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Assessment of Respiratory System Resistance during High-Frequency Oscillatory Ventilation Based on In Vitro Experiment

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Abstract: High-frequency oscillatory ventilation (HFOV) is a type of mechanical ventilation with a protective potential characterized by a small tidal volume. Unfortunately, HFOV has limited monitoring of ventilation parameters and mechanical parameters of the respiratory system, which makes it difficult to adjust the continuous distension pressure (CDP) according to the individual patient's airway status. Airway resistance R_{aw} is one of the important parameters describing the mechanics of the respiratory system. The aim of the presented study was to verify in vitro whether the resistance of the respiratory system R_{rs} can be reliably determined during HFOV to evaluate R_{aw} in pediatric and adult patients. An experiment was performed with a 3100B high-frequency oscillator, a physical model of the respiratory system, and a pressure and flow measurement system. The physical model with different combinations of resistance and compliance was ventilated during the experiment. The resistance R_{rs} was calculated from the impedance of the physical model, which was determined from the spectral density of the pressure at airway opening and the spectral cross-density of the gas flow and pressure at airway opening. R_{rs} of the model increased with an added resistor and did not change significantly with a change in compliance. The method is feasible for monitoring respiratory system resistance during HFOV and has the potential to optimize CDP settings during HFOV in clinical practice.

Keywords: high-frequency oscillatory ventilation; continuous distending pressure; respiratory system resistance; rigid respiratory system model; forced oscillation technique

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1. Introduction

High-frequency oscillatory ventilation (HFOV) is one of the unconventional methods of mechanical lung ventilation. It is characterized by a small tidal volume, approaching an anatomical dead space, with a protective potential [1]. Attenuation of pressure amplitude along the bronchial tree may contribute to less mechanical stress on lung tissue during HFOV compared with conventional mechanical ventilation (CMV) [2]. The patients with severe acute respiratory distress syndrome (ARDS) that do not tolerate CMV may be the target group for HFOV [3] if an alternative rescue therapy to ECMO is considered. With a number of etiologies and subtypes, ARDS is manifested by noncardiogenic pulmonary edema and hypoxia. Although new personalized pharmacological therapies for ARDS subtypes are being sought, also in the context of the COVID-19 pandemic, targeted treatment is lacking and ARDS is still the leading cause of death in critically ill patients [4,5]. Continuous distension pressure (CDP) and a set fraction of inspired oxygen determine the oxygenation of the ventilated subject in HFOV. Carbon dioxide is eliminated from the lungs by pressure oscillations that are added to CDP [6]. Recently, there have been studies that emphasize the need for an individualized approach in setting the ventilation parameters of HFOV [7,8]. It has also been shown that other monitoring and computational methods, including electrical impedance tomography (EIT) [9], optoelectronic plethysmography [10],

or impedance analysis of the respiratory system [11], can lead to optimization of HFOV settings. The results of previous studies conducted with HFOV may have been influenced by settings that were not sufficiently individualized to the needs of individual patients [12,13].

Currently, there is no unified approach on how to properly set up CDP with respect to the respiratory status of individual patients. Airway resistance R_{aw} is one of the important parameters describing the mechanics of the respiratory system. Besides tissue resistance, airway resistance R_{aw} is a substantial part of respiratory system resistance R_{rs}. Elevated R_{aw} can lead to air trapping and hyperinflation, which can result in pulmonary barotrauma [14]. R_{aw} depends on lung volume [15,16], which is directly related to the CDP value [17]. Both ventilation at low lung volumes (CDP is too low for the patient) and ventilation at high lung volumes (CDP is too high) lead to an increase in R_{aw}. Moreover, the increase in resistance at low lung volumes is accompanied by a significant increase in peripheral resistance, which can account for 15% of R_{aw}. The contribution of peripheral resistance to R_{aw} is otherwise negligible [15]. However, the possibilities for monitoring ventilation parameters are small for HFOV. The high-frequency oscillatory ventilators 3100A and 3100B (Vyaire Medical, Mettawa, IL, USA) also lack monitoring of respiratory system mechanics, such as R_{aw}. The 3100B ventilator, designed for adult patients, was used in this study.

