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Airflow-Related Shear Stress: The Main Cause of VILI or not?

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Background: The physical basis of ventilator-induced lung injury has been explored extensively in the last decades. The three mechanisms named volutrauma (overdistension of alveoli), barotrauma (high airway pressure), and atelectrauma (cyclic opening and closing of alveoli) have been known as the main mechanisms of lung injury. Lowering tidal volume and applying positive end-expiratory pressure have been suggested to minimize these mechanisms. Besides, some researchers believe that elevated airflow-related shear stress on the epithelial cell layer could cause an inflammatory response.

Materials and Method: In this study, a simplified 0-D model for air flow in human lungs has computed the airflow-related shear stress. The airway resistance, compliance, and inertance have been calculated using Womersley analysis and included in this model. Considering a constant flow, volume-controlled mechanical ventilation, the effect of ventilation parameters including tidal volume, respiratory rate, and inspiratory/expiratory ratio on the magnitude of shear stress has been investigated.

Results: The results show that high tidal volume, high respiratory rate, and low inspiratory/expiratory ratio, increase the magnitude of wall shear stress but still in the safety range.

Conclusion: This result suggests that airflow-related shear stress is not the primary cause of mechanical damage. So far, it has been assumed that wall shear stress plays a critical role in ventilator-induced lung injury. This paper enhances our understanding of wall shear stress magnitude, indicating that the shear stress from airflow in mechanical ventilation is not high enough to inflict mechanical damage on pulmonary epithelial cells.

Keywords: Ventilator Induced Lung Injury; Wall Shear Stress; Resistance; Compliance; Inertance

INTRODUCTION

Ventilator-induced lung injury (VILI) is the most prevalent side effect of mechanical ventilation. Different techniques have been suggested to decrease this type of lung injury. Common strategies include lowering tidal volume based on the ideal body weight (6 ml/kg IBW) and utilizing positive end-expiratory pressure (PEEP). In the physical view, applying these methods would decrease the mechanical stress and strain imposed on the lung airways or decrease the damage of recruitment/derecruitment. Although lowering tidal volume based on the ideal body weight of the patient is effective in preventing VILI but not much in acute respiratory distress syndrome (ARDS) patients.

Since the available volume of lung for ventilation in these patients has been decreased, the standard tidal volume which is not invasive for healthy lung patients could cause high stress and strain in their smaller lungs.

So, the idea of adjusting tidal volume based on the concept of driving pressure is presented by Amato et al. (1). Driving pressure is the difference between Plateau Pressure and PEEP which is equivalent to the ratio of tidal volume to the patient's static lung compliance. Amato et al. claimed that in ARDS patients, the magnitude of driving pressure can be used as a predictive tool for VILI. Chiumello et al. (2) stated that the same lung airway pressure could be caused by different tidal volumes because of the probability of difference in the chest wall compliance concerning the lung compliance. So, similar tidal volumes could cause different transpulmonary pressures. By this explanation, they suggested that dynamic driving pressure or transpulmonary driving pressure should be considered for the prediction of VILI. They found that driving pressure is well correlated with transpulmonary driving pressure and lung mechanical stress. Although high driving pressure can inform us about the situation of high-stress incidence, it is not informative about other associated factors.

Cressoni et al. (3) and Gattinoni et al. (4) studied the correlation between energy delivered to the lung per time unit and the prevalence of VILI. They remarked that the mechanical power delivered to the lung is the main determinant of VILI development. Gatatinoni et al. (4) found the contribution of ventilator adjustable parameters such as tidal volume/driving pressure, breathing frequency, PEEP, or respiratory rate in the mechanical power value. Marini and Jaber (5) recommended that the lung dissipated energy per breathing cycle is a better identifier of VILI development. This energy originates from the nonreversible deformation of the lung tissue caused by viscoelastance or surface tension and can be found by the hysteresis area enclosed within the pressure-volume curve times breathing frequency.

