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Gas Exchange Mechanism of High Frequency Ventilation: A Brief Narrative Review and Prospect

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Abstract: The high frequency ventilation (HFV) can well support the breathing of respiratory patient with 20%—40% of normal tidal volume. Now as a therapy of rescue ventilation when conversional ventilation failed, the HFV has been applied in the treatments of severe patients with acute respiratory failure (ARF), acute respiratory distress syndrome (ARDS), etc. However, the gas exchange mechanism (GEM) of HFV is still not fully understood by researchers. In this paper, the GEM of HFV is reviewed to track the studies in last decades and prospect for the next likely studies. And inspired by previous studies, the GEM of HFV is suggested to be continually developed with various hypotheses which will be testified in simulation, experiment and clinic trail. One of the significant measures is to study the GEM of HFV under the cross-disciplinary integration of medicine and engineering. Fully understanding the GEM can theoretically support and expand the applications of HFV, and is helpful in investigating the potential indications and contraindications of HFV.
Key words: mechanical ventilation, high frequency ventilation, gas exchange mechanisms
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0 Introduction

The purpose of breathing is to inhale plenty of fresh air called tidal volume (V_t = 6—8 mL/kg) into the lung and exhale the exhaust gas out to the atmosphere. When the breathing of human being is hindered, one of the necessary measures is to be supplemented with the mechanical ventilation for sufficient fresh air being delivered into and exhaust gas fully being removed from the lung. Nevertheless, in current mechanical ventilation modes, the high frequency ventilation (HFV) is a special method which superimposes the oscillation airflow in the conventional ventilation airflow. Usually, the oscillation frequency of HFV is 2—15 Hz, and output V_t is 1—3 mL/kg. One of the typical characteristics in HFV is that the provided V_t is just 20%—40% of the normal. The V_t provided by HFV is even lower than the volume of the respiratory anatomical dead ($V_\mathrm{d} \approx 2.2$ mL/kg). This means that the fresh air delivered by the HFV justly fills the shaded area as shown in Fig. 1, and does not enter into the alveoli. But the HFV can well support the breathing of a patient with respiratory diseases[1-2]. How can the HFV with a small V_t well support the breathing of respiratory patient? Since the middle of 20th century, many researchers and scholars have devoted their attentions on the gas exchange mechanism (GEM) of HFV[3-4].

Currently, as a rescue ventilation therapy for the failure of conventional ventilation, the HFV has beenusually applied in the patients with severe acute respiratory failure (ARF), severe acute respiratory

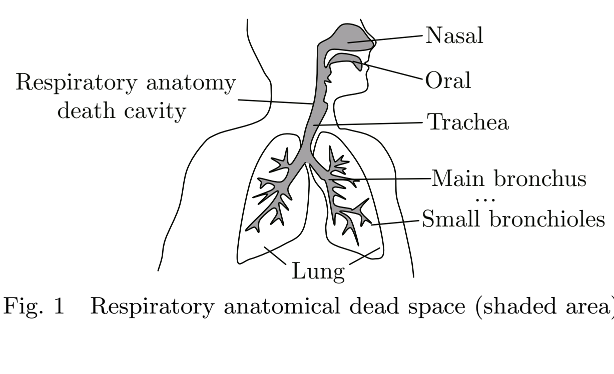

Fig. 1　Respiratory anatomical dead space (shaded area)

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distress syndrome (ARDS), etc[5-10]. Additionally, the HFV also prevents the ventilation induced lung injury (VILI) by reducing the risk of volutrauma. And by reducing the mean airwaypressure[11-15], the HFV as well is beneficial to increasing cardiac output and to alleviating the harmful effect on arterial blood. Especially for neonates with severe ARDS, the early application of HFV is more helpful to improve the curative effect of the ventilation[16-18]. Although HFV has shown its advantages in clinical trials, the GEM as a puzzled topic is still not fully understood[3,7]. In the next years, to fully disclose the GEM of HFV will theoretically support the application of HFV, and will help the doctors to analysis the HFV in indications and contraindications. Fully understanding the GEM will expand the scope of application of HFV. For example, according to the symptoms of patient with corona virus disease 2019 (COVID-19)[19-23], the HFV is probably considered as one of the potential measures.

1 Reviewing

1.1 Early Studies on GEM of HFV

As for the GEM of HFV in early studies, many hypotheses were put forward for explaining the characteristics of HFV with small V_t. As shown in Fig. 2, the typical hypotheses mainly include: direct alveolar ventilation, convective dispersion, swing ventilation (pendelluft), turbulent dispersion, collateral ventilation, etc[3,7,24-25].

