



Effect of IFN- α and other commonly used nebulization drugs in different nebulization methods on the resistance of breathing circuit filters under invasive mechanical ventilation

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Background: Interferon (IFN) is widely used in clinical practice and nebulization inhalation is one of the commonly used routes of administration. However, nebulization drugs such as interferon- α (IFN- α) with large molecular weights may deposit in the membrane of the breathing filters, causing its resistance to gradually increase. Thus, our study explores the effect of IFN- α and other nebulization drugs on the resistance of breathing circuit filters under invasive mechanical ventilation.

Methods: We divided 96 breathing filters into eight groups. The baseline group was not treated while the blank group was installed but were not nebulized. The remaining groups received jet nebulized or vibrating nebulized with either normal saline, Combivent, Amphotericin B, or IFN- α at a frequency of once every 12 hours separately and were removed from the breathing circuit after 24 hours. The resistance of the filter of each group was then measured and statistical comparisons were made.

Results: Filter resistance of the IFN- α jet nebulization group was greater than that of the other groups, and there were statistical differences except for the Amphotericin B jet nebulization group. Comparison of the resistance [cmH₂O/(L·s)] of the IFN- α jet nebulization group *vs.* the baseline group showed 2.56 (2.40, 2.68) *vs.* 2.26 (2.03, 2.40), $P=0.037$; of the IFN- α jet nebulization group *vs.* the blank group showed 2.56 (2.40, 2.68) *vs.* 2.11 (1.98, 2.27), $P=0.003$; of the IFN- α jet nebulization group *vs.* the normal saline group: 2.56 (2.40, 2.68) *vs.* 2.16 (2.08, 2.32), $P=0.023$; of the IFN- α jet nebulization group *vs.* the Combivent jet nebulization group: 2.56 (2.40, 2.68) *vs.* 2.18 (2.14, 2.27), $P=0.018$; and of the IFN- α jet nebulization group *vs.* the Amphotericin B jet nebulization group: 2.56 (2.40, 2.68) *vs.* 2.33 (2.05, 2.45), $P=0.221$. The effect of jet nebulization and vibrating mesh nebulization on the resistance of breathing filters showed no significant statistical difference.

Conclusions: Jet nebulization with IFN- α significantly increased the resistance of the breathing filter within 24 hours and there was no significant difference in filter resistance between jet nebulization and vibrating mesh nebulization of IFN- α or Amphotericin B.

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Introduction

Interferon (IFN) is a critical cytokine in human innate immunity and has a broad-spectrum antiviral effect. It is widely used in clinical practice, and nebulization inhalation is one of the commonly used routes of administration. There is *in vitro* study have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is significantly sensitive to interferon- α (IFN- α) (1), and after nebulization inhalation for 12 hours, the interferon concentration in lung tissue can reach more than four times that of intramuscular injection (2). Therefore, nebulization inhalation may be an ideal route of administration for the application of IFN to treat coronavirus disease 2019 (COVID-19). At present, commonly used nebulization methods include the jet nebulization method and the vibrating mesh nebulization method.

Breathing circuit filters are air filtering devices used in the ventilator circuit, which can help maintain stability of the gas temperature and humidity in the breathing circuit (3,4) and effectively filter out pathogenic microorganisms, avoiding the formation of aerosols which cause cross-infection (5-7). At the same time, breathing filters can also prevent drug particles entering the exhalation valve during the nebulization process to form crystallization causing the exhalation valve to leak, ensuring the synchronization of the man-machine and prolonging the service life of the ventilator.

In the process of using the filters, water vapour accumulates in the breathing circuit (8) and dust, respiratory secretions, and pathogenic microorganisms can gather on the filter membrane, causing the filters' performance of filtering bacteria to gradually decline (9). However, there is no uniform standard for the timing of replacement of the filters. Patients receiving mechanical ventilation often receive nebulization inhalation therapy, and the impact of resistance of the breathing filters on their respiratory mechanics needs to be considered. While nebulization drugs such as IFN- α and Amphotericin B have relatively large molecular weights that easily filter and deposit, there is still a lack of relevant research on their impact on the resistance of the filters.

This study explored the effects of different nebulization drugs such as normal saline, Combivent, Amphotericin

B, and IFN- α on the resistance of breathing circuit filters *in vitro* simulated breathing circuits and examined the effect of different nebulization methods on the resistance of breathing circuit filters. The results may provide a reference for the timing of breathing filter replacement after nebulization in clinical work. We present the following article in accordance with the MDAR reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-84/rc>).