Besides these hypotheses which mainly try to overcome the overstretching of the airways and alveoli, some researchers argued the role of changing levels of wall shear stress on the cellular responses (6-8). Kotani et al. (7) found that shear stress levels of 0.5-5 Pa can activate MAPK (mitogen-activated protein kinases) and increase the release of inflammatory cytokines. Garcia and his colleagues (6) research shows that cell damage can be aggravated by increasing the inhalation flow rate. They increased breathing frequency in constant tidal volume. So, the reported cell damage may also be due to a reduction of inspiration time and the effect of shear stress is not decisive. Besides, Protti et al. (9) investigated the strain rate (the strain produced in the inspiration time) as the major causative factor for VILI. They increase strain rate by decreasing inspiration time in constant tidal volume. So, they indirectly increased the inhalation flow rate and wall shear stress. Thus, the decision about the effect of shear stress on the development of VILI is not reliable and needs further research.

In this paper, we have simulated the lung airways with a mechanical model that considers the resistance, compliance, and inertance of each airway. Considering a typical flow profile for the ventilator, the wall shear stress in all generations has been computed. The effect of changes in tidal volume, respiratory rate, and inspiratory-to-expiratory time ratio on the value of shear stress has been investigated.

The contribution of this work consists in deriving a mechanical model for computing the wall shear stress in the lung airways. The proposed model allows us to investigate the effect of ventilator setting on the wall shear stress.

MATERIALS AND METHODS

It has been assumed that the respiratory system is self-similar up to generation 24 with the geometrical properties shown in Table 1 (10).

To find shear stress in the lung airways, the flow and pressure characteristics should be modeled. In this regard, Womersley's theory for pulsatile flow in compliant airways is adopted. This method has been previously presented for arterial flow (11). The airways are modeled as a 1D flexible elastic tube. Then, the 1D fluid momentum equation (Eqs. (1), (2)) is applied to each peripheral airway. In these

equations, *u* is the velocity in the streamwise direction, p is pressure, *t* is time, ρ is density, ν=μ/ρ is kinematic viscosity, and r, x are along the radius and length of the airway.

$$\frac{\partial u}{\partial t}+u\frac{\partial u}{\partial x}+\frac{1}{\rho}\frac{\partial p}{\partial x}=\frac{\upsilon}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u}{\partial r}\right) \quad (1)$$

Table 1. Morphological details of lung airways

Generation	Length (cm)	Radius (cm)	Wall thickness (cm)	Cartilage fraction κ
1	10.000	0.800	0.3724	0.6700
2	5.000	0.600	0.1735	0.5000
3	2.200	0.550	0.1348	0.5000
4	1.100	0.400	0.0528	0.3300
5	1.050	0.365	0.0409	0.2500
6	1.130	0.295	0.0182	0.2000
7	1.130	0.295	0.0182	0.0922
8	0.970	0.270	0.0168	0.0848
9	1.080	0.215	0.0137	0.0669
10	0.950	0.175	0.0114	0.0525
11	0.860	0.175	0.0114	0.0525
12	0.990	0.155	0.0103	0.0449
13	0.800	0.145	0.0097	0.0409
14	0.920	0.140	0.0094	0.0389
15	0.820	0.135	0.0091	0.0369
16	0.810	0.125	0.0086	0.0329
17	0.770	0.120	0.0083	0.0308
18	0.640	0.109	0.0077	0.0262
19	0.630	0.100	0.0072	0.0224
20	0.517	0.090	0.0066	0.0000
21	0.480	0.080	0.0060	0.0000
22	0.420	0.070	0.0055	0.0000
23	0.360	0.055	0.0047	0.0000
24	0.310	0.048	0.0043	0.0000

Neglecting convection term and assuming that all variables are periodic and can be written as $u(r,x,t)=U(r,x)e^{i\omega t}$, $p(x,t)=P(x)e^{i\omega t}$ where ω is the angular frequency in rad/s, the above equation can be rewritten as Eq. (2) by Fourier transformation.

$$i\omega U+\frac{1}{\rho}\frac{\partial P}{\partial x}=\frac{\upsilon}{r}\frac{\partial}{\partial r}\left(r\frac{\partial U}{\partial r}\right) \quad (2)$$