The forced oscillation technique (FOT) can be used to evaluate the mechanics of the respiratory system including total respiratory system resistance R_{rs} [18,19]. In FOT, pressure oscillations with typical frequency f = 5 Hz are applied at the airway opening and R_{rs} is assessed from the induced flow. Pressure oscillations at 5 Hz can penetrate the peripheral airways and detect changes in resistance in this region of the lung, allowing the assessment of R_{rs} [18]. In a conventional FOT configuration, an external tool with an oscillator is used to generate high-frequency oscillations. The flow caused by the external oscillations is measured at the airway opening. However, some studies have demonstrated that a high-frequency ventilator itself can be used as a generator of the pressure oscillations utilized by FOT [20,21]. The studies used small animal models whose respiratory mechanics are consistent with neonatal patients. On the contrary, we have not found a study describing the use of the method in larger physical or animal models that correspond to pediatric or adult patients.

Recently, FOT has been integrated into commercially available neonatal ventilator Fabian (Acutronic, Hirzel, Switzerland) to determine the reactance of the respiratory system of a neonatal patient. Studies described the usefulness of reactance analysis in ventilated [22] or spontaneously breathing neonatal patients [23]. In general, there is no information about the analysis of R_{rs} in HFOV. As the method of assessing reactance of the respiratory system by FOT becomes clinically available, we suppose that monitoring of R_{rs} might have similar clinical potential and could provide an early warning to elevated airway resistance.

The aim of the presented study is to verify whether it is possible, under stable and well-defined laboratory conditions, to use pressure oscillations generated by the high-frequency oscillatory ventilator to determine the resistance of the respiratory system R_{rs} from the measured proximal airway pressure and flow. We hypothesize that this method could be used to assess R_{aw} at the bedside in neonatal, pediatric, and adult patients ventilated by HFOV similarly as reactance of the respiratory system. The presented method could be used also with ventilators 3100A and 3100B.

2. Materials and Methods

The configuration of the experiment is shown in Figure 1 [24]. The high-frequency oscillatory ventilator 3100B with standard accessories was used for the experiment. The patient circuit was connected via an endotracheal tube to a model of the respiratory system that consisted of a glass demijohn. At one phase of the experiment, an Rp5 parabolic resistor (Michigan Instruments, Grand Rapids, MI, USA) was added to the circuit. The Rp5 simulated the increased resistance of the respiratory system and the glass demijohn simulated the compliance of the lungs. Measurements performed without and with Rp5

were repeated for three glass demijohns of 54, 35, and 25 L. Values of corresponding compliances were 37, 24, and 17 mL/cmH_2O, respectively [24]. The following ventilation parameters were used in the experiment: bias flow = 30 L/min, ventilatory frequency f = 5 Hz, CDP = 12 cmH_2O, and pressure oscillation amplitude ΔP = 20 cmH_2O. Inspiration to expiration time was set as I:E = 1:1. The ventilation parameters were set according to [25]. Pressure p_{aw} and flow q_{aw} were recorded at the inlet of the model of the respiratory system using a measurement system specifically designed for HFOV monitoring [26]. The flow was calculated based on the pressure difference measured across an orifice. Both the signals p_{aw} and q_{aw} were recorded at a sampling frequency f = 1000 Hz.

