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## **A bench comparison of the effect of High Flow Oxygen devices on work of breathing**

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## **ABSTRACT**

### **Background**

High flow oxygen has been extensively used during the COVID-19 pandemic. The number of devices have also increased. We underwent this study to answer the following two questions: Do devices to deliver high flow oxygen through nasal cannula differ from the original Optiflow device for work of breathing and generated positive-end expiratory pressure?

### **Methods**

Seven devices were tested on ASL5000 lung model. Compliance was set to 40ml/cmH<sub>2</sub>O and resistance to 10cmH<sub>2</sub>O/L/s. The devices were connected to a manikin head via a nasal cannula and F<sub>I</sub>O<sub>2</sub> set at 0.21. The measurements were performed at baseline (manikin head free of nasal cannula), and then with the cannula and the device attached with oxygen flow set at 20, 40, 60 L/min. Work of breathing and positive end expiratory pressure were assessed at 3 simulated inspiratory efforts (-5, -10,-15 cmH<sub>2</sub>O muscular pressure) and at 2 respiratory rates (20 and 30 breaths/min). Data were expressed as median (1st-3rd quartiles) and compared with non-parametric tests to Optiflow device taken as reference.

### **Results**

The baseline work of breathing and positive end expiratory pressure were not different between devices. Over all the conditions tested, work of breathing was 4.2 (1.0-9.4) J/min with the reference device and the relative variations from it were 0 (0-0), 3 (2-4), 1 (0-1), 2 (1-2), 1 (1-2) and 1 (1-2) % with Airvo2, G5, HM80, T60, V500 and V60 devices, respectively (P<0.05 Kruskal-Wallis test). Positive end expiratory pressure was 0.9 (0.3-1.5) cmH<sub>2</sub>O with Optiflow

and the relative differences were 28 (22-33), 41 (38-46), 30 (26-36), 31 (28-34), 37 (32-42), and 24 (21-34) % with Airvo2, G5, HM80, T60, V500 and V60 devices, respectively (P<0.05 Kruskal-Wallis test).

### **Conclusion**

Work of breathing was marginally higher and positive end expiratory pressure marginally lower with devices as compared to the reference device.

### **KEY WORDS**

High oxygen flow, COVID-19, hypoxemia, work of breathing, positive end-expiratory pressure

## INTRODUCTION

High flow oxygen delivery through nasal cannula (HFNC) has been shown to reduce intubation and mortality in patients with hypoxemic acute respiratory failure before the COVID-19 pandemic<sup>1</sup>. HFNC can also improve the weaning success in patients with low<sup>2</sup> or high<sup>3</sup> risk of extubation failure. During the COVID-19 pandemic HFNC has been extensively used in the pre-hospital setting, in the emergency room, in the dedicated high-dependency units and in the intensive care unit (ICU) to support failing oxygenation, to prevent intubation and hence, to spare the ICU resources. Coupled with prone positioning HFNC can reduce the rate of intubation as compared to a group of patients kept in supine position<sup>4</sup>. The recommended set oxygen flow is in the range 50-60 L/min depending on patient's tolerance and efficacy on oxygenation<sup>5</sup>. In the same time, the original device used in the landmark trial improved<sup>1</sup> while the HFNC function was proposed as option in several ventilators used in the ICU or in the step-down units. HFNC settings include  $F_{iO_2}$  from 21 to 100% and inspiratory flow up to 60 L/min or even higher with the most recent devices.

Early bench studies found that HFNC devices differed each other regarding the achieved level of  $F_{iO_2}$  and the quality of humidification of inspired air<sup>6</sup>. In non-intubated patients with acute hypoxemic respiratory failure, the use of HFNC can decrease both the patient's inspiratory effort and the work of breathing (WOB)<sup>7</sup>. However, no study compared the HFNC devices on WOB. Since many HFNC devices from different manufacturers are now available, such a comparison makes sense. Indeed, it is important to verify whether or not the WOB differed substantially between devices. Of note, the V-60 was recalled in the US over failures when used in the HFNC mode. This was related to a bug in the software. If it is verified that the WOB does not increase between devices, changing the devices between patients or even in a given patient would be safe.

Another issue relates to the cost between devices. The fact that after extubation the ventilator the patient was on can be used to provide HFNC and if extubation fails, have the ventilator readily available is an interesting feature but not any cost.

