EFFECT OF INSPIRATORY-TO-EXPIRATORY TIME RATIO AND AMPLITUDE OF OSCILLATIONS ON THE DEVELOPMENT AND MAGNITUDE OF DYNAMIC HYPERINFLATION AND HYPOINFLATION OF LUNGS DURING HFOV

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Abstract
During high-frequency oscillatory ventilation (HFOV), a situation may occur where the mean alveolar pressure (\(mP_{alv}\)) differs significantly from the mean airway pressure (\(mP_{aw}\)). Studies investigating the differences between these pressures during HFOV have documented states of both higher and lower \(mP_{alv}\) compared to \(mP_{aw}\). The effect of HFOV parameters on the pressure difference is not yet understood. The aim of this study is to investigate how this phenomenon is affected by the inspiratory to expiratory time ratio and the amplitude of HFOV oscillations (\(\Delta P\)). The effect of the listed ventilation parameters was investigated in vitro in seven laboratory models and in vivo on nine pigs. The study found that the inspiratory to expiratory time ratio of 1:1 always results in a positive pressure difference between \(mP_{alv}\) and \(mP_{aw}\), referred to as dynamic hyperinflation. At the inspiratory to expiratory ratio of 1:2 this pressure difference is negative in the majority of in vitro models of the respiratory system and in all animals. In addition, the study found that the magnitude of the pressure difference is affected by the \(\Delta P\). There is a critical value of \(\Delta P\) at which the trend of the pressure gradient between the alveolar space and the airways is reversed in relation to the oscillation amplitude.

Keywords
dynamic hyperinflation, dynamic hypoinflation, high frequency oscillatory ventilation, determinants of dynamic hyperinflation

Introduction
Mechanical lung ventilation is an effective therapy for patients with respiratory failure, however, it can cause severe damage to the respiratory system (RS) \[1, 2\]. High-frequency oscillatory ventilation (HFOV) is a ventilation strategy that utilizes small tidal volumes at high frequencies. The use of small tidal volumes during HFOV reduces the risk of lung volumotrauma and barotrauma \[3, 4\]. Since HFOV is considered as an unconventional ventilatory strategy, there are still several limiting factors for its use, especially in adult patients, and there are several potential risks.

In their studies, several authors have documented significant differences between mean airway pressure (\(mP_{aw}\)) and mean alveolar pressure (\(mP_{alv}\)). They have reported conditions where \(mP_{alv}\) was greater \[5–8\], equal \[9–11\] or even lower \[8, 10, 11\] than \(mP_{aw}\). The RS condition where \(mP_{alv}\) is greater than \(mP_{aw}\) is called dynamic hyperinflation (DH) \[5\]. The DH develops due to an insufficient time for the expiration, truncated by the subsequent inspiration \[7, 12\]. This leaves some of the unexhaled gas in the lungs, the volume of which is usually referred to as "air-trapping" \[13\]. Air-trapping can cause barotrauma and cardiovascular compromise \[14\]. Usually, the occurrence of this condition is attributed to asymmetric inspiratory and expiratory resistances \[5, 15\].

The name of the opposite condition, where \(mP_{alv}\) is less than \(mP_{aw}\), is not well defined in the literature. Since this is the opposite of dynamic hyperinflation, we will refer to it, as in our previous study \[8\], as dynamic hypoinflation. The magnitude of DH expressed in units of pressure is usually referred to as auto-PEEP in the case of conventional ventilation. However, because of
the unclear definition of PEEP in HFOV, we will not use the term auto-PEEP in this study and will stick with the term magnitude of DH.