The solution to Eq. (2) is given by:

$$U=\frac{1}{i\omega\rho}\frac{\partial P}{\partial x}\left(1-\frac{J_0(\delta i^{3/2}r/r_0)}{J_0(\delta i^{3/2})}\right) \quad (3)$$

In the abovementioned equation, $\delta=r_0(\omega/\upsilon)^{1/2}$ is the Womersley number and $J_0(x)$ and $J_1(x)$ are respectively the Bessel functions of the zeroth and first order.
The wall shear stress can be expressed by $\tau(x,t)=T(x)e^{i\omega t}$, it can be found as:

$$T=\mu\frac{\partial U}{\partial r}\bigg|_{r=r_0}=\frac{\mu}{A_0 r_0}\frac{w_0^{\,2}F_J}{2(1-F_J)}Q \quad (4)$$

where,

$$F_j=\frac{2J_1(\delta i^{3/2})}{\delta i^{3/2}J_0(\delta i^{3/2})} \quad (5)$$

A_0 and r_0 are the initial cross-section and radius and $q(x,t)=Q(x)e^{i\omega t}$ is the flow rate in the airway.
Based on the electrical analogy, each airway is considered to have resistance, compliance, and inertance. By some mathematical analysis, the following equations can be obtained (12):

$$R=\frac{l\mu\delta^2\sin(\varepsilon'_{10})}{\pi r_0^{\,4}M'_{10}} \quad (6)$$

$$L=\frac{l\rho\cos(\varepsilon'_{10})}{\pi r_0^{\,2}M'_{10}} \quad (7)$$

$$C=\frac{2l\pi r_0^{\,3}(1-\nu^2)}{Eh} \quad (8)$$

where E, h, and ν stand for Young's modulus, wall thickness, and Poisson's coefficient of each airway, respectively, and M'_{10} e $\varepsilon'_{10}=1-F_j$.

The air is assumed to be incompressible with constant density ρ=1.075 kg/m3 and viscosity μ=1.8e-5 kg/m-s. The effective elastic modulus is considered a function of the airway tissue structure; $E=\kappa E_c+(1-\kappa)E_s$; where the indexes of c and s stand for cartilage and soft tissue and fraction κ is defined in each generation according to Table 1. The Young's modulus for cartilage and soft tissue are Ec = 400 kPa and Es = 60 kPa, respectively (12).

Zero dimensional equations for change in pressure and volume flux in each airway can be expressed by:

$$\left\{\begin{array}{l} C\dfrac{dp_{in}}{dt}+q_{out}-q_{in}=0, \\ L\dfrac{dq_{out}}{dt}+R\,q+p_{out}-p_{in}=0. \end{array}\right\} \quad (9)$$

The inlet flow rate $q_{in}(t)$ for the first generation and zero outlet pressure for the last generation have been assumed. For each bifurcation, the following boundary conditions have been applied:

$$p_{in}^{gen+1}=p_{out}^{gen} \quad (10)$$

$$q_{in}^{gen+1}=\frac{1}{2}q_{out}^{gen} \quad (11)$$

Considering all 24 generations, the 0-D model can be described as a system of ordinary differential equations using the Fourier transform.

$$\frac{dy}{dt}=Ay+b(y,t) \quad (12)$$

where $y\epsilon R^m$ is a vector of variables, $A\epsilon R^{m\times m}$ is a matrix of parameters, and $b\epsilon R^m$ is a source term that provides external data to the system.

The solution of this system of ODE equations gives the Fourier transform of desired variables including q_{in}, q_{out}, p_{in}, and p_{out}. Then incorporating Eq. (4), the wall shear stress can be computed for airways of each generation.

