Additional Expiratory Resistance Elevates Airway Pressure and Lung Volume during High-Flow Tracheal Oxygen via Tracheostomy

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The standard high-flow tracheal (HFT) interface was modified by adding a 5-cm H2O/L/s resistor to the expiratory port. First, in a test lung simulating spontaneous breathing, we found that the modified HFT caused an elevation in airway pressure as a power function of flow. Then, three tracheal oxygen treatments (T-piece oxygen at 10 L/min, HFT and modified HFT at 40 L/min) were delivered in a random crossover fashion to six tracheostomized pigs before and after the induction of lung injury. The modified HFT induced a significantly higher airway pressure compared with that in either T-piece or HFT (p < 0.001). Expiratory resistance significantly increased during modified HFT (p < 0.05) to a mean value of 4.9 to 6.7 cm H2O/L/s. The modified HFT induced significant augmentation in end-expiratory lung volume (p < 0.05) and improved oxygenation for lung injury model (p = 0.038) compared with the HFT and T-piece. There was no significant difference in esophageal pressure swings, transpulmonary driving pressure or pressure time product among the three treatments (p > 0.05). In conclusion, the modified HFT with additional expiratory resistance generated a clinically relevant elevation in airway pressure and lung volume. Although expiratory resistance increased, inspiratory effort, lung stress and work of breathing remained within an acceptable range.

After the discontinuation of mechanical ventilation, approximately 10 to 20% of patients require an artificial airway1–4. For patients who cannot protect their own airway, tracheostomy is often performed, and relatively long-term oxygen therapy is required5,6. Studies have shown that tracheostomy tubes decrease airway resistance and the work of breathing; however, diminishing the physiological positive end-expiratory pressure (PEEP) via bypassing the larynx and upper airway may also result in a reduction of the functional residual capacity7,8. The latter may put the patient at risk for atelectasis and respiratory failure.

High-flow nasal cannula (HFNC) oxygen therapy, which delivers heated and humidified oxygen and air with a maximum flow rate of 60 L/min at a prescribed inspired oxygen concentration, has drawn increasing attention in treating adult patients with mild-to-moderate respiratory failure or after extubation9–11. Studies involving bench models12, healthy volunteers13,14 and surgical patients15,16 have demonstrated that HFNC can generate a flow-dependent positive airway pressure (Paw), which is proposed to be the main contributor to the improvement in oxygenation and lung volume using HFNC over conventional oxygen therapy17–19. However, limited data20–22 did not show clinically relevant changes in Paw and end-expiratory lung volume (EELV) during high-flow tracheal (HFT) oxygen therapy via tracheostomy that might be caused by the different mechanisms of action during HFT compared with HFNC20. Additionally, controversial results were reported for the impact of HFT on oxygenation compared with T-piece21,22. These findings may be the major reasons for the limited use of HFT in tracheostomized patients.

In the present study, we modified the HFT system by adding a resistor with a physiological level of resistance to the expiratory port of the interface. HFT was delivered via tracheostomy in a bench model simulating spontaneous breathing, and thereafter, in pigs before and after the induction of mild lung injury. We primarily aimed to test whether the modified HFT could induce elevations of Paw and EELV. As secondary study endpoints, we assessed the effects of modified HFT on inspiratory effort, work of breathing, lung stress, ventilation and gas exchange.
Methods
Modification of the HFT Interface. A 5-cm H2O/L/s resistor (Michigan Instruments, Grand Rapids, MI, USA) was connected to the expiratory port of an HFT interface (OPT870, Fisher & Paykel Healthcare, Auckland, New Zealand) (Fig. 1). During the study, HFT was delivered via the standard or modified interface using an AIRVO 2 device (Fisher & Paykel Healthcare, Auckland, New Zealand) and the manufacturer’s standard assembly composed of a heated breathing circuit and an auto-fill humidification chamber (900PT501, Fisher & Paykel Healthcare, Auckland, New Zealand).