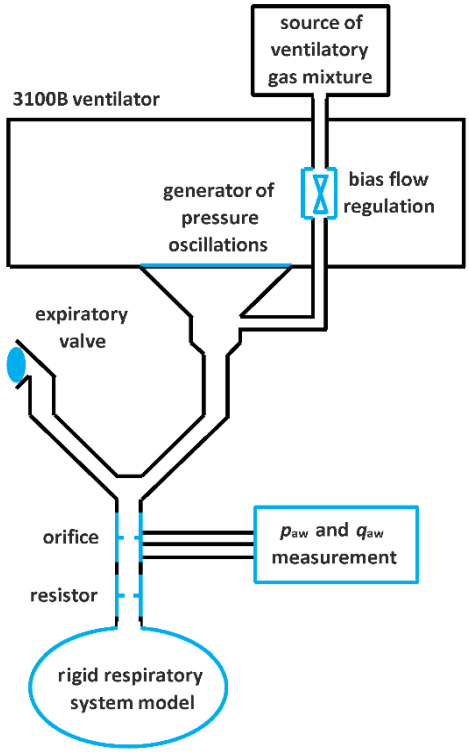

Figure 1. Setup of in vitro experiment [24].

The respiratory system resistance R_{rs} measured at a pressure oscillation frequency of f = 5 Hz was calculated from the respiratory system impedance Z_{rs} following the spectral density method described in [24]. R_{rs} was obtained from Z_{rs} by converting from polar to Cartesian coordinates according to Equation (1):

$$R_{rs} = Z_{mag} \cdot cos(Z_{ang}), \quad (1)$$

where Z_{mag} stands for the amplitude of the respiratory system impedance and Z_{ang} stands for the angle of the respiratory system impedance.

3. Results

The measurements of R_{rs} in our experiment are summarized in Figure 2 and Table 1. Measurements 1–3 correspond to no added resistor and measurements 4–6 correspond to the phase of the experiment with the added resistor Rp. Three demijohns representing different compliances (37, 24, and 17 mL/cmH_2O) were used in both phases of the experiment. The resistance R_{rs} substantially increased by more than 100 cmH_2O·s/L (over 220% increase) after the addition of the resistor to the model of the respiratory system (the change between Sections 3 and 4). The change in the compliance value did not have a substantial effect on the measured R_{rs} values as the mean R_{rs} did not differ for more than 4 cmH_2O·s/L (less than 10%) when Rp remained unchanged.

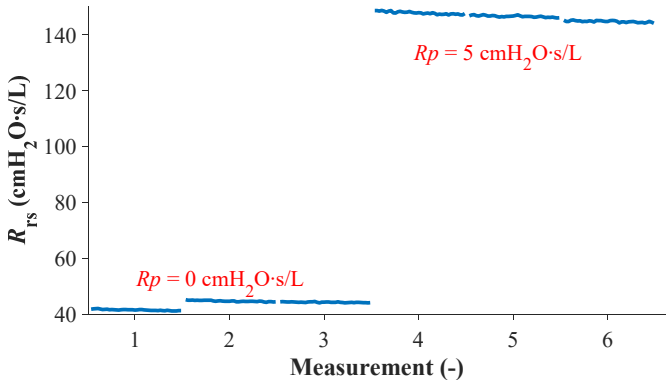

Figure 2. The computed R_{rs} during ventilation of the respiratory system model without an added resistor (measurement sections 1, 2, and 3) and with added resistor Rp (measurement sections 4, 5, and 6). To investigate the effect of compliance on the measured resistance of the respiratory system, three glass demijohns with different compliance (37, 24, and 17 mL/cmH_2O) were ventilated. Negligible change in R_{rs} signal amplitude during measurement and a small change in R_{rs} when compliance changed contrast with a large change in R_{rs} when the resistance increased.

Table 1. Values of computed R_{rs} (cmH_2O·s/L) in both phases of the experiment (without/with the resistor) for glass demijohns of three different compliances *C*.

C	R_{rs} with No Resistor		R_{rs} with Resistor Rp5	
(mL/cmH_2O)	Mean	SD [1]	Mean	SD [1]
37	41.5	0.2	147.8	0.5
24	44.7	0.2	146.6	0.3
17	44.3	0.1	144.7	0.3

[1] SD stands for standard deviation.

Figures 3 and 4 describe in more detail the measured signal of R_{rs} without and with the added resistor Rp5, respectively. It can be seen in the figures that R_{rs} decreased over time. However, the decay of R_{rs} is negligible compared to the R_{rs} value. The decay over 40 s, estimated from the linear interpolation of R_{rs} signals, was 3.8% of R_{rs} without the resistor and 1.8% with the resistor.