Methods

The following experimental materials were used: Breathing circuit filters and an Airvo2 Nasal High Flow System (provided by Fisher & Paykel Healthcare Limited, Auckland, New Zealand); Dräger SelfTestLung, Dräger XL ventilator and its supporting silicone pipeline (provided by Dräger Medical Equipment Co., Ltd., Frankfurt, Germany); LabChart physiological data analysis software; PowerLab16/35 data acquisition device and Signal Conditioners (provided by At ADInstruments International Trading Co., Ltd., New South Wales, Australia); Pressure Sensor DP15-34-N-1-S-4-A and Pressure amplifier CD280-4C (provided by Validyne Engineering Co., Ltd., Los Angeles, the US); Flow Sensors MLT 300L (provided by HANS RUDOLPH Co., Ltd., Boston, the US); Aerogen Solo vibrating mesh nebulizers (provided by Aerogen Co., Ltd., Galway, the UK); Recombinant human interferon α 2b injection (provided by Beijing Kawin Technology Share-Holding Co., Ltd., Beijing, China); and Amphotericin B for Injection (provided by North China Pharmaceutical Co., Ltd., Shijiazhuang, China).

Experimental process

Inclusion criteria: (I) the quality of the filter meets the standard of use; (II) the filters package is in good condition with no obvious damage; (III) the filter is within its expiration date. Exclusion criteria: (I) the breathing filters were used in the breathing circuit for less than or more than 24 hours due to various reasons; (II) the filter is fouled due to human causes during installation or use; (III) due to

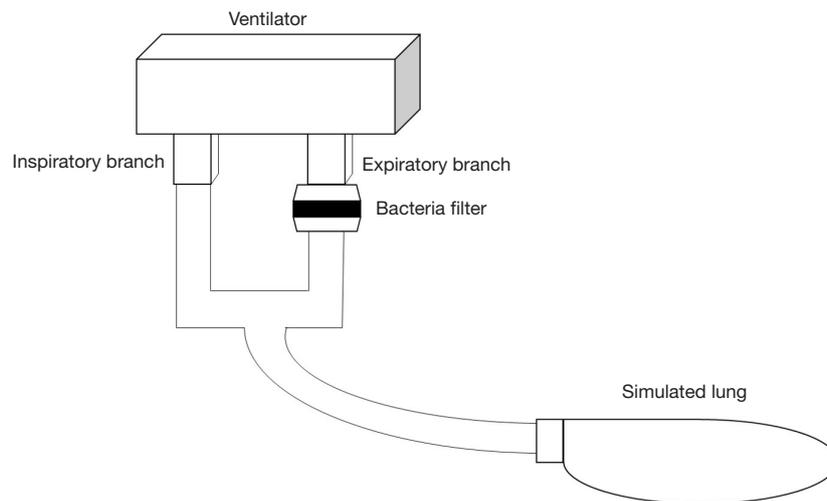


Figure 1 Schematic diagram of the filter placed in the simulated breathing circuit.

various reasons, the nebulization frequency and time did not meet the experimental requirements.

We divided 96 breathing filters into eight groups randomly (the filters are from the same manufacturer and the same batch number, and there is no difference between the filters): baseline group, blank group, normal saline group, Combivent jet nebulization group, Amphotericin B jet nebulization group, Amphotericin B vibrating mesh nebulization group, IFN- α jet nebulization group, and IFN- α vibrating mesh nebulization group. Each group used independent breathing filters to perform the experiment.

Baseline group: the breathing filters of this group did not undergo experimental processing, and their resistance was directly measured.

Filters used by the remaining groups were installed in an *in vitro* simulated breathing circuit composed of a ventilator and simulated lung (Figure 1) and were processed as follows.