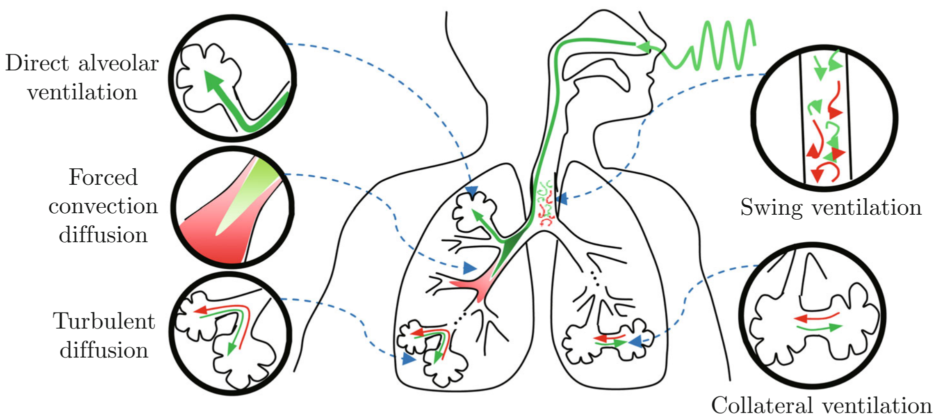

Fig. 2 Diagram of GEMs

The fresh gas in the front of the airflow column can possibly directly enter into those alveoli which are close to the upper airway, and provide a direct ventilation to support the breathing of a respiratory patient during HFV[26-27]. Scherer and Haselton[28] and Chang and Masry[29] found a phenomenon to possibly cause a convective dispersion when the airflow breathed into the central trachea meets the airflow breathed out from the bronchus. Otis et al.[30] inferred that the swing ventilation exists between the parallel adjacent lungs based on the time constant (τ) expressed by

$$\tau = RC, \tag{1}$$

where R and C respectively represent the resistance in the airway and the compliance in the alveoli. Taylor[31] believed the airflow in airway repeatedly being accelerated and decelerated during HFV, the random convective eddies would be resulted in, and a turbulent diffusion would be caused in the lung. Armengol et al.[32] found that the resistance to the airflow between the collaterally connected alveoli is reduced during HFV, and proposed that the collateral ventilation exists in the collaterally connected alveoli.

According to the researches carried out by Scherer and Haselton[28], the early researches on the GEM of HFV may be concluded that a serial of hypotheses were proposed based on the observations in practical experiments and theoretical inferences. From then on, these proposed hypotheses would be tested and verified with more experimental and clinical results.

1.2 Recent Studies on GEM of HFV

As shown in Table 1, with a designed physical lung model, Lee et al.[33] observed that the micro-particles in the oscillating airflow were constantly moving between the adjacent “alveoli”. And they testified the existence of swing ventilation with the micro-particles motion. By calculating the total volume of the alveoli inflated and deflated repeatedly with the oscillation airflow ($V_{\text{in-de}}$), Greenblatt et al.[34] found that the $V_{\text{in-de}}$ is larger than the volume delivered into the alveoli. And they believed that the swing ventilation probably exists between the adjacent alveoli. Yuan et al.[35] conducted their HFV experiments with using two fresh animal lungs to imitate the left and right lungs of human being. They found that the magnitude of the oscillatory airflow into the left/or right lung is larger than that into the right/or left lung at some frequencies during HFV. Yuan et al.[36] continually noticed that there is a

Table 1 List of main studies on GEM of HFV in the latest 2 decades

Authors	In the year of	Main work and conclusions
Lee et al.[33]	2006	They observed the movement of tiny particles in oscillating airflow and speculated that swing ventilation exists between alveoli.
Greenblatt et al.[34]	2014	They found that the total volume of the alveoli inflated and deflated repeatedly is larger than the volume delivered into the alveoli.
Yuan et al.[35]	2014	They found that the distribution of oscillating air flow between the left and right lungs will be changed accordingly with the change of frequency.
Jacob et al.[37]	2018	They verified the turbulence ventilation which is generated via the curvature of the bifurcation.
Yuan et al.[36]	2019	They found that there is a significant phase difference between the airflows in the left and right lungs, and put forward the mechanism of the ventilation between the left and right lungs.
Leontini et al.[38]	2019	They discovered the turbulence in the bifurcation of bronchi during HFV.
González-Pacheco et al.[39]	2020	They concluded that the CO_2 diffusion coefficient is nonlinear related to the tidal volume and frequency of HFV.

significant phase difference between the airflows in the left lung and right lung. And they proposed that the swing ventilation exists between the left and right lungs during HFV. Jacob et al.[37-38] testified the turbulent ventilation with experiments in a prepared computer model of preterm infants, and suggested that the turbulence is generated via an instability of the Dean vortices (a pair of reverse symmetric vortices generated by the viscous fluid in the elbow at a certain mainstream velocity) in the curvature of a bifurcation. Leontini et al.[38] observed the airflow in the neonatal airway through the computed tomography (CT), and found the turbulence airflow in the bifurcation of the airway during HFV. González-Pacheco et al.[39] conducted their HFV clinical trial with 2-day-old piglets to investigate the CO_2 elimination, and found that the CO_2 diffusion coefficient (D_{CO_2}) is related to the tidal volume (V_t) and frequency (f) of HFV:

$$D_{CO_2} = V_t^{1.78} f^{1.15}. \tag{2}$$

According to study of Lee et al.[33] in recent years, the studies on the GEM of HFV tend to focus on the verifications with experiments. There seems to be a lack of new conclusions to describe the GEM of HFV. But the molecular diffusion such as CO_2 diffusion was attended by researchers.