However, comparing several HFNC devices can hardly be done in patients, henceforth we underwent the present study on the bench to explore this question. We choose to take the original device as the control and to compare the other devices presently tested to it. Our hypothesis was that the WOB was lower with the original device than with any other due to its configuration and its beneficial clinical effect. The algorithms to deliver flow and FIO<sub>2</sub> used by the devices are a priori unknown and probably different in many respects, like the kind of internal flowmeters, how is made the mixture of oxygen and air, and so forth.

## **METHODS**

Seven HFNC devices were tested: Optiflow (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand), Airvo2 (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand), HM80 (BMC medical, Tianjin, China), T60 (Air Liquide Medical System, Antony, France), V500 (Draeger, Lübeck, Germany), V60 (Philips, Amsterdam, The Netherlands), G5 (Hamilton Med, Inc., Bonaruz, Switzerland). The first three were specifically designed for HFNC delivery when the last four were ventilators on which the HFNC option was implemented. The main characteristics of the devices are shown in Table 1.

The same kind of nasal cannula (Optiflow 3S large size; Fisher and Paykel Healthcare Ltd) was used with each device. It was attached to the nose of a manikin head (Laerdal Health Care, Stavanger, Norway) (Figure 1). To minimize the leaks the manikin esophagus was clamped and the manikin mouth occluded by a strap (Figure 1). Each device was also connected to the

ASL5000 lung simulator (Ingram Inc., Pittsburgh, PA, USA). The ASL5000 was set with a linear compliance of 40 mL/cmH<sub>2</sub>O and a resistance (inspiratory and expiratory being equal) of 10 cmH<sub>2</sub>O/Ls. To set the respiratory system compliance, we first took into consideration the current COVID-19 pandemic and used the value of 40 mL/cmH<sub>2</sub>O found by Grasselli et al <sup>8</sup> in intubated patients. We then attempted to determine the lung compliance in patients under HFNC. In the study by Delorme et al <sup>9</sup> the vital capacity averaged 2.77 L in 12 patients. The corresponding chest wall compliance computed as 4% of vital capacity <sup>10</sup> is 111 mL/cmH<sub>2</sub>O. In the study of Mauri et al <sup>7</sup> the mean trans-pulmonary driving pressure averaged 4.3 cmH<sub>2</sub>O. At a mean tidal volume of 0.270 L in Delorme et al <sup>9</sup>, lung compliance can be estimated to 63 mL/cmH<sub>2</sub>O, and hence respiratory system compliance to 40 mL/cmH<sub>2</sub>O, using the above value of the chest wall compliance. We set the resistance to 10 cmH<sub>2</sub>O/L/s according to the found by Delorme et al <sup>9</sup> in patients under 60 L/min HFNC.

A sinusoidal half-wave inspiratory effort was simulated with the following settings: muscular pressure (P<sub>mus</sub>) contraction during 16%, then pause during 2%, then relaxation during 20% of total breath duration, then passive expiration. Each effort was applied at two respiratory rates of 20 and 30 breaths/min. The duration of inspiration and expiration was therefore 1.14 and 1.86 s, and 0.76 and 1.24 s, at 20 and 30 breaths/min, respectively. The 30 breaths/min rate was chosen because it was close to the mean value at the time of inclusion in the Florali trial of patients with acute hypoxemic respiratory failure <sup>1</sup>. The 20 breaths/min rate was chosen because it was far from the previous one and close to the mean value found by Mauri et al in patients under HFNC<sup>7</sup>. Therefore, these two breathing rates of effort were clinically-based and hence likely clinical relevant. Low, medium and strong effort intensities were defined as -5, -10 and -15 cmH<sub>2</sub>O P<sub>mus</sub>, respectively. These levels were selected because a -10 cmH<sub>2</sub>O esophageal pressure swing was



found, on average, in clinical studies<sup>7, 9, 11, 12</sup>. The two other values were defined 50% below and above apart.

Three inspiratory flows set at the HFNC devices (20, 40 and 60 L/min) were tested in that order, with each device (except for the V500 in which the highest inspiratory flow available was 50 L/min). We did not measure these set flows and assumed that the set flows were provided as such by the devices.