Blank group: the filters of this group were not treated with nebulization and were removed from the breathing circuit after 24 hours; **normal saline group:** the filters of this group were jet nebulized with 5 mL normal saline at a frequency of once every 12 hours and removed from the breathing circuit after 24 hours; **Combivent jet nebulization group:** The filters of this group were jet nebulized with 2.5 mL normal saline and 2.5 mL Combivent at a frequency of once every 12 hours and removed from the breathing circuit after 24 hours; **Amphotericin B jet nebulization group/Amphotericin B vibrating mesh nebulization group:** 5 mg Amphotericin B was dissolved in 5 mL normal saline and the two groups of filters were treated with jet nebulization/

vibrating mesh nebulization separately with these medicines. Both groups were removed from the breathing circuit after 24 hours; **IFN- α jet nebulization group/IFN- α vibrating mesh nebulization group:** in the two groups, we mixed 0.3 mL (3 million IU) of recombinant human interferon α 2b injection and normal saline into a 5 mL solution and treated the two groups of filters with jet nebulization/vibrating mesh nebulization separately before removing them from the breathing circuit after 24 hours.

Measurement process

After the pressure sensor and flow sensor were calibrated and zeroed, the gas flow rate regulator, pressure sensor, flow sensor, and breathing filter were connected and tested (Figure 2).

The gas flow rate was set to 40 L/min and the temperature to 34 °C. After the gas flow rate was stabilized, the LabChart physiological data analysis software collected and recorded the pre-filtered air pressure (P1), the post-filtered air pressure (P2), and the gas flow (Q) per unit time in real-time to obtain the average value of the data mentioned above. According to Poiseuille's Law: $Q = \frac{\pi^4 \Delta P}{8 \eta L}$, $R = \frac{8 \eta L}{\pi^4}$, $Q = \frac{\Delta P}{R}$, $R = \frac{\Delta P}{Q} = \frac{P_1 - P_2}{Q}$, substituting the above P1, P2, and Q into the above formula, the breathing filter resistance was determined as R.

Statistical analysis

All statistical analyses were performed using R software

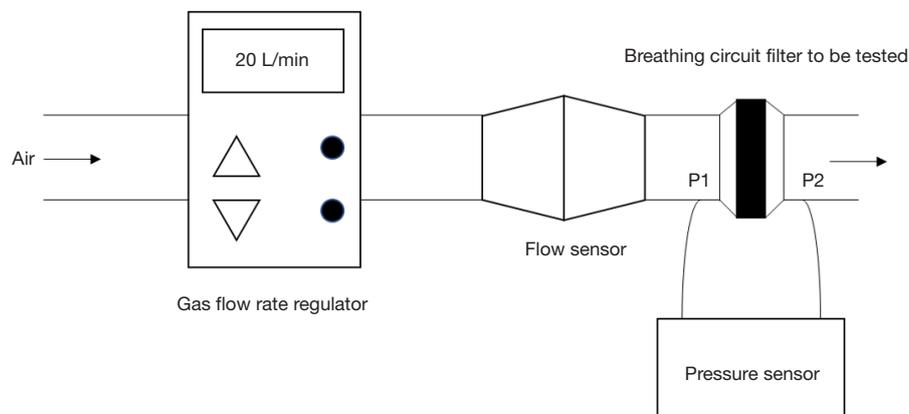


Figure 2 Breathing circuit filter resistance measurement schematic.

Table 1 Effect of different nebulization drugs on the resistance of breathing circuit filters

Group	R [cmH ₂ O/(L·s)]
Baseline group	2.26 (2.03, 2.40)
Blank group	2.11 (1.98, 2.27)
Normal saline group	2.16 (2.08, 2.32)
Combivent jet nebulization group	2.18 (2.14, 2.27)
Amphotericin B jet nebulization group	2.33 (2.05, 2.45)
IFN- α jet nebulization group	2.56 (2.40, 2.68)

The data above were expressed as median (interquartile range). IFN, interferon.

(v4.1.1), and given the small sample sizes, we adopted conservative non-parametric tests (10,11). Differences between groups were assessed with Kruskal-Wallis, and continuous variables were presented as medians with interquartile ranges. P value <0.05 was considered statistically significant.

Results

The filter resistance of the groups was compared in pairs. The results showed that: in terms of the effect of different nebulization drugs on the resistance of breathing circuit filters, the filter resistance of the IFN- α jet nebulization group was greater than that of the other groups, and there were statistical differences except for the Amphotericin B jet nebulization group ($P < 0.05$) (Tables 1, 2, Figure 3).

Regarding the effect of different nebulization methods on the resistance of breathing circuit filters, we compared

the filter resistance of the Amphotericin B jet nebulization group with the Amphotericin B vibrating mesh nebulization group and the IFN- α jet nebulization group with the IFN- α vibrating mesh nebulization group. The results showed that within 24 hours of use, there was no significant statistical difference in the impact of the above two drugs on the resistance of the breathing filters under the two different nebulization methods (Table 3, Figures 4, 5).