Only one of the cited studies performed a systematic analysis of the parameters of HFOV ventilation on the magnitude of the pressure gradient between $mP_{alv}$ and $mP_{aw}$. In this study [11], dynamic hypoinflation was observed to occur at an $I:E$ 1:2. Its magnitude increased with increasing oscillation amplitude ($\Delta P$) as well as oscillation frequency and decreased as the $I:E$ ratio increased to 1:1. Dynamic hyperinflation was not detected in their study. Their study was performed on a laboratory model of RS and euthanized ventilated rabbits. The laboratory model of RS consisted of a glass flask intubated with an endotracheal tube. The endotracheal tube was the only flow resistance of the RS model in this study. An alveolar capsule placed in the right lung of the euthanized rabbit was used to measure $mP_{alv}$.

In contrast to other cited studies, the described study did not detect the occurrence of dynamic hyperinflation in any of the set parameter combinations. We can speculate that this is because insufficient asymmetry of inspiratory and expiratory resistances was achieved in the laboratory experiment due to the lack of use of additional airway resistance other than the endotracheal tube. A limitation of the $mP_{alv}$ measurement using the alveolar capsule method may be the possibility to measure only local pressure conditions in the lungs. The distribution of dynamic hyperinflation within the lung may vary [9], and it is possible that the local pressure measured by the alveolar capsule may not be representative of the global magnitude of dynamic hyperinflation.

The aim of the current study is to determine the effect of parameters of high-frequency oscillatory ventilation on the development and magnitude of dynamic hyperinflation in the lung in laboratory models using different airway resistance characteristics and to compare these results with those of animal experiments measuring the overall magnitude of dynamic hyperinflation using chest electrical impedance tomography.

**Methods**

The present study analyses data obtained during experiments conducted using laboratory models of RS and animal models. *In vitro* and *in vivo* experiments were performed using the same 3100B ventilator (CareFusion, Yorba Linda, CA, USA) and under comparable conditions.

**In vitro experiment**

A total of seven RS models were developed for experimental studies of DH. All models were designed as a series of specific flow resistance and compliance models formed by a rigid glass container with a volume of 54 L. The characteristics of the flow resistances were chosen to match those reported in the literature associated with the development of DH.

The first three laboratory models included Rudolph Linear Resistors (Hans Rudolph, Shawnee, USA) labeled R5, R20, and R50. The next three models included Pneuflo parabolic resistors (Michigan Instruments, Michigan, USA) labelled Rp5, Rp20 and Rp50. These six models were created and verified as a part of our previous study to investigate the possibility of dynamic hypoinflation *in vitro* published at the 5th IEEE International Conference on E-Health and Bioengineering [16]. The seventh model utilized the expiratory flow limitation (EFL) inducing resistance developed by us earlier [17]. The EFL resistor was formed by using a collapsible tube with a pressed aperture in its distal part. This tubing was inserted into the interior of a rigid glass container. The aperture at the end of the tubing acts as a parabolic resistor during the inspiration phase. The collapsible tubing is compressed by the pressure inside the rigid glass container during the expiration phase in such a manner that it forms an EFL. The EFL resistor parameters are a flow resistance of 19.3 cmH2O·s·L−1 at 1 L·s−1 in the inspiratory direction and a maximum expiratory flow rate of 0.43 L·min−1 with a critical pressure limiting expiratory flow rate of 12 cmH2O in the expiratory direction.

Models were connected to a 3100B HFOV ventilator (CareFusion, Yorba Linda, CA, USA). The ventilator was set as follows: bias flow 25 L·min−1, oscillatory frequency 5 Hz, continuous distending pressure (CDP) 18 cmH2O and inspiratory oxygen fraction 0.21 (dry air). The amplitude of oscillations ($\Delta P$) was set successively at 40, 60, 80 and 100 cmH2O in a study using linear and parabolic resistors [16] and at values of 50, 75 and 100 cmH2O in a study employing EFL resistor [17]. The ratio of inspiration to expiration time ($I:E$) was set to 1:1 and 1:2. Both airway pressure ($P_{aw}$) and alveolar pressure ($P_{alv}$) were measured using the iMON HFOV monitor [18]. $P_{aw}$ was measured in the Y-piece of the patient circuit. $P_{alv}$ was measured in the inner space of the rigid container using rigid tubing. A schematic of the measurement system is presented in Figure 1.