Bench experiment. Details of methods in the bench experiment are provided in Supplementary File. A two-chamber Michigan test lung (Model 5600i, Michigan Instruments, MI, USA) was used to simulate spontaneous breathing, as previously described by Thille and coworkers\(^{23}\). Normal, strong and very strong inspiratory drives were simulated by setting the tidal volume (VT) at 300, 600 and 900 mL with peak inspiratory flows of 25, 50 and 75 L/min, respectively. The respiratory rate (RR) was set at 15 breaths/min to minimize the risk of air trapping, and no PEEP was used. Two levels of compliance were set to simulate a normal lung (60 mL/cm H2O) and a mild-injured lung (40 mL/cm H2O)\(^{24}\). Thus, six conditions were established with different inspiratory drives (normal, strong and very strong) and respiratory system compliances (normal and injured lung).

Under each condition, HFT was delivered via an 8.0 ID tracheostomy tube (Smiths Medical International Ltd, Kent, UK) using the standard and modified interface, and the flow rate was incrementally adjusted to 10, 20, 30, 40, 50 or 60 L/min with the HFT setting at inspired fraction of oxygen (FIO2) 0.21 and temperature of 37 °C.

Pressure within the test lung (breathing chamber) was also measured by positioning the pressure transducer at the opening of test lung, defined as intrapulmonary pressure.

Animal study. The animal study was approved by the Ethical Committee for Experimental Studies at Beijing Neurosurgical Institute, Beijing, China. All animal procedures were performed in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. Detailed methods of the animal study are presented in Supplementary File.

Six healthy female pigs [Bama, weight: 38 to 45 kg (mean ± SD, 42 ± 3 kg), age: 11 to 13 months (mean ± SD, 12 ± 1 months)] were anesthetized via intramuscular ketamine (10 mg kg\(^{-1}\)) and xylazine (1 mg kg\(^{-1}\)). The animals were placed in the supine position on a thermo-controlled operation table to maintain rectal temperature at approximately 37 °C. A tracheostomy was performed, and an 8.0 ID tube (Smiths Medical International Ltd, Kent, UK) was placed. Mechanical ventilation was initiated in a pressure support (PS) mode with PS 10 cm H2O, PEEP 5 cm H2O and Fio2 0.4. The pulse oxygen saturation and partial pressure of end-tidal carbon dioxide (PETCO2) was monitored (BeneView T5, Mindray, Shenzhen, China). During the study, propofol (10 mg kg\(^{-1}\) h\(^{-1}\)) and fentanyl (0.05 mg kg\(^{-1}\) h\(^{-1}\)) were continuously infused to provide sedation and analgesia, minimizing suffering. Paw was measured by inserting a 6-French catheter at 1 cm proximal to the end of the tracheostomy tube. An esophageal balloon catheter (Cooper: LOT 177405, Cooper Surgical, USA) was inserted for esophageal pressure (Peso) measurement. The position of the balloon was confirmed by Baydur’s occlusion test\(^{25}\).

Figure 1. Standard and modified high-flow tracheal interface. (A) standard high-flow tracheal oxygen therapy interface; (B) test lung resistor (5 cm H2O/L/s); (C) modified interface by connecting the resistor to the expiratory port of the standard interface.
Electrical impedance tomography (EIT) monitoring (PulmoVista 500; Dräger Medical GmbH, Lübeck, Germany) was set up using a dedicated belt with 16 electrodes placed just below the axilla and one reference electrocardiogram electrode placed at the right lead leg. The images were continuously recorded at 40 Hz. Data were downloaded and analyzed off-line using a dedicated software (Dräger EIT Data Analysis Tool 6.3, Lübeck, Germany).

T-piece oxygen and HFT were delivered in the six animals before and after the induction of mild lung injury by surfactant depletion. Warmed normal saline (5 mL/kg at 37–39 °C) was instilled into the tracheostomy tube and then drained by gravity. Lavage was repeated until the partial pressure of oxygen in arterial blood (P_{aO2}) to FIO2 (P_{aO2}/FIO2) ratio was lower than 300 for 30 min.

Before each investigation in the normal and injured lung model, the animal was mechanically ventilated in the PS mode. Propofol and fentanyl were titrated to maintain the absence of limb movement but adequate and stable spontaneous breathing for at least 30 min. Then, the animal was weaned from mechanical ventilation, and the following three tracheal oxygen treatments were performed in a random crossover fashion without washout period, lasting 20 min each:

1. Humidified T-piece oxygen
2. HFT via standard interface
3. HFT via modified interface

Humidified T-piece oxygen was delivered using an OxyfloTM system composed of an RT308 circuit and MR850 heated humidifier (Fisher & Paykel Healthcare, Auchland, New Zealand) at flow rate 10 L/min and temperature 37 °C. HFT was delivered using the same system mentioned in the bench experiment. HFT was set at flow rate 40 L/min, FIO2 0.4 and temperature of 37 °C.