Discussion

COVID-19 caused by SARS-CoV-2 has swept the world. As of November 17, 2021, there were more than 250 million confirmed cases worldwide and more than 5.11 million deaths (12). There are currently no targeted antiviral drugs for COVID-19 validated through rigorous trials, and only some show specific treatment effects in clinical observation and research. In the “Chinese recommendations for diagnosis and treatment of novel coronavirus SARS-CoV2 infection (Trial 8th version)”, it is recommended that adult patients try nebulization inhalation treatment of 5 million IU or an equivalent dose of interferon at the frequency of twice a day, and the course of treatment should not exceed 10 days (13).

In the context of the widespread epidemic of COVID-19, breathing filters are widely used in clinical practice due to their advantages in reducing respiratory circuit pollution and avoiding nosocomial infections. However, a study has shown that the performance indicators of filters gradually change during use, including resistance (9). For critically ill patients with COVID-19 who require invasive ventilation, the increase in the resistance of the breathing filters is more likely to cause an increase in the patient’s labour of

Table 2 Comparison of P value between different groups

Groups	P values				
	Baseline group	Blank group	Normal saline group	Combivent jet nebulization group	Amphotericin B jet nebulization group
Baseline group					
Blank group	0.993				
Normal saline group	>0.999	0.998			
Combivent jet nebulization group	>0.999	0.999	>0.999		
Amphotericin B jet nebulization group	0.995	0.787	0.984	0.976	
IFN- α jet nebulization group	0.037	0.003	0.023	0.018	0.221

IFN, interferon.

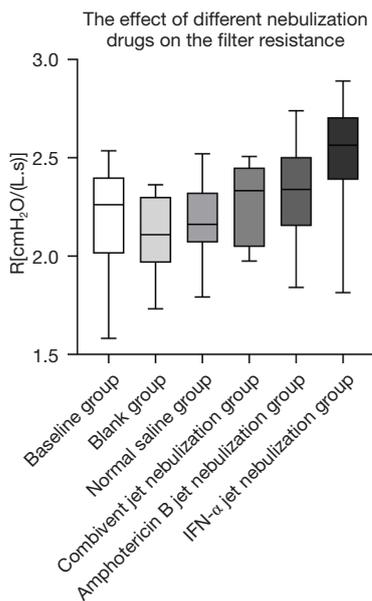


Figure 3 The effect of different nebulization drugs on the filter resistance.

Table 3 Different nebulization methods on the resistance of breathing circuit filters

Group	R [cmH ₂ O/(L.s)]	P
Amphotericin B jet nebulization group	2.33 (2.05, 2.45)	0.999
Amphotericin B vibrating mesh nebulization group	2.34 (2.18, 2.49)	
IFN- α jet nebulization group	2.56 (2.40, 2.68)	0.928
IFN- α vibrating mesh nebulization group	2.32 (2.29, 2.54)	

The data above were expressed as median (interquartile range). IFN, interferon.

Amphotericin B nebulized with different methods on the resistance of breathing circuit filters

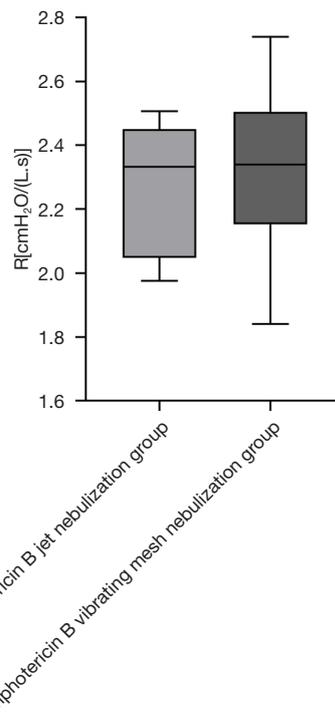


Figure 4 Amphotericin B nebulized with different methods on the resistance of breathing circuit filters.