2 Discussions and Prospect

How can the respiratory patient survive if he takes such a small V_t as delivered by the HFV? Many theoretical and experimental studies demonstrated that a number of mechanisms acted in concert on affecting gas transport during HFV, such as direct alveolar ventilation, convective dispersion, swing ventilation, turbulent dispersion, and collateral ventilation[3,7,24-25]. In the 20th century, the researches on the GEM of HFV mainly focused on theoretically hypothesis and inference. Recently, researchers have devoted their contributions on testing and verification for the proposed GEM of HFV.

Now although the HFV has been applied in clinic, there is still no clear conclusion on the GEM of HFV. Referring to the previous hypotheses, experiments and trails, more potential mechanisms are needed to be excavated and demonstrated. For an example of this, the HFV should be probably affirmative on cleaning the sputum and mucus in the respiratory tract. If the HFV is helpful to keep the respiratory tract clean and unblocked, it will benefit the patient in mechanical ventilation with timely sputum excretion. As another example, it is questionable that the gas exchanges (swing ventilation) between lung lobes, lung segments or other low-level organs of lung. Because the adjacent parallel parts of the lung share the more same bronchi, the time constants (expressed by Eq. (1)) between them are closer, and the swing ventilation should be more impossible to happen between them.

Inspired by the work of predecessors, as the experiments and observations are difficult to carry out in respiratory tract (especially with living body), the research approach to the GEM of HFV is still conducted in Fig. 3. Based on the observed phenomenon and theoretical analysis, the reasonable hypothesis is suggested and then demonstrated and proved with simulations, physical experiments and clinic trails. In simulation, developing the virtual model of respiratory system is critical to the validity and reliability of the results. Based on the structures of respiratory system and the characteristics of airflow movement in tube, developing a multistage bronchi lung model is possible to benefit the simulation. For example, Jacob et al.[37-38] demonstrated the turbulence ventilation based on their designed computer model of preterm infants. In physical experiments, designing a practical test platform is fundamental. In this platform, the physical model, the

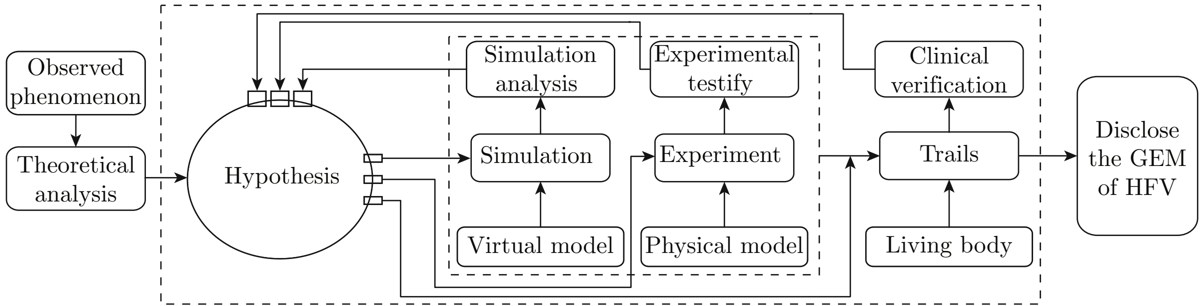

Fig. 3 Diagram to develop GEM of HFV

signal processor, and the data acquisition device have to be prepared with high quality. For example, Yuan et al.[36] built a test platform for HFV experiment with animal lungs. In clinic trails with the suitable living body, it is often needed to ask for the authorization from the ethics committee. For example, Leontini et al.[38] observed the turbulence ventilation in the neonatal airway through the CT.

Furthermore, the goal in studying the GEM of HFV is to help people to disclose why the HFV can well support the breath of a respiratory patient with a small V_t. According to the previous suggestions, researchers mainly exposed the characters of airflow in the respiratory tract during HFV, and tried to theoretically interpret the mechanisms. It is well known that one of the essential conditions for the effective mechanical ventilation is to deliver sufficient O_2 into and remove CO_2 out from the pulmonary capillary. It is very definitely possible that on the basis of knowledge in the kinetic theory of molecules, studying the process of O_2 molecules entering and CO_2 molecules leaving from the lung capillaries during HFV will be advantageous for revealing the GEM of HFV.

3 Conclusion

The GEM of HFV is still an important topic to discover the reasons why a small tidal volume can well support the breath of severe respiratory patient. This paper reviews the developments of GEM in last decades and helps to find more potential GEM in theory. Despite the narrative review in the GEM of HFV, the next studies are more directional. Besides continuing the conventional study in the airflow of HFV, the exploration in the molecular movement during HFV would be an important solution to disclose the GEM of HFV. The study on the GEM of HFV is not only a medical subject, but also a physical and engineering subject. One of the considerable measures is to disclose the GEM of HFV with the cross perspective in medicine and engineering. In a word, full disclosure in the GEM of HFV will contribute to the application of HFV in some severe respiratory diseases.

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