Propofol and fentanyl were not adjusted during each sequence of tests. At the end of study, the animals were sacrificed by intravenous infusion of 20 ml 10% potassium chloride under deep anesthesia.

Data collection and measurements. Detailed methods of measurements are also provided in Supplementary File.

In the bench experiment and the animal study, pressures were measured by pressure transducers (KT 100D-2, Kleis TEK di CosimoMicelli, Italy, range: ±/− 100 cmH2O) connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari, Italy) by 80 cm rigid tube lines. Flow tracings were continuously collected by a heated Fleisch pneumotachograph (Vitalograph Inc, Lenexa, KS, USA) placed between the high-flow tracheal (HFT) oxygen interface and the tracheostomy tube. Pressure and flow signals were displayed continuously and saved (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) in a laptop for further analysis, at a sample rate of 200 Hz.

In the animal study, at the end of each tested phase (T-piece, HFT or modified HFT), hemodynamic data (HR and MAP), PETCO2, PaO2 and partial pressure of carbon dioxide in arterial blood (PaCO2) were collected. The alveolar dead space fraction was calculated.

Pressure and flow tracings in the last minute at each phase were analyzed, and the following parameters were collected:

1. The mean Paw during either the inspiratory or expiratory phase;
2. The peak inspiratory and expiratory flow rate (PIF and PEF);
3. The inspiratory VT integrated by flow tracing, and RR and minute ventilation (MV);
4. The Pes swing during inspiration (ΔPes);
5. The inspiratory and expiratory airway resistance estimated at flow rate of 200 mL/s using the method introduced by Mead et al. as follows:

\[ R = \frac{(P_0 - P_{p_{\text{ex}}})V'}{V_C} \]

where R is the resistance, P_0 is the P_{p_{\text{ex}}} at the start of inspiratory and expiratory flow, V is the instantaneous volume integrated from flow, C is the dynamic compliance obtained for the same breath as the ratio of VT to ΔPes, and V' is the instantaneous flow rate (=0.2 L/s);

6. The intrinsic PEEP that was equal to difference in P_{p_{\text{ex}}} between onset of decrease of P_{p_{\text{ex}}} and the start of inspiratory flow;
7. The per-breath pressure time product (PTP) and the averaged PTP over a minute (PTP_{\text{ave}}) derived from P_{p_{\text{ex}}} tracing. The per-breath PTP was derived by integrating the area of the P_{p_{\text{ex}}} waveform during inspiration of each breath in the last minute. PTP_{\text{ave}} was calculated as the sum of per breath PTP in the last minute;
8. The dynamic end-inspiratory and end-expiratory transpulmonary pressure (P_{\text{△p}}) that were measured as the difference between P_{aw} and the absolute P_{p_{\text{ex}}} measured at the end of inspiration and end of expiration (all at zero flow), and the driving transpulmonary pressure (ΔP) was calculated as the difference between end-inspiratory and end-expiratory P_{\text{△p}};
9. F1O2 estimated by the sum of fresh gas volume and room air entrainment as follows:

\[ F_{1O2} \] during T-piece oxygen was estimated as:
where $\text{Ti}$ is inspiratory time (s), 167 represents T-piece oxygen flow rate ($10 \text{L/min} = 167 \text{mL/s}$), and 0.21 represents oxygen concentration in air.

Actual $F_{102}$ during HFT was estimated as:

$$F_{102} = \frac{(Ti \times 167 \times 1.0) + (V_T - Ti \times 167 \times 1.0) \times 0.21}{V_T}$$

where 667 represents HFT flow rate used in the present study ($40 \text{L/min} = 667 \text{mL/s}$) and 0.40 represents set $F_{102}$ during HFT.

And the $P_{aw}/F_{102}$ ratio was also calculated.

In off-line EIT analysis, we defined the thoracic cross-section using a matrix of $32 \times 32$ pixels. The dorsal $8 \times 32$ pixels of this matrix were discarded because no lung was contained in this region of the pig's anatomy.