We have considered a constant flow, volume-controlled mechanical ventilation with physiological tidal volume (0.5 lit, i.e. 7 ml/kg for a 70-kg subject), respiratory rate (RR) of 15 breaths/min, and inspiratory-to-expiratory ratio (I:E) of 1:3 to mimic a typical ventilator pattern. The ventilator flow profile for a typical lung with resistance and compliance of R and C is considered as Eq. (13).

$$\begin{array}{ll} \dot{V}_I=\dfrac{V_T}{t_i} & t\le t_i \\ \dot{V}_E=-\dfrac{\Delta P}{R}e^{-\left(\frac{t-t_i}{RC}\right)} & t>t_i \end{array} \quad (13)$$

which $\Delta P=V_T/C$. The resulting flow profile for R=2 kPa.s/lit and C=0.4 lit/kPa is shown in figure 1.

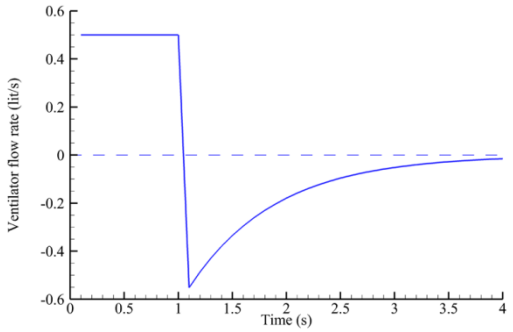

Figure 1. Default pattern for ventilator airflow

RESULTS

The variations of the mechanical parameters including resistance, inertance, and capacitance with airway generation at the end-inspiratory time are given in figure 2. Our results are well validated by Ionescu et al.(12).

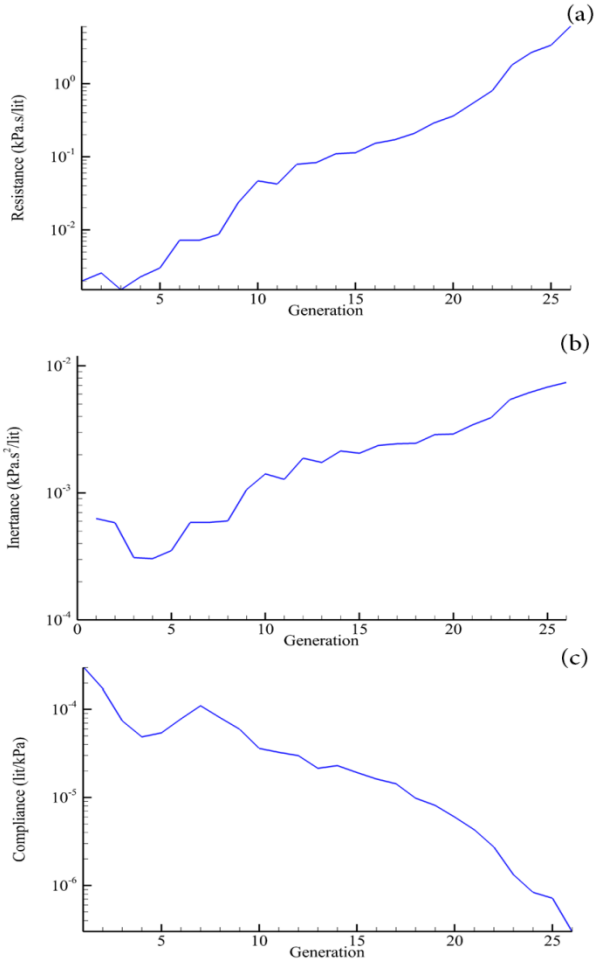

Figure 2. Variation of resistance, inertance and compliance in different generations

The profile of flow with time through downstream generations is similar to inspiratory flow except that it has been decreased due to consecutive branching and also the compliance of the airways.

In our model, the flow-developing region is ignored and a fully developed flow is assumed. For this assumption, the length-to-diameter ratio of the respiratory airways should exceed 0.05 Re. While this assumption is not valid for the first 6 generations, the flow in lower generations is fully developed after passing through a limited length of the airway. So, our results are meaningful for the airways downstream of generation 6.

