} \quad (6)$$

where: t is the current time during expiration, t_{exp} the total expiration time and $\max(\Delta\dot{V})$ is the maximal change in flow during one expiration phase.

The additional parameters settings used for this simulation are listed in Table 1.

Table 1 simulation parameters

parameter	value
C	50 ml/mmHg
R	0.015 mmHg·sec/ml
R_{exp}	0.001 mmHg·sec/ml
$\Delta P_{closing\ threshold}$	15 mmHg
$\Delta P_{opening\ threshold}$	14 mmHg
$P_{alv\_initial}$	20 mmHg

This simulation was done using MATLAB (R2015a, The MathWorks, Natick, USA).

3. RESULTS

The expiration phases of breathing cycles can be seen in Fig. 4, simulated for a healthy patient (left column), a patient with severe COPD without control resistance (middle column) and patient with severe COPD and applied control resistance (right column). The ΔP-threshold of the closing of the bronchioles is shown by the red dotted line and the green dotted line shows the corresponding opening threshold. The black dashed line shows the pressure difference ΔP, limited on positive pressures. It can be seen that the expired volume of a patient with severe COPD and an active R_c was comparable to the expired volume of a healthy patient, while the exhaled volume of a COPD patient without R_c is considerably smaller. At the end of expiration (2sec) there are still 410ml of air in the lung.

Table 2. lung volumes at different times

	t = 1 sec	t = 2 sec
$Volume_{healthy}(t)$	264 ml	70 ml
$Volume_{COPD}(t)$	790 ml	410 ml
$Volume_{COPD+control\ resistance}(t)$	298 ml	78 ml

4. DISCUSSION

PLB is an easy and useful treatment of flow limitation and is able to reduce its negative effects. Though in experiments a commercial ventilator was already equipped with a controllable resistance via the PEEP controller (Arntz et al. 2008, Möller et al. 2010) for diagnostic and therapeutic issues, a separate external device which guarantees the independence of the collaboration of the patients would be very helpful for clinicians. This study showed the simulated effects of the additional control resistance on flow limitation in patients with severe COPD. Therefore, the expiratory phases of a healthy patient, a patient with COPD and flow limitation and a patient with COPD (flow limitation) and control resistance were simulated.

The simulation of a healthy patient can be seen in the left column of Fig. 4. The resistances R_{fl} and R_c were always 0 (Fig. 4C) – neither a blockage of the bronchioles occurs, nor the intervention of the control resistance was necessary. After 2sec of expiration nearly all air was exhaled and the alveolar pressure was close to the atmospheric pressure. However, in case of a patient with severe COPD (middle column of Fig. 4), at the beginning of the expiration phase, the pressure difference ΔP (3) immediately exceeded the closing threshold of 15 mmHg (Fig. 4B). Hence, after a short delay (0.1 sec) the bronchioles were blocked. This was simulated through R_{fl} (Fig. 4H), which was set to 0.16mmHg·sec/ml. This resistance reduced the flow considerably from 1170ml/sec to 100ml/sec, so it dropped down (Fig. 4E) by $\Delta\dot{V}$=1070ml/sec. Afterwards, the small flow, which was still present (100ml/sec) reduced the pressure difference ΔP. As the pressure difference dropped below the opening threshold, the bronchioles reopened and some of the air, which was still trapped in the lungs, could be exhaled. But at the end of the expiration there was still air trapped in the lungs of the patient (410ml) (Fig. 4K). During the next breathing cycle the volume in the lungs built up further. Thus, the flow limitation increases the amount of the trapped air in the lungs of the patient breath by breath.

Finally, regarding a patient with severe COPD under the control of an additional control resistance R_c (right column of Fig. 4), it can be seen that at the time the flow limitation occurs, the control resistance was "activated" (Fig. 4I). This control resistance increased the airway pressure P_{aw}, so the pressure difference ΔP dropped under the opening threshold (Fig. 4E) and the bronchioles reopened. The flow increased to the level of a healthy patient and comparable to a healthy patient, nearly all air could be exhaled (Fig. 4L).

Therefore, this simulation showed that the aim of a positive airway pressure just in time when it is needed, useable for all patients can be reached. Both the disadvantage of the dependency on the collaboration of the patient and potentially the disadvantage of a continuous positive airway pressure (PEEP) would be reduced.

For the sake of a simplified illustration of the results in Fig. 4, this simulation used a step change for the blockage resistance $R_{fl}(\Delta P)$ to illustrate the effect of an additional airway resistance in the treatment of flow limitation in severe COPD. Most likely this step change doesn't reflect exactly all pathophysiological effects of a blockage of airways, but it clearly illustrates the outcomes that we wanted to show.

This study was a first step in the implementation of a device, which realizes an additional expiratory control resistance R_c. More sophisticated simulations are the next step, followed by a subsequent hardware simulation, which realizes the control resistance via an iris diaphragm (Fig. 5). Controlled by a step motor, this resistance is quick off the mark and can fulfil the demands.