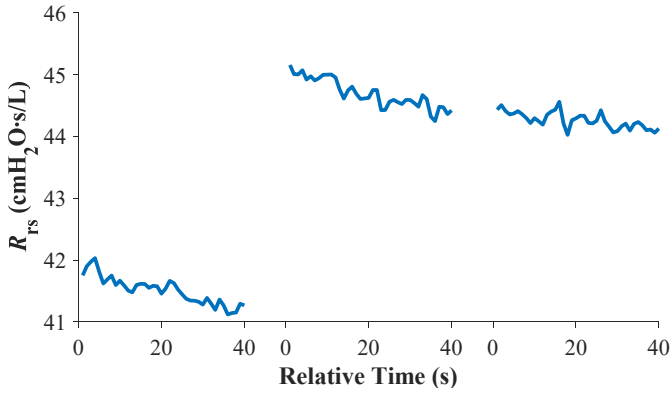

Figure 3. The course of computed R_{rs} during ventilation of the respiratory system model without an added resistor (three 40 s long measurements correspond to measurement sections 1, 2, and 3 in Figure 2). Three glass demijohns with different compliance (37, 24, and 17 mL/cmH_2O) were ventilated to investigate the effect of compliance on the measured resistance of the respiratory system.

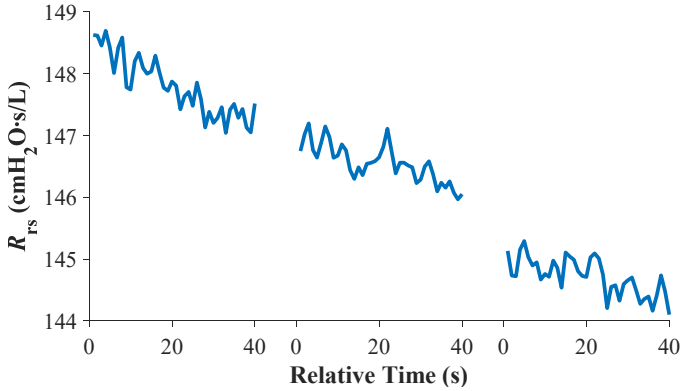

Figure 4. The course of computed R_{rs} during ventilation of the respiratory system model with added resistor Rp5 (three 40 s long measurements correspond to measurement sections 4, 5, and 6 in Figure 2). Three glass demijohns with different compliance (37, 24, and 17 mL/cmH_2O) were ventilated to investigate the effect of compliance on the measured resistance of the respiratory system.

It can also be seen from Figures 3 and 4 in detail that change of the compliance of the respiratory system model does not affect substantially measured R_{rs}. For a measurement without an added resistor (Figure 3), a small increase in R_{rs} of 3.2 cmH_2O·s/L (7.7%) was observed with the change of compliance from 37 to 24 mL/cmH_2O and a very small change in R_{rs} of about 0.4 cmH_2O·s/L (1.0%) was observed with the change of compliance from 24 to 17 mL/cmH_2O. A decrease in R_{rs} about 1.2 cmH_2O·s/L and 1.8 cmH_2O·s/L (0.8% and 1.3%, respectively) was observed for measurements with the resistor.

4. Discussion

The presented results show that changes in R_{aw} can be monitored during HFOV by measuring the resistance R_{rs} at an oscillation frequency of 5 Hz, when the basic mechanical properties of the respiratory system are consistent with larger animals or pediatric and adult patients. A physical model of the respiratory system was designed and an in vitro lab experiment was performed using different combinations of resistance and airway compliance values. It was shown that R_{rs} increases when R_{aw} increases. The results of this in vitro study also suggest that it is possible to follow the trend of R_{aw} under conditions of changing lung compliance.