The distribution of the wall shear stress in different generations of the lung is shown in figure 3. In order to show the effect of heterogeneity on the wall shear stress in different generations, the results are shown by mean and error bars. The mean values are the average shear stress computed for the airways lied in a generation and the error values are obtained by the difference between the average and maximum shear stress. The average shear stress is computed considering an airway with the average diameter occurred in that generation while the maximum shear stress is computed considering an airway with the smallest diameter occurred in that generation. Our results show that in a default ventilator setting, the wall shear stress is smaller than 0.02 Pa.

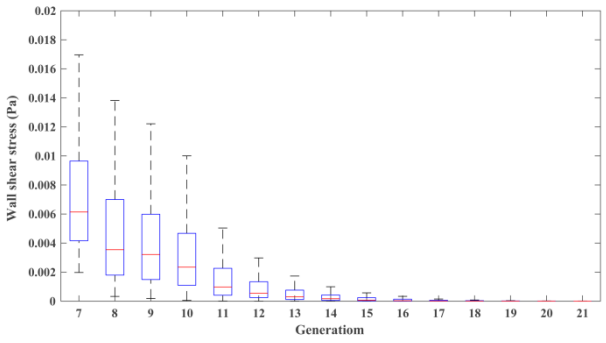

Figure 3. Variation of maximum wall shear stress with generation

The effect of tidal volume on the wall shear stress is investigated with physiological tidal volumes of 6-12 ml/kg for a 70-kg subject. The results for typical airway in generation 7 are shown in figure 4.

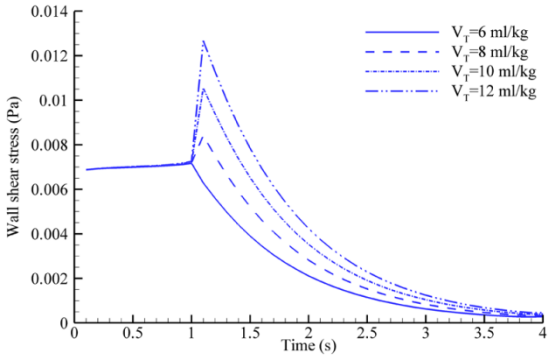

Figure 4. Variation of wall shear stress for typical generation 7 with different tidal volumes

As shown by increasing tidal volume and holding other parameters constant, the maximum wall shear stress in generation 7 is increased linearly from 0.006 to 0.012 Pa.

The effect of respiratory rate is studied considering 12-18 breaths/min and the results are shown in figure 5. It can be deduced that the maximum wall shear stress and respiratory rate are directly related .

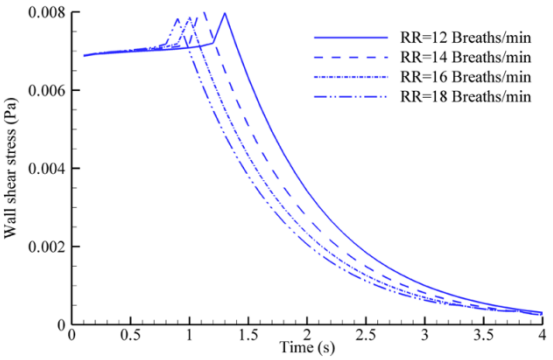

Figure 5. Variation of wall shear stress for typical generation 7 with different Respiratory Rates

The final parameter for investigation is inspiratory-to-expiratory ratio which the results for generation 7 with 1:3, 1:4, 1:5 and 1:6 ratios are shown in figure 6.

By decreasing I:E ratio, the maximum wall shear stress is increased exponentially. Since the inspiratory time is related to I:E, decreasing I:E ratio in similar respiratory rate results in decrease of inspiratory time which consequently will increase the flow rate and wall shear stress. The results emphasized that the wall shear stress would be increased

by any increase in flow rate. The increase of flow rate can be occurred by increasing tidal volume, increasing respiratory rate or decreasing inspiratory-to-expiratory time ratio. So, ventilator settings can directly affect the magnitude of wall shear stress.