![Fig. 1: Schematic of the experimental setup.](image)
All measurements using laboratory models were repeated five times and the results present the calculated averages of these values.

**In vivo experiment**

The analyzed data were measured in our study investigating the possibility of using electrical impedance tomography to measure dynamic lung hyperinflation [8]. Measurements were performed on nine female pigs (sus scrofa domestica) weighing 42 kg (SD ±3 kg).

Animals were ventilated with a 3100B HFOV ventilator (CareFusion, Yorba Linda, CA, USA). Measurements were taken at CDP levels of 12, 18 and, if tolerated by the animal, 24 cmH2O. At each CDP level I:E was set to 1:1 and 1:2. Bias flow was set at 25 L·min⁻¹ and oscillatory frequency at 5 Hz. Animals were maintained in normocapnia by individually adjusting \( \Delta m \).

Paw was measured with the iMON device on a spirometry sensor placed between the Y-piece of the patient circuit and the endotracheal tube. For \( P_{alv} \) measurement, our proposed and tested method for recalculating chest bioimpedance measured by electrical impedance tomography (EIT) to \( P_{alv} \) was used [8]. Chest bioimpedance was measured with a PulmoVista 500 (Dräger Medical, Lübeck, Germany).

A developed calibration maneuver was used to recalculate the EIT data for DH magnitude measurements. The calibration maneuver consisted of an occlusion of the RS with oscillations off followed by injection of 60 mL of air into the occluded RS while simultaneously measuring EIT and \( P_{aw} \). With the oscillations turned off, the RS can be considered as a static system in which \( P_{aw} \) and \( P_{alv} \) are equal. The injection of 60 mL of gas will increase the pressure in the closed RS, which will be reflected by a simultaneous change in the \( P_{aw} \) and EIT signals. Since the changes in both signals were caused by the same intervention, a relationship can be obtained by means of their comparison to recalculate the EIT signal to \( P_{alv} \).

**Data analysis**

The magnitude of DH was calculated as the difference between mean alveolar pressure (\( mP_{alv} \)) and mean airway pressure (\( mP_{aw} \)) in both laboratory and animal experiments. The effect of I:E and \( \Delta P \) on the magnitude and character of dynamic hyperinflation were investigated.

The resulting magnitudes of DH are presented using graphs created in Microsoft Excel (Microsoft, Redmond, WA, USA). Data based on in vitro experiments are always the average of five measurements. Therefore, we decided to use a smoothed line graph to connect the data points. This type of graph respects both the position of the data points and the assumed continuous relationship between them.

The data obtained in animal experiments are by their nature affected by interindividual variability between the studied animals, as each data point was obtained in a different animal with a specific RS condition and at different \( \Delta P \) values due to the need to maintain the normocapnia of the animals.

Therefore, regression analysis was performed to present these data. The data were fitted with a second-order polynomial, as its shape best fits the results obtained in the laboratory experiments. The resulting data are presented in the form of a dot plot with the regression curve showing the coefficient of determination.

**Results**

Experiments performed in vitro as well as experiments performed in vivo show a fundamental dependence of the occurrence of dynamic hyperinflation on the ratio of inspiration to expiration time (I:E). Therefore, the resulting data were divided into two groups of data sets just according to the I:E parameter.

Figure 2 shows the dependence of the magnitude of the pressure gradient between \( mP_{alv} \) and \( mP_{aw} \) on \( \Delta P \) for I:E 1:1. All values shown are positive, indicating the occurrence of dynamic hyperinflation (\( mP_{alv} > mP_{aw} \)) in all cases. The most pronounced effect of \( \Delta P \) on the magnitude of dynamic hyperinflation is seen in the EFL model, where the magnitude of measured dynamic hyperinflation increases significantly with increasing \( \Delta P \).