The low standard deviations of R_{rs} summarized in Table 1 indicate sufficient robustness of the algorithm used in signal processing. In Figures 3 and 4, small oscillations of the calculated R_{rs} values can be seen. The oscillations are due to the processing of the noisy pressure and flow signals. The addition of a resistor to the ventilated system increased the standard deviation of R_{rs}. The flow was more turbulent with the added resistor and this resulted in an increase in the noise in the flow signal [24]. However, the increased turbulence did not degrade the evaluation of R_{rs}.

Our in vitro study has some limitations. First, a single ventilation frequency of 5 Hz was investigated. The choice of ventilation frequency as the most appropriate was based on previous studies [18,19,24,27,28]. Second, we did not vary the CDP during the test, as this would be of little importance in a physical model with rigid walls. Animal studies [20,29,30], which mimicked immature patients and used the same FOT measurement method, reported a significant increase in R_{rs} during lung derecruitment because of the low CDP applied during HFOV or the low positive end-expiratory pressure (PEEP) applied during CMV. The results are in agreement with the findings presented in [15], where the decrease in airway diameter was explained by a decrease in mean airway pressure. In contrast, only small changes in R_{rs} are observed at CDP or PEEP values that are sufficient to maintain lung inflation. This is consistent with our simulation performed on a rigid model. Third, the results show that when the Rp5 resistor was added to the model, the measured R_{rs} increased by more than 100 cmH_2O·s/L on average, but the physical properties of the Rp5

resistor may have contributed to such a large increase in R_{rs}. Resistor Rp5 is designed as parabolic, which means that the actual resistance value depends on gas flow rate. Moreover, the resistance of Rp5 is determined by its sudden and short decrease in airway diameter, a mechanism that is not present in vivo. The choke point created by the addition of Rp5 may cause the part of pressure-flow oscillation to be reflected into the glass demijohn and not return to the measuring system, resulting in an apparently more pronounced increase in resistance. It should also be taken into account that the physical properties of the glass demijohns used differ from the actual lungs. Pressure and flow oscillations could be deflected on the wall of the glass demijohn such that the oscillations could not return to the measuring system and would instead be damped within the glass demijohn. Such deflection does not occur in the airway tree in the lungs and could explain the difference between the actual resistance and the measured R_{rs}. Finally, small changes in the shape of the patient circuit and endotracheal tube between measurements could also account for some of the inaccuracies in the calculation of R_{rs}.

The presented method of measuring R_{rs} during HFOV is suitable for bedside patient monitoring because only a pressure and flow orifice is added to the patient circuit. In our study, a custom-made system consisting of an orifice, sensors, digitizing hardware, and a laptop with evaluation software was used [14]. In a real clinical scenario, any monitoring device capable of measuring proximal pressure and flow during HFOV and transmitting data in real time could be used. The disadvantage of the presented method may be the increased flow resistance and dead space caused by the addition of an orifice to the patient's circuit.

Assessment of respiratory mechanics using FOT in mechanical ventilators is now available to physicians with the Fabian neonatal ventilator [22,23]. However, the Fabian currently only determines the respiratory system reactance measured at an oscillation frequency of f = 10 Hz, which is typical for neonates. Besides the fact that in our study both parameters were measured at a frequency of f = 5 Hz, we believe that there is no significant difference between the method investigated in our study and the FOT method used by the Fabian ventilator. Therefore, no additional hardware would be required to simultaneously measure reactance and R_{rs} at the patient's bedside. Based on our study, we propose that not only reactance [24] but also R_{rs} could be assessed during HFOV.

5. Conclusions

In this study, for the first time, the feasibility of monitoring respiratory system resistance using the FOT method during HFOV under stable well-defined laboratory conditions was verified in a physical model whose properties correspond to a large laboratory animal. The FOT method used is simple enough to be applied at the patient's bedside in clinical practice, requires no circuit disconnection, and can be used for long-term monitoring. Ventilator operators could have information on the resistance of the respiratory system, which could facilitate an early response to an increase in resistance and thus prevent pulmonary barotrauma. As the FOT method is already used in a commercially available neonatal ventilator to determine respiratory system reactance, simultaneous measurement of resistance could be readily available in clinical practice.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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