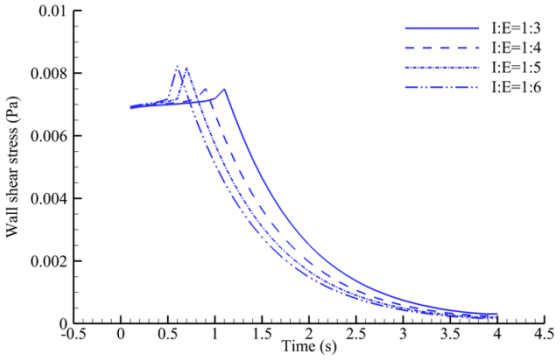

Figure 6. Variation of wall shear stress for typical generation 7 with different Inspiratory to Expiratory ratio

DISCUSSION

The 0-D model provided in this paper is a fast tool to approximate flow rate and shear stress in respiratory airways. According to our modeling results, it can be concluded that by increasing the maximum flow rate, the wall shear stress is increased but still in the normal range. Our simulation shows that the default ventilator setting with physiological range could not generate wall shear stresses higher than the sustainable limit of airway cellular level (0.5 Pa). It should be noted that due to the 0-D flow assumption made to exploit the results, the values for the first 6 generations are not valid. Previously, Lin et al. (13) and Green (14) found the wall shear stress in the upper airways and reported a flow rate of 1 lit/s by computational fluid dynamics (CFD) modeling. However, our study is focused on the small airways and their involvement in VILI is more prevalent. This result confirms that the shear stress in small airways does not exceed the sustainable limit of defense mechanisms. Although we have not considered the liquid lining at the alveolar level, which can play a critical role in pulmonary airway reopening, previous experiments by Kay et al. (15) showed that the pressure gradient and not shear stress is responsible for the epithelial cell layer damage during airway reopening (15, 16). They found that cells in the thin-film region experience a continuous outward-directed normal stress and these normal stresses can cause stretching of the airway wall.

Although there are several limitations to our result, the idealized models used for this study have allowed us to elucidate the magnitude of shear stress exerted on lung airways. However, to prevent elevated wall shear stresses in highly heterogeneous constrictive airways (17), it is recommended to use a small tidal volume, low respiratory rate, and normal inspiratory-to-expiratory time ratio.

Already, there was a conception that VILI is related to high airflow-related shear stress. In a relevant study, the effect of increasing airflow on normal ventilated rats has been investigated on the development of VILI (6). They reported that ventilation with high inspiratory airflow may result in lung mechanical and ultrastructural modifications. The increase in airflow was followed by an increase in respiratory rate with I:E ratio maintained at 1:2 constant. So, ultrastructural damages observed in their study could be a result of high-frequency ventilation. They also examined the normal respiratory rate with I:E ratio of 1:8 and observed cellular damage again. They concluded that reduction of RR did not protect the lungs from functional, morphologic, and inflammatory abnormalities induced by high inspiratory airflow. This conclusion is somewhat questionable because the peak inspiratory pressure in this case is as high as 17 cmH2O which is just enough for the development of the barotrauma mechanism of VILI. So, high PIP may be the main reason for their observations. Besides, a decrease in I:E will reduce the duration of inspiration time (lung inflation time), which means faster inflation of lung tissue. Protti and his colleagues argue it by the concept of strain rate and present that high strain rate can contribute to the development of VILI (9).

CONCLUSION

Overall, we have concluded that airflow-related shear stress generated by mechanical ventilation is not higher than the critical threshold for epithelial cells. Our finding is in agreement with the previous study of Sul et al. (18) in which the increase of shear stress in obstructed airways was modeled. They presented that even in the heavy activities (i.e., flow rates smaller than 2300 ml/s), the wall shear stress in both normal and obstructed airways was less than 0.3 Pa, which can be tolerated by promoting the respiratory defense mechanism and enhancing epithelial barrier function. Although shear stress is higher for patients with obstructed airways, it should be considered that VILI can also be developed in ICU-ventilated patients with normal lungs. So, according to our results, it seems that the airflow-related shear stress could not be the main factor in the development of VILI.

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