The experimental set-up also included a pneumotachograph (3700 series, Hans-Rudolph, Shawnee, Kansas, USA) and a port to measure airway pressure inserted at the ASL inlet (Figure 1). The Paw port was connected to a pressure transducer (Gabarith PMSET 1DT-XX, Becton-Dickinson, Singapore). This set had a 0.79 cmH<sub>2</sub>O/L/s resistance<sup>13</sup>. Pressure transducer and pneumotachograph were calibrated at room air before each experiment by using a pressure calibrator (717G, Fluke Biomedical, Everett, Washington, USA) and a calibration pump of 1000 mL ±12mL precision (Viasys Healthcare, Hoechberg, Germany), respectively. This was used to ascertain that compliance and resistance set in the ASL were actually reached. Paw and flow signals were recorded separately by a data logger (Biopac150, Biopac Inc., Goletta, CA, USA).

The experiments were performed in a dedicated room at ambient air temperature and pressure.

Each device was investigated in a single day. Heated and humidifier was placed in the circuit (Figure 1) but switched off and F<sub>I</sub>O<sub>2</sub> set to 0.21. At first, without HFNC device and without nasal cannula in place each combination of breathing rate and simulated effort was run to define the baseline condition. The data logger and the ASL5000 were started simultaneously in each

condition, at a sampling rate of 200 Hz and 512 Hz, respectively. After a 2-minute recording the data were stored for off-line analysis.

### **Data analysis**

The last 30 breaths of each record were used for the off-line data analysis. This was automatically done via an application specifically designed in the Matlab environment (Matlab2019b, The MathWorks, inc.). The WOB per breath was determined breath-by-breath from the Campbell diagram (Figure 2). The WOB done by the lungs, the device and the cannula lumped all together was measured as the area under the curve subtended by the tidal volume in Y axis and the Pmus-atmospheric pressure difference in the X axis.

The primary end point was WOB. The secondary end-points were the resistive and the elastic components of WOB, and PEEP. WOB was expressed as J/min by multiplying the WOB per breath by the respiratory rate. We also provided the data of inspired tidal volume and the peak inspiratory and expiratory flows measured on the same breaths as for WOB.

The values are expressed as median (first-to-third quartiles). To make the summary of the results easier to follow the relative variation of each device from the reference for the WOB and PEEP over all the conditions tested were also shown.

The cost of each device was estimated by using the data provided by and pertaining to our institution, which may not be representative to that in other hospitals. It includes the cost of the device (the cost of the ventilator as an example) and of the ancillary components with the exception of the cost of the L/min oxygen flow rate. Because these costs are confidential only the relative change from the reference was given.

The normal distribution of the variables was tested by using the Shapiro-Wilkes test.

First, baseline WOB was compared between devices. It is expected that no difference should be found because no device was attached to the manikin. Second, WOB was compared across devices at each nominal high flow oxygen rate, i.e. 20, 40 and 60 L/min (except for V500, which does not provide with 60 L/min) for each effort intensity and rate. Since a significant interaction between these three factors was anticipated, a series of Kruskal-Wallis or one-way ANOVA test was planned, and, if significant, a pairwise comparison was done from the Optiflow device taken as reference by using the Dunnett's test. The Optiflow device was chosen as the reference because it was the first used in the clinical practice and because of its specific design. We anticipated that the bench design with a large number of highly reproducible breaths would make small differences between devices statistically significant though the clinical relevance of them would be meaningless. To deal with this issue, we apply a Bonferroni's correction by dividing 0.05 by the number of comparisons, i.e. 966 for the seven variables mentioned above as the various end-points, including the pairwise comparisons. Therefore, the P-value deeming statistical significance was  $<0.00005$ . With such a more stringent critical P-value, the statistical significance of the differences would be closer to the clinical relevance. Second, a 30% relative variation between devices was thought to reflect a clinical significance because it was the mean difference in pressure-time product of  $P_{es}$  between oxygen and HFNC found by Mauri et al in patients with acute hypoxemic respiratory failure <sup>7</sup>. The statistical analysis was conducted by using the R software version 4.0.3 (2020) (The R Foundation for Statistical Computing).

## **RESULTS**

WOB did not follow a normal distribution.

## **Work of breathing**

As expected, the baseline WOB was not different across the device for resistive, elastic and total WOB. Over all of the devices, it was 0.85 (0.84-0.85) vs 1.0 (1.01-1.02) J/min for low effort, 3.8 (3.8-3.8) vs 4.3 (4.3-4.4) J/min for medium effort and 8.5 (8.5-8.5) vs 9.6 (9.6-9.6) J/min for strong effort, at 20 vs 30 breaths/min effort rate, respectively. The same was true for its resistive and elastic components.