The remaining $24 \times 32$ pixels were defined as the global region of interest (ROI), which were further evenly divided into the ventral ROI (non-dependent lung region), middle ROI and dorsal ROI (dependent lung region). EIT measurements were collected in the last minute of each phase, including the following:

1) Considering T-piece as the reference value, global and regional changes in EELV ($\Delta$EELV) during HFT via the two interfaces were evaluated as the respective change in end-expiratory impedance multiplied by the ratio between $V_T$ measured by flow integration (in mL) and the global tidal impedance change (in absolute unit).\(^{18,19}\)

2) The regional distribution of tidal ventilation in the three ROIs was collected. The center of ventilation (COV) was calculated as the percentage of tidal ventilation distributed to the dorsal ROI in the global ROI.\(^{18}\) The higher the COV, the more tidal ventilation is distributed to the dependent lung region.

**Statistical analysis.** Normally distributed variables were presented as the means ± SD, and non-normally distributed variables were reported as the medians (25th to 75th percentile).

In the bench experiment, two-way analysis of variance (ANOVA) with repeated-measures was used to compare the $P_{aw}$ and resistance across different HFT flow levels (10 to 60 L/min) as well as between the two HFT interfaces (standard and modified). A post hoc pairwise comparison was performed using the Bonferroni correction.

During modified HFT, the $P_{aw}$ and flow rate were fitted using the following power equation:

$$P_{aw} = a \times \text{Flow}^b + c$$

The flow-$P_{aw}$ curve was fitted using the Levenberg-Marquardt iterative algorithm, which was set to run until the change in the sum of squared residuals was lower than $10^{-8}$. The coefficient of determination ($R^2$) was calculated.

For the modified interface, a multiple stepwise linear regression was performed to find the potential determinants of the mean expiratory $P_{aw}$. The covariates that were entered into the model included the quadratic element of flow rate ($\text{Flow}^2$), set compliance of the breathing chamber and expiratory resistance.

In the animal study, differences in variables across different tracheal oxygen treatments (T-piece, HFT and modified HFT) were compared by one-way ANOVA with repeated-measures or by Friedman test, as appropriate. Post hoc pairwise comparisons were performed using the Bonferroni correction. The correlations were analyzed using the Pearson coefficient ($R$).

Analyses were conducted using SPSS 20.0 (SPSS, Chicago, Illinois, USA). A $p < 0.05$ was considered statistically significant.

**Results**

**Bench experiment.** The bench experiment results are detailed in Supplementary File.

Compared with the HFT, the modified HFT generated significantly higher mean expiratory $P_{aw}$ at each flow rate level, and significantly higher mean inspiratory $P_{aw}$ at flow rates from 30 to 60 L/min ($p < 0.05$, Table 1).

For the modified HFT, either inspiratory or expiratory $P_{aw}$ increased as a power function of flow rate (see the Supplementary Fig. S1).

Compared with the HFT, the modified HFT significantly increased expiratory resistance at each flow rate level ($p < 0.05$) with the maximal change from $6.6 \pm 0.9 \text{cm H}_2\text{O}/\text{L/s}$ to $11.9 \pm 1.3 \text{cm H}_2\text{O}/\text{L/s}$ at flow rate of 60 L/min. Although there was also a statistical significance in inspiratory resistance during modified HFT, the magnitude was relatively minor. (Table 1).

For the modified HFT, the covariates that determined the mean expiratory $P_{aw}$ included the flow ($\text{Flow}^2$) and expiratory resistance ($R^2 = 0.963$, see the Supplementary Table S1).

**Animal study.** After a normal saline lavage of the lungs, the $P_{O2}/F_{102}$ ratio decreased from $352 \pm 77$ to $228 \pm 45$ (see the Supplementary Table S2). All the animals tolerated tracheal oxygen treatments during the study.

**Effects of Modified HFT on $P_{aw}$ and Resistance.** In both normal and injured lung models, modified HFT induced significantly higher inspiratory and expiratory $P_{aw}$ compared with either T-piece or HFT ($p < 0.05$, Fig. 2). Although there was an increasing tendency in inspiratory resistance via modified HFT, no significant difference was found among the three treatment groups in both lung conditions (Fig. 3A). Expiratory resistance
significantly increased during modified HFT ($p < 0.05$, Fig. 3B) to a mean value of $6.7 \pm 2.9$ (range: $4.1–11.6$) and $4.9 \pm 2.7$ (1.9–9.2) cm H$_2$O/L/s in the normal and injured lung model, respectively. There was a significant correlation between expiratory Paw and resistance ($R = 0.577$, $p < 0.001$).