The other types of RS models show a rather slower increase in the magnitude of dynamic hyperinflation with increasing \( \Delta P \). For models with higher values of parabolic resistors (Rp20 and Rp50), there is initially a stagnation or slight decrease in the magnitude of dynamic hyperinflation as \( \Delta m \) increases from 40 to 60 cmH2O.
Figure 3 shows the dependence of the magnitude of the pressure gradient between $mP_{alv}$ and $mP_{aw}$ on the amplitude of the oscillations for $I:E$ 1:2 for the laboratory models. Except for models with linear resistors $R_{20}$ and $R_{50}$, dynamic hypoinflation ($mP_{alv} < mP_{aw}$) or no difference between $mP_{alv}$ and $mP_{aw}$ occurs in all cases.

For the curves characterizing models with resistors $R_{5}$, $Rp_{5}$, $R_{20}$ and $Rp_{20}$, it is clear that there is an amplitude of oscillations at which the magnitude of dynamic hypoinflation ($mP_{alv} < mP_{aw}$) is the highest. For the purpose of this paper, we will call this amplitude the critical amplitude ($\Delta P_{crit}$). If we increase or decrease the magnitude of the oscillations relative to $\Delta P_{crit}$, the magnitude of the gradient between $mP_{aw}$ and $mP_{alv}$ will decrease.

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Figure 4 shows the dependence of the magnitude of dynamic hyperinflation on $\Delta m$ at $I:E$ 1:1 for the animal models. Based on the results of laboratory experiments, these data were fitted with a second-order polynomial with a resulting coefficient of determination $r^2 = 0.57$. A local minimum on the fitted curve around the $\Delta m$ value of 70 cmH$_2$O is evident.

Figure 5 shows the dependence of the magnitude of dynamic hypoinflation on $\Delta P$ at $I:E$ 1:2 for the animal models. Based on the results of laboratory experiments, these data were fitted with a second-order polynomial with a resulting coefficient of determination $r^2 = 0.50$. The resulting curve shows the highest magnitude of dynamic hypoinflation ($mP_{alv} < mP_{aw}$) around a $\Delta P$ value of 85 cmH$_2$O. The data suggest that increasing or decreasing $\Delta P$ from 85 cmH$_2$O reduces the magnitude of dynamic hypoinflation.

Fig. 3: Magnitude of dynamic lung hypoinflation in different models of the respiratory system at $I:E$ 1:2.

Fig. 4: Dependence of the magnitude of dynamic hyperinflation on $\Delta m$ at $I:E$ 1:1 in animal experiments with 95% confidence interval.

Fig. 5: Dependence of the magnitude of dynamic hypoinflation on $\Delta P$ at $I:E$ 1:2 in animal experiments with 95% confidence interval.

Discussion

The main result of this study is the confirmation of the fundamental effect of the ratio of inspiratory to expiratory time ($I:E$) on the development of dynamic hyperinflation and dynamic hypoinflation, in both in vivo and in vitro experiments. At $I:E$ 1:1, dynamic hyperinflation ($mP_{alv} > mP_{aw}$) occurred in all in vitro and in vivo models. At $I:E$ 1:2, dynamic hypoinflation ($mP_{alv} < mP_{aw}$) occurred in most in vitro and all in vivo models.
The only two cases in which dynamic hypoinflation did not occur in vitro at I:E 1:2, or occurred only at higher values of amplitude of oscillations (ΔP), are shown by models with linear resistors. Asymmetry of inspiratory and expiratory resistances has been reported as one of the main causes of dynamic hyperinflation and hypoinflation of the lungs [5; 15]. This condition is fulfilled in the expiratory flow limitation (EFL) model, in models with parabolic resistors, but only minimally in models with linear resistors. When a linear resistor is used, the resistance of the respiratory system (RS) model is equal to the sum of the flow resistance of the linear resistor used and the endotracheal cannula used. The inspiratory and expiratory resistances of the linear resistor are inherently symmetrical even at different inspiratory and expiratory flow rates during ventilation. Thus, the only nonlinearity in the linear resistor model arises due to the endotracheal cannula, whose characteristics are in between the linear and parabolic resistors in shape.