Over all the conditions tested, work of breathing was 4.2 (1.0-9.4) J/min with the reference device and the relative variations from it were 0 (0-0), 3 (2-4), 1 (0-1), 2 (1-2), 1 (1-2) and 1 (1-2) % with Airvo2, G5, HM80, T60, V500 and V60 devices, respectively (P<0.05 Kruskal-Wallis test).

Over all the efforts, the WOB was 4.9 (1.1-9.7), 4.3 (1.1-9.7), 4.3 (1.1-9.8), 4.2 (1.1-9.7), 4.6 (1.1-9.7), 4.9 (1.1-9.7), and 4.9 (1.1-9.7) J/min for Optiflow, Airvo2, G5, HM80, T60, V500 and V60 devices, respectively, at HFNC 20 L/min (Table 2), with a significant interaction between effort intensity and rate. The same was true at 40 and 60/min HFNC for total (Figure 3) and resistive (Figure 4) and elastic (Figure 5) values of WOB. As of the 18 instances (3 effort intensities x2 effort rates x3 HFNC flows) for each device (except for V500 with 12 instances), the comparison to the reference device showed that the total WOB was significantly higher than Optiflow in 83% (15/18) for Airvo2, 83% (15/18) for G5, 50% (9/18) for HM80, 61% (11/18) for T60, 66% (8/12) for V500 and 50% (9/18) for V60 and it was significantly lower than Optiflow in 0, 5.5 (1/18), 11 (2/18), 16 (3/18), 17 (2/12) and 12% (2/18) for the corresponding devices, respectively. The resistive WOB was lower than Optiflow in no instance for each device and it

was significantly higher than with Optiflow in 50 (9/18), 44 (8/18), 44 (8/18), 28 (5/18), 50 (6/12) and 17% (2/18) for the corresponding devices, respectively. The elastic WOB was not significantly lower than Optiflow with any device. It was significantly higher than Optiflow in 44 (8/18), 33 (6/18), 22 (4/18), 5.5 (1/18), 33 (4/12) and 39% (7/18) of the cases for the corresponding devices, respectively. The threshold of 30% difference between devices was never reached.

### **Positive end-expiratory pressure**

Over the all conditions tested PEEP was 0.9 (0.3-1.5) cmH<sub>2</sub>O with Optiflow and the relative differences were 28 (22-33), 41 (38-46), 30 (26-36), 31 (28-34), 37 (32-42), and 24 (21-34) % with Airvo2, G5, HM80, T60, V500 and V60 devices, respectively (P<0.05 Kruskal-Wallis test).

The PEEP generated by the high flow oxygen increased with increasing oxygen flow rate, as expected. This was the case with any device (Figure 6). However, the level of that PEEP was consistently (100% of the occurrences for each device) higher with the Optiflow device than with any other and the median difference between devices and reference was lower than 30% (Figure 6). The difference in PEEP between Optiflow and other devices increased with increasing flow. PEEP never surpassed 2 cmH<sub>2</sub>O.

### **Tidal volume and peak flows**

As can be seen in tables 1-3 in the supplementary materials the inspired tidal volume with the devices were higher than that with the reference. Even though these differences may not be clinically relevant they explain why the WOB is slightly higher with them than with reference. The same was true regarding the values of peak inspiratory and expiratory flows, which were consistently higher with the devices than with the reference.

## **Cost estimates**

Setting to 1 the overall cost of the reference, the cost amounted to 1.17, 10.7, 1.46, 6.1, 11.8 and 6.3 for Airvo2, G5, HM80, T60, V500 and V60, respectively.

## **DISCUSSION**

The main findings of present study, which is the first to compare on the bench the effect of HFNC devices on the WOB, can be summarized as follows: 1) the total WOB was higher with the HFNC devices than with the reference device, 2) the differences were very small and may not be clinically relevant, 3) the PEEP generated by the devices were lower with the HFNC devices than with the reference.