During modified HFT, a significant decrease was found in PEF in both models and in PIF in the injured lung model ($p < 0.05$). There was a decreasing tendency in PIF in the normal lung model, but it was not statistically significant (Table 2).

No obvious intrinsic PEEP was identified during each tracheal oxygen treatment (Table 2).

**Effects of Modified HFT on Lung Volume, Ventilation and Distribution.** Global $\Delta$EELV increased significantly with the modified HFT when compared to HFT in both lung conditions, normal and injured, respectively ($p < 0.05$, Fig. 4A). $\Delta$EELV was mainly distributed to the middle ROI (Fig. 4B). Furthermore, $\Delta$EELV positively correlated with expiratory $P_{aw}$ ($R = 0.766$, $p < 0.001$).

No significant differences were found in $V_{T_i}$, $T_i$ and expiratory time (Te) among the three treatments, whereas RR decreased only, but significantly in the modified HFT group for the injured lung model ($p = 0.011$, Table 2). However, there was no significant change in MV observed among any treatment groups and/or between the two lung conditions.

No significant difference in COV was observed among the three treatment groups with the only exception of a higher COV for the modified HFT group compared to the HFT group ($p = 0.037$) and the T-piece group ($p = 0.018$) in the injured lung condition (Fig. 4C).

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**Table 1.** Airway pressure and resistance during high-flow tracheal oxygen in the bench experiment. HFT: high-flow tracheal oxygen; $P_{aw}$: airway pressure. Data are shown as mean ± standard deviation.

| HFT flow rates (L/min) | Mean inspiratory $P_{aw}$ (cmH$_2$O) | Mean expiratory $P_{aw}$ (cmH$_2$O) | Inspiratory resistance (cmH$_2$O/L/s) | Expiratory resistance (cmH$_2$O/L/s) |
|------------------------|--------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|
| 10                     | Standard interface $-0.9 \pm 0.6$ | Standard interface $0.5 \pm 0.3$ | Standard interface $3.8 \pm 0.4$ | Standard interface $6.2 \pm 1.0$ |
| 20                     | $-1.1 \pm 0.8$                     | $0.6 \pm 0.3$                     | $3.8 \pm 0.6$                     | $6.2 \pm 0.9$                     |
| 30                     | $-0.8 \pm 0.7$                     | $1.0 \pm 0.3$                     | $3.9 \pm 0.7$                     | $6.4 \pm 0.7$                     |
| 40                     | $-0.7 \pm 0.7$                     | $1.2 \pm 0.3$                     | $4.1 \pm 0.6$                     | $6.6 \pm 0.9$                     |
| 50                     | $-0.6 \pm 0.8$                     | $1.5 \pm 0.3$                     | $4.1 \pm 0.5$                     | $6.6 \pm 0.8$                     |
| 60                     | $-0.4 \pm 0.8$                     | $<0.001$                          | $4.4 \pm 0.6$                     | $<0.001$                          |

$p$ values in pairwise comparisons are also shown.

**Figure 2.** Airway pressure ($P_{aw}$) during T-piece, high-flow tracheal (HFT) oxygen and modified HFT. In both normal and injured lung models, modified HFT induced significantly higher inspiratory (A) and expiratory (B) $P_{aw}$ compared with either T-piece or HFT. Data are presented as means and standard deviations, and $p$ values in pairwise comparisons are also shown.
Effects of Modified HFT on Ventilation, Inspiratory Efforts, Transpulmonary Pressure and Work of Breathing. There was no significant difference in inspiratory resistance (A) among the three tracheal oxygen treatments \( (p = 0.484) \) in normal lung group and \( p = 0.056 \) in injured lung group). Expiratory resistance (B) significantly increased during modified HFT compared with T-piece. Data are presented as means and standard deviations, and \( P \) values in pairwise comparisons are also shown.