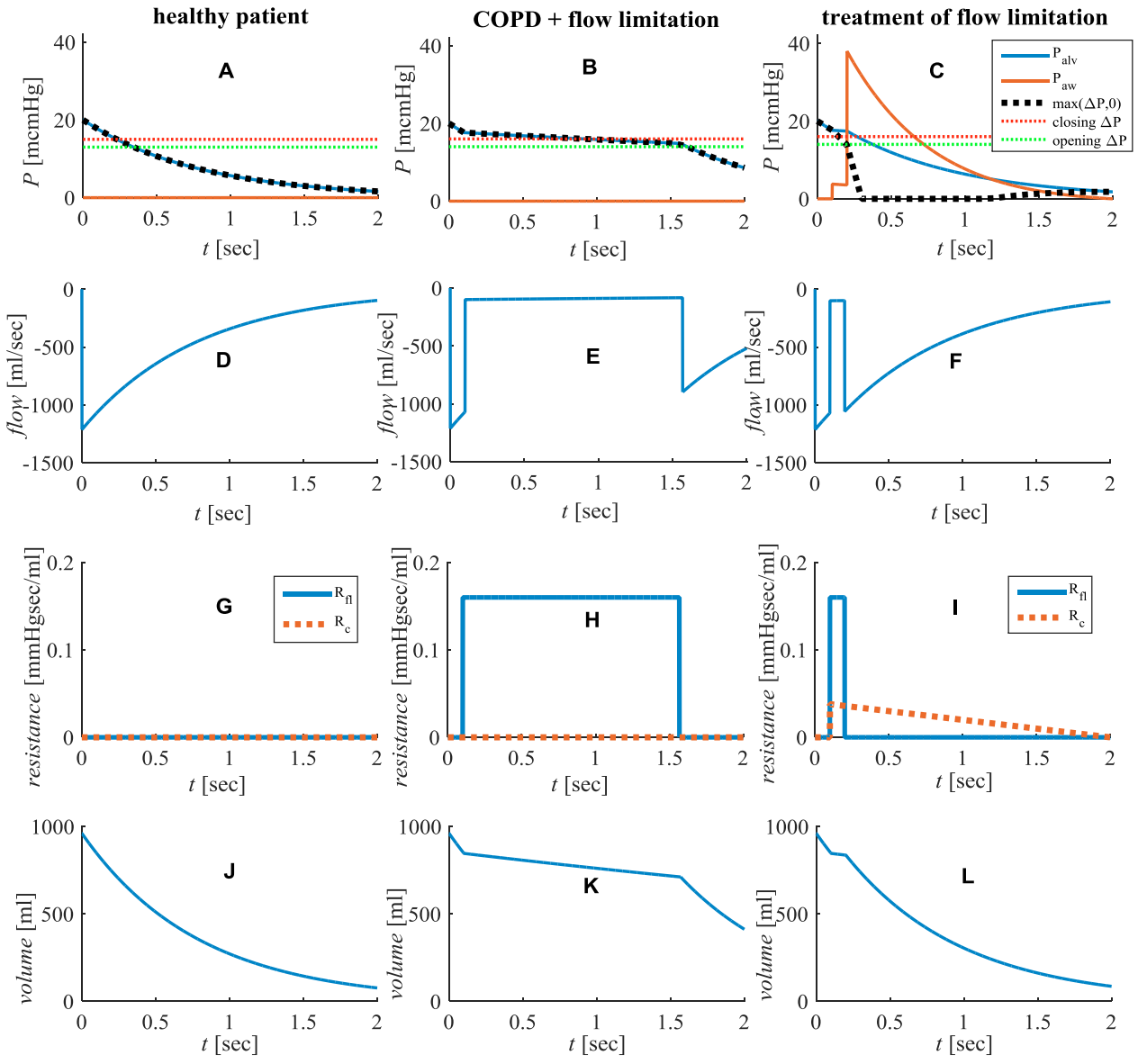

Fig. 4. Expiration curve of P (top row), flow (second row), the resistance (third row) and volume (bottom row) in case of a healthy patient (left column), severe COPD patient (middle column) and a severe COPD patient with control resistance (right column). The red and green doted lines are symbolizing the closing and opening thresholds of the bronchioles.

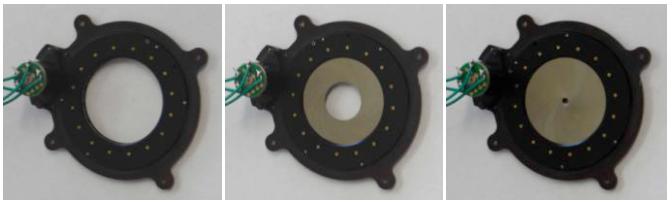

Fig. 5. Iris diaphragm – totally opened (left hand side), medium opened (middle) and closed (right hand side)

5. CONCLUSION

This study, based on a simulation, showed that an external control resistance can effectively counteract flow limitation in severe COPD. The aim of a positive airway pressure, just if needed, useable for all patients can be reached. Both, the disadvantage of the dependency on the collaboration of the patient and potentially the disadvantage of a continuous positive airway pressure are reduced. This device might be helpful for clinicians to treat flow limitation in severe COPD and other diseases.

6. ACKNOWLEDGEMENTS

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7. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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