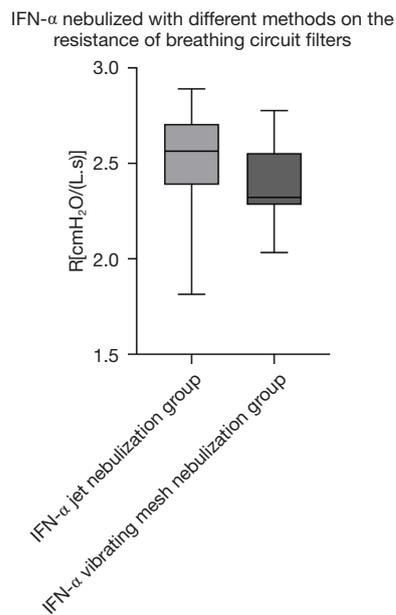


Figure 5 Interferon- α nebulized with different methods on the resistance of breathing circuit filters.

breathing, leading to human-machine asynchrony (14) and aggravating breathing difficulties. However, replacing the filters too frequently not only increases labour and medical costs but as the respiratory circuit is connected to the outside world during the replacement process, the risk of infectious aerosol spread increases (15). Currently, there is no consensus on the replacement time of breathing filters—Branson (16) recommended replacement after one week while Boyer *et al.* (17) recommended replacement after 48 h. There are many factors that may affect breathing filter resistance, including the type and concentration of nebulization drugs, different modes and parameter settings of the ventilator, nebulization equipment and the patient's own disease conditions. Breathing filters mainly play a filtering role through direct interception (particle size $>1 \mu\text{m}$), inertial impact (particle size $0.5\text{--}1 \mu\text{m}$), and diffusion interception (particle size $<0.5 \mu\text{m}$) (18). Therefore, the size and mass of the aerosol particles in the breathing circuit will affect the resistance of the filter. The size and weight of the nebulization aerosol may be affected by the type of the drug itself, the relative molecular weight, nebulization equipment and even the solvent of the drugs (19). The nebulization aerosol with a large particle size and molecular weight is easy to be directly intercepted and easier to deviate from the direction of the airflow and hit the fiber of the membrane, resulting in an increase in filter

resistance. When the drug concentration is high, more molecules pass through the filter membrane per unit time, and more nebulization drug molecules are deposited on the filter membrane, and the resistance of the respiratory filter may increase more significantly within the same use time. Similarly, some specific parameters and modes of the ventilator may also affect the resistance of the filter. For example, when the gas flow rate in the breathing circuit is fast, the gas is more likely to form turbulent flow when passing through the filter, and lead to an increase in resistance as well. At the same time, the humidified gas in the ventilator circuit may also have an effect on the resistance of the filter—the humidified airflow in the respiratory circuit makes water accumulate in the filter membrane. A study has shown that the resistance of the breathing filters can be increased by 70% to 480% after the breathing filter absorbs water (20). Finally, for patients with massive or thick respiratory secretions, the application of breathing filters should also be cautious (21)—these secretions have the risk of blocking the filters and causing a sharp increase in resistance.

The factors mentioned above are closely related to the type of the disease because the airway resistance is further increased due to the increase of breathing filter resistance. In patients with acute respiratory distress syndrome (ARDS), the airflow rate of the ventilator is often faster, and the increase of the resistance of the breathing filter at this time may cause the increase in intrinsic positive end expiratory pressure (PEEPi), aggravating lung damage (22). At the same time, it may also affect the flow triggering of the ventilator, increasing the risk of human-machine asynchrony. For patients with airway obstruction diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD), the increase in filter resistance may lead to increased inspiratory work (23,24) and insufficient inspiratory process, resulting in delayed ventilator delivery. Therefore, the timing of filter replacement is worthy of discussion.

The results of our study showed that the filter resistance of the IFN- α jet nebulization group was greater than that of all other groups in the 24 h use time, and the differences between the IFN- α jet nebulization and the baseline, blank, normal saline, and Combivent jet nebulization groups were statistically significant. At the same time, although there was no statistical difference in the filter resistance of the Amphotericin B jet nebulization group compared with other groups, the median of filter resistance of this group was still greater than that of all groups except the IFN- α group, suggesting an increase in the experimental sample



Figure 6 The filter membrane is stained yellow after Amphotericin B nebulization.