Table 2. Effects of modified high-flow tracheal oxygen on ventilation, inspiratory efforts, transpulmonary pressure and work of breathing HFT: high-flow tracheal oxygen; MV: minute ventilation; PEEP: positive end-expiratory pressure; PIF: peak inspiratory flow; PTP: per-breath pressure time product; PTPmin: averaged pressure time product over a minute; RR: respiratory rate; Ti: inspiratory time; Te: expiratory time; VT: tidal volume; \( \Delta \)Pes, \( \Delta \)PL, \( \Delta \)PIF, \( \Delta \)MV, \( \Delta \)VT, \( \Delta \)PTP: driving transpulmonary pressure. Data are shown as mean \pm standard deviation. aSignificantly different compared with T-piece. bSignificantly different compared with HFT.

Effects of Modified HFT on Inspiratory Effort, \( \Delta \)PL and Work of Breathing. There was no significant difference in either \( \Delta \)Pes, \( \Delta \)Pl, per-breath PTP or PTPmin among the three treatments (Table 2).

Effects of Modified HFT on Gas Exchange and Hemodynamics. \( FIO_2 \) and \( PaO_2 \) during T-piece were significantly higher than those during HFT and modified HFT (Table 3). \( PaCO_2/FIO_2 \) ratios were unchanged among the three treatment groups in the normal lung model but increased significantly during modified HFT compared to those during HFT and T-piece in the injured lung model \( (p = 0.038, \text{Table 3}) \).

There was no significant difference in MAP and HR among the three treatments, with the exception of a significantly decreased HR in the modified HFT group compared to the T-piece group in the injured lung model \( (p = 0.041, \text{Table 3}) \).