The results of this study further suggest the possible existence of a critical value of ΔP at which the lowest value of dynamic hypoinflation (mP_{alv} < mP_{aw}) occurs at I:E 1:2. This ΔP can be referred to as the critical amplitude of oscillations (ΔP_{crit}). The results show that if we increase ΔP above ΔP_{crit} or decrease it below ΔP_{crit}, the pressure gradient between mP_{alv} and mP_{aw} will decrease for dynamic hypoinflation. This behavior is evident in the results of the in vivo and in most in vitro experiments.

Moreover, the results of the magnitude of dynamic hyperinflation as a function of ΔP measured in vivo at I:E 1:1 support the existence of ΔP_{crit}. In the in vitro measurements at I:E 1:1, ΔP_{crit} is only evident in the Rp20 model. However, it is possible that ΔP_{crit} in the other models is outside the adjustable range of ΔP values on the 3100B ventilator. With dynamic hyperinflation, the ΔP_{crit} value is again the lowest value on the displayed curve, indicating the smallest dynamic hyperinflation. Increasing or decreasing the amplitude relative to the ΔP_{crit} value causes an increase in the magnitude of dynamic hyperinflation.

Furthermore, a previous study [16] shows that the value of ΔP_{crit} can be shifted to higher or lower ΔP values by changing the inertance of the model. This can be achieved, for example, by lengthening or shortening a portion of the patient circuit beyond the Y-piece.

Analysis of the magnitudes of the pressure gradients between mP_{alv} and mP_{aw} in vivo shows a similar shape of the pressure gradient dependence on amplitude as in vitro. Figure 4 and Figure 5 again suggest the existence of ΔP_{crit}. The value of the coefficient of determination (0.57 for dynamic hyperinflation and 0.50 for dynamic hypoinflation) after fitting these data with a second-order polynomial shows that ΔP only partially affects the resulting magnitude of the pressure gradient between mP_{alv} and mP_{aw}. Thus, there are more effects on the magnitude of dynamic hyperinflation and dynamic hypoinflation and only the value of ΔP cannot fully explain their magnitude.

Another possible effect on the magnitude of dynamic hyperinflation and dynamic hypoinflation is the CDP setpoint. Figures 4 and 5 summarize data from in vivo experiments for CDP values of 12 cmH2O, 18 cmH2O, and 24 cmH2O. Combining the data for each CDP level into a single chart was performed based on statistical analyses [8] that showed no statistically significant difference between the magnitude of dynamic hyperinflation and dynamic hypoinflation at different CDP levels. For verification, P_{crit} analysis was performed for CDP values of 12 and 18 cmH2O. The result of this analysis is shown in Table 1. Data for CDP 24 cmH2O were not analyzed due to the small number of data points.

Table 1: P_{crit} values obtained in vivo for different levels of CDP and I:E 1:1 and 1:2.

<table>
<thead>
<tr>
<th>I:E</th>
<th>CDP (cmH2O)</th>
<th>P_{crit} (cmH2O)</th>
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</thead>
<tbody>
<tr>
<td>1:1</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>76</td>
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<tr>
<td>1:2</td>
<td>12</td>
<td>90</td>
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<td></td>
<td>18</td>
<td>83</td>
</tr>
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</table>

However, the confidence intervals of the second-order polynomials used in the analysis of the effect of mP_{aw} on ΔP_{crit} overlap, as can be seen in Fig. 6 for dynamic hyperinflation (I:E 1:1) and Fig. 7 for dynamic hypoinflation (I:E 1:2). Thus, the differences reported in Table 1 are not statistically significant with this small sample size.