Figure 7 Liquid medicine remains in the jet nebulizer.

size may render the difference statistically significant. The reason for the above phenomenon may be that compared with normal saline, which has a relative molecular mass of 58.4, Ipratropium bromide and salbutamol, which are the main ingredients of Combivent, have relative molecular masses of 412.3 and 239.3, respectively). In addition, the relative molecular masses of Amphotericin B and IFN- α 2b are significantly larger [the former is 924.08, and the latter can reach 65,000 (25)]. The above differences may lead to differences in particle size and weight of the aerosols formed by their nebulization. When the drug-aerosol with larger size and higher weight flows through the filter it is filtered out and deposited on the filter membrane easier and gradually blocks the sieve holes, thereby increasing the resistance of the filter, which is consistent with clinical

observations. Taking the coloured drug Amphotericin B as an example, we often see apparent yellow staining of the filter membrane with the naked eye after nebulization treatment (Figure 6). Therefore, we suggest that intubation patients should have their breathing filters promptly replaced after nebulization treatment with Amphotericin B, IFN- α , and other macromolecular drugs.

At the same time, the results of our study also showed that for Amphotericin B and IFN- α 2b, jet nebulization and vibrating mesh nebulization had no significant difference on breathing filter resistance. Jet nebulization is currently the most used nebulization method, and uses high-speed airflow to impact the liquid and form a negative pressure around it, which entrains the liquid into the airflow forming aerosols (26). However, the aerosol particles produced by jet nebulization are of different sizes, and part of the liquid medicine remains in the equipment (Figure 7), which reduces nebulization efficiency. A study shows that in the process of jet nebulization, the activity of IFN- α may be reduced due to the formation of insoluble non-covalent polymers because of mechanical damage (27). The method of vibrating mesh nebulization uses electricity to vibrate the liquid through small sieves to form aerosols (28). Therefore, the aerosol particles created are smaller and uniform in size (29) allowing the nebulizer to deliver more inhaled medication to the lungs, in less time, with less residual volume (30,31). In terms of the effect of nebulized inhalation on respiratory mechanics indicators during mechanical ventilation, compared with jet nebulization, vibrating mesh nebulization also has certain advantages. Driven by additional airflow, jet nebulization increases the base airflow. It may affect mechanical indicators such as tidal volume (VT), peak inspiratory pressure (P_{peak}), positive end expiratory pressure (PEEP) etc., result in the increase of them (especially in Volume Control Ventilation Mode) and lead to poor triggering, affecting the air supply of the ventilator (32,33). When the resistance of the breathing filter increases due to nebulization treatment, the above effects on respiratory mechanics may be more significant. Vibrating mesh nebulization forms aerosols through vibrate liquid, which will not have a significant impact on the mechanical indicators of respiratory mechanics (28). As the two nebulization methods have similar effects on breathing filter resistance, combined with the above advantages, vibrating mesh nebulization may be a better IFN- α nebulization method.

Nebulization inhalation therapy is one of the important treatment methods for patients receiving mechanical

ventilation. Ehrmann *et al.* (34) investigated 854 ICUs from 611 departments in 70 countries around the world and concluded that 99% of the patients needed mechanical ventilation combined with nebulization inhalation therapy. The type of nebulized drug, whether the choice of nebulization device and method is reasonable (35), the clinical operation in the nebulization process, etc., may all affect the nebulization effect. Therefore, it is necessary to further standardize the operation of nebulization therapy. The results of this study may provide some reference for the timing of breathing filter replacement and the choice of nebulization methods for patients receiving nebulization treatment in clinical practice.

Conclusions

Compared with other commonly used nebulization drugs, IFN- α nebulization significantly increases the resistance of breathing filters, while Amphotericin B may also affect it. Therefore, breathing filters should be replaced in a timely manner after nebulization treatment with macromolecular drugs. While jet nebulization and vibrating mesh nebulization did not significantly differ in their effect on the resistance of breathing filters, other advantages of vibrating mesh nebulization may render it a better method.

Limitations

The study still has some limitations: first, it is an *in vitro* simulation experiment with relatively short observation and during the experiment, the gas flow rate in the breathing circuit is basically constant. In a practical situation, the factors that affect the resistance of breathing filter are much more complex, including the patient's conditions mentioned above such as the massive and thick secretions, the specific mode parameters of the ventilator, or even the degree of standardization of the clinician's operation. Thus, a longer *in vivo* experimental observation is required. Secondly, although the results of the study clarified that IFN- α 2b significantly increases the resistance of the breathing filter, whether the degree of change of the filter resistance is sufficient to cause significant changes in respiratory mechanics indicators including airway resistance, airway peak pressure, and the work of breathing, requires further study.

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Footnote

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Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-84/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-84/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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