Discussion
In the present study, we modified the HFT system by adding a 5 cm H\(_2\)O/L/S resistor to the expiratory port of the standard interface. The effect of modified HFT on Paw was first reported in a bench model. Then, the performance of modified HFT via tracheostomy was evaluated in pigs with normal and mildly injured lungs. Our results demonstrated that the modified HFT generated flow-dependent positive Paw and, consequently, an increase in EELV, which might be the main reasons for the improvement in ventilation homogeneity and oxygenation. Meanwhile, the increase in expiratory resistance was within an acceptable range and did not significantly affect the inspiratory efforts, lung stress and work of breathing.
Supplemental oxygen therapy is one of the most commonly used treatment modalities in critically ill patients. Recent evidence suggested that when compared with standard oxygen therapy, HFNC improved oxygenation and respiratory mechanics. These improvements were proposed to be mainly due to the elevations in P_{aw} and EELV, which might have resulted from increased expiratory resistance as the high inward flow encounters the nasal airway. However, this encountered resistance is diminished after tracheostomy because the larynx and upper airway are bypassed. Accordingly, limited investigations revealed that no clinically significant positive P_{aw} and EELV effects were found during HFT via tracheostomy when compared with T-piece. These findings somewhat resembled the delivery of HFNC with opened mouth, during which the extra expiratory resistance vanished, and the P_{aw} effect disappeared. Therefore, we speculated that adding a resistor to the expiratory port of the HFT interface might mimic the nasal resistance during expiration, thus inducing a positive P_{aw} effect and consequently elevating EELV. Our results confirmed...
These resistance levels were also comparable to those obtained during HFNC in the bench study (10.15 ± 1.37 cm H₂O/L/s) in the bench experiment (Table 1), and 6.7 ± 2.9 and 4.9 ± 2.7 cm H₂O/L/s in the animal model with normal and injured lungs, respectively (Fig. 3B). These resistance levels were also comparable to those obtained during HFNC in the bench study (10.15 ± 1.37 cm H₂O/L/s) and in patients recovering from acute respiratory failure (median [25th to 75th percentile] of 6.7 [5.6–8.8] cm H₂O/L/s at 40 L/min flow rate). Meanwhile, the inspiratory resistance also slightly increased in the modified HFT. But the increment is within physiological range. The reason for the elevation of inspiratory resistance might be due to the increase of end-expiratory Paw during the modified HFT, which is the component in the calculation of resistance introduced by Mead, et al. The second safety concern is whether the elevated resistance affects inspiratory efforts and lung stress. Strong inspiratory efforts with collateral elevation of resistance could have resulted in high Pj, i.e., high lung stress, which could aggravate lung injury. ∆Pj is a validated measurement of inspiratory effort and respiratory system, such as T-piece. Our animal results preliminarily demonstrated some potential clinical benefits of the Paw effect produced by modified HFT, which is the component in the calculation of resistance introduced by Mead, et al. Our data suggested that oxygenation during T-piece should be interpreted with caution because of the unstable Fesp delivery during low-flow oxygen system. As far as we know, due to the influence of Vₚ, RR and inspiratory time, actual Fesp is not stable during low-flow oxygen system, such as T-piece. The HFT had an advantage of providing an accurate setting of Fesp in the studies comparing oxygenation during HFT and T-piece, Fesp delivered by T-piece was usually estimated by the approximation of oxygen flow rate and physiological dead space. In the present study, we used a pneumotachograph to measure the inspiratory flow rate, and actual Fesp was calculated by the sum of fresh gas volume and room air entrainment as previously described. This method could provide relatively accurate Fesp measurement. A significantly higher Fesp was found during T-piece oxygen than HFNC, which was in accordance with the results presented by Corley et al. Our data suggested that oxygenation during T-piece should be interpreted with caution because of the unstable Fesp delivery during low-flow oxygen system. Our animal results preliminarily demonstrated some potential clinical benefits of the Paw effect produced by modified HFT. AEEVL, indicating an improvement in lung volume and a reduction of alveolar collapse, correlated directly to the mean expiratory Paw. The increase in Paw/Pesp ratio in the injured lung model might have largely resulted from the elevation in AEEVL. Additionally, the increase in AEEVL in combination with unchanged Vj suggested a reduction in lung strain, indicating that there was a low risk in causing lung injury, e.g., hyperinflation. These findings are comparable to those reported in lung-injured patients receiving HFNC. Finally, a slight but significant increase in COV in the injured lung model suggested a potential reduction in the stress generated by inhomogeneity between the dependent and non-dependent lung regions. There are limitations in the present study. First, in the animal study, we only tested a single HFT flow rate (40 L/min) and investigated the acute physiological responses (within 20 min of treatment) to the tracheal oxygen treatments without washout period; it was relatively difficult to maintain an optimal sedation level with stable spontaneous breathing and no agitation in the tested animal for an extended period of time. However, the flow rate chosen in the present study represented the low flow level used in the clinical studies of HFNC and HFT, making it convenient to compare our results with previous reports. Additionally, our equilibrating time was likely chosen in the present study represented the low flow level used in the clinical studies of HFNC and HFT, making it convenient to compare our results with previous reports. Additionally, our equilibrating time was likely enough for the main endpoints of Paw and lung volume effects. Second, although the measurement of resistance introduced by Mead et al. has been employed in clinical studies, the use of dynamic compliance in the equation might overestimate the airway resistance, even though our measured expiratory resistance remained...
within an acceptable range. Third, we only calculated $F_{O2}$ using an equation based on the proportion of delivered fresh gas volume and entrainment volume room air, rather than direct measurement. This might have influenced the $F_{O2}/F_{O2}$ ratio results, especially during T-piece oxygen. Forth, in bench and animal experiment, we did not observe the effects of modified HFT on conditions with obstructive diseases. Although the rationale and physiology were recently discussed for the use of HFNC in stable chronic obstructive pulmonary disease, high-flow oxygen therapy in a severe airway obstructive condition still remains to be clarified. Fifth, although portable continuous positive airway pressure (CPAP) devices are available (such as Boussignac™ oxygen therapy device), they are not widely used. Thus, we didn't compare HFT with CPAP devices in our study.

Conclusions
Our modified HFT with additional inspiratory resistance generated clinically relevant flow-dependent $P_{aw}$ and lung volume effects, which might be the main reasons for improvements in oxygenation and ventilation homogeneity. Meanwhile, inspiratory effort, lung stress and work of breathing remained within normal ranges. Our introduced modification provides an opportunity for potential improvements in the HFT instrument, which may be beneficial for oxygen therapy in tracheostomized patients. Clinical feasibility and safety require further investigation.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Study concept and design: G.Q.C., X.M.S. and J.X.Z. Data acquisition: G.Q.C., X.M.S., Y.M.W., Y.M.Z., J.R.C. and J.X.Z. Analysis of data: G.Q.C., X.M.S., Y.M.Z., J.R.C. K.M.C., Y.L.Y. and J.X.Z. Manuscript preparation: G.Q.C. and J.X.Z. All authors reviewed the manuscript.

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