![Fig. 6: Dependence of the magnitude of dynamic hyperinflation on ΔP at I:E 1:1 in animal experiments at mP_{aw} 12 and 18 cmH2O with 95% confidence interval.](image)

Thus, it is possible that the level of CDP affects the P_{crit} value during in vivo experiments. This may be caused, for example, by a change in the geometrical dimensions of the RS resulting in a change in inertance. We can speculate that the statistical insignificance of the effect of CDP on the magnitude of the pressure gradient...
between \( m_{P_{\text{alv}}} \) and \( m_{P_{\text{aw}}} \) in the previous study [8] is false negative due to the small number of samples in each CDP group.

Another effect on the magnitude of the pressure gradient between \( m_{P_{\text{alv}}} \) and \( m_{P_{\text{aw}}} \) at different \( \Delta P \) may be caused by the different RS state of individual animals in relation to the lung P-V curve. For each animal, up to three CDP values (12, 18, and, if tolerated by the animal, 24 cmH\(_2\)O) and two I:E values were used. Both parameters affect the mean lung volume and this means that at each measurement the RS of the animal could be in a different state with respect to the inflection points on the P-V curve of the lungs.

A limitation of fitting second-order polynomials to data from in vivo experiments is that these curves do not pass through zero. If we set \( \Delta P \) to zero, dynamic hyperinflation will cease and the pressure gradient between \( m_{P_{\text{alv}}} \) and \( m_{P_{\text{aw}}} \) will be zero. In vitro measurements in experiments in a previous study [16] suggest that the shape of the curve may be more complex than a second-order polynomial. However, within the animal experiments [8] from which the dataset analyzed here comes, we do not have a sufficient range of amplitudes used to consider fitting the data with a more complex curve.

Adler et al. [19] reported that lung volume changes calculated from EIT are linearly dependent on the volume injected into the lungs using a syringe in the range of 50–1000 mL. The linearity of the relationship of chest bioimpedance changes to gas injections in the range of 200–800 mL was also confirmed by Lindgren et al. [20]. Considering the good linear correlation between changes in bioimpedance and changes in lung volume in a measured chest section, it can be stated that, at least in homogeneous lungs, changes in lung volume can be measured by EIT [20]. In contrast to these findings, a study by Bikker et al. [21] was performed at several levels of PEEP (0–15 cmH\(_2\)O) during conventional ventilation. Although a significant correlation between the change in chest bioimpedance and the change in lung volume was found, its linearity is questioned. In their study, Grivans et al. [22] found that the relationship between EIT signal changes and lung volume changes varied at different PEEP levels. When a calibration of the EIT was performed in relation to the lung volume at each PEEP level, this led to a better linear correlation between these two modalities.

In our animal study [8], the EIT calibration was performed as a part of a measurement and calibration manoeuvre for each measured parameter combination with a few seconds interval after the measurement. In addition, the linearity of the relationship between \( P_{\text{alv}} \), lung volume change and EIT signal was verified by injecting the calculated air-trapping volume from previous measurements performed with the exact same parameters into an occluded respiratory system. The change in EIT signal after this injection corresponded to the magnitude of the change in EIT signal at the cessation of DH. In addition, the pressure magnitude of DH corresponded to the measured change in equilibrium pressure measured in the closed respiratory system.

**Conclusion**

The ratio of inspiratory to expiratory time in high-frequency oscillatory ventilation fundamentally affects the occurrence of dynamic hyperinflation and dynamic hypoinflation in both in vivo and in vitro models. In all in vivo and in vitro models, dynamic hyperinflation occurred at a 1:1 ratio of inspiratory to expiratory time. In all in vivo and in vitro models with nonlinear characteristics of inspiratory and expiratory resistance, a dynamic hypoinflation occurred at a ratio of 1:2.

The results of this study further suggest the existence of a certain critical value of the amplitude of pressure oscillations during high-frequency oscillatory ventilation, at which the value of dynamic hyperinflation is the smallest and the value of dynamic hypoinflation is the largest. This critical value of the pressure oscillations may not have the same value for the condition of dynamic hyperinflation and dynamic hypoinflation. This behavior has been observed in most in vitro models and in an in vivo experiment carried out on 9 animals.

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