In patients with acute hypoxemic respiratory failure the high flow of oxygen relieves patient's effort and the WOB decreases as compared to the pre-HFNC condition, i.e. low oxygen flow. By contrast the bench set-up, by nature, does not allow any interaction between patient's effort and oxygen flow delivery, i.e. no change in patient's effort in response to higher oxygen flow as compared to the baseline condition. Therefore, after having checked that the baseline condition was the same before each HFNC device was run, the comparisons between devices, our main goal, were performed at a given flow oxygen. Furthermore, with increasing effort in present study the WOB increased due to higher tidal volume. Therefore, the increased WOB was also partly due to the higher tidal volume resulting from higher effort.

It makes sense to compare the devices from a reference device and to use as such the original device used and tested in a landmark clinical trial. A good appraisal of the values of WOB measured in present study is informed by comparing them with data reported in the literature. As

an example, in patients treated with HFNC the WOB was almost 4.5 J/min before HFNC<sup>9</sup>. This level of WOB was almost reached in present study at 40 L/min oxygen flow for a medium effort (Figure 3). In the study by Delorme et al.<sup>1</sup>, the total WOB went down to 3.5 and 2.0 J/min at 40 and 60 L/min HFNC, respectively.

The total WOB was indeed very close between devices, including the reference device, which is a positive result as regards of different perspectives. HFNC was used in many fields before the COVID pandemic<sup>14</sup> and has expanded with the COVID-19 pandemic in many locations managing the patients. Our results suggest that HFNC device would not adversely affect patients in terms of WOB. The enrollment of different centers in studies on HFNC would not be hindered by the fact that the different centers used different HFNC. It should be noted, however, that the decreased elastic WOB resulting from increased compliance with higher oxygen flow in patients<sup>9</sup> can be offset by the higher elastic WOB with some devices according to present result (Figure 5).

The most striking difference, even modest, between devices found in present study was about the PEEP generated. It was lower with the devices than with the reference device. These differences were small, < 2 cmH<sub>2</sub>O, but suggest that the regulation of oxygen flow delivery was different between the devices with an apparent advantage for the most recent devices. However, the PEEP generated by the device is a mechanism by which HFNC improves oxygenation in patients as the end-expiratory lung volume increases with PEEP<sup>15</sup>. Assuming a lung compliance of 60 ml/cmH<sub>2</sub>O in patients would expect a change in lung volume by 60 ml for a change in PEEP by 1 cmH<sub>2</sub>O. This value looks negligible. However, it is the mean increase in dependent or non-dependent end-expiratory lung volume at HFNC 45 L/min, and hence half of the overall increase in end-expiratory lung volume, assessed by lung electrical impedance tomography in patients<sup>11</sup>.

Therefore, this result of a different PEEP between HFNC devices may be clinically relevant regarding the change in oxygenation it may promote and warrants further investigations in patients.

**Limitations and strengths.** In addition to the intrinsic limitation of a bench study to assess the relationship between inspiratory effort and WOB mentioned above, present study did not investigate the difference in devices in terms of  $F_{I}O_2$  and humidification performance. Another issue not herein covered is the risk of environment contamination due to high oxygen flow. This risk was raised up at the onset of COVID pandemic and may have contributed to an early intubation strategy during the first wave. Studies done then found that the risk was limited. The implication for humans is also a limitation of present study because the effect of hypoxia or hypercapnia could not be tested in our preparation. We did not change the respiratory mechanics. Finally, we tested configuration for adults, which are different in children and neonates. Our study is strengthened by a rigorous and objective evaluation of the devices in controlled conditions, the fact that a baseline condition was assessed before HFNC process with the devices and that this baseline was similar across each of them.

## CONCLUSIONS

As compared to the reference HFNC device the most recent devices were associated with higher WOB but these differences were likely meaningless in term of clinical impact. The PEEP generated by the devices were lower than with the reference, which may have clinical relevance.



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## Legends for figures

**Figure 1.** Schematic drawing-up of the set-up. In the bottom-left representative tracing recorded by ASL5000 during baseline condition with the Optiflow device without cannula. Paw: airway pressure, Pmus: muscular pressure.

**Figure 2.** Method used to measure the work of breathing. Panel A: Tile waves of flow and volume (right vertical axis) and airway (Paw), muscular (Pmus), chest wall elastic recoil (Pel,cw) pressures (left vertical axis) against time over one breath recorded with Optiflow device, strong effort, respiratory rate 30 breaths/min without cannula and without oxygen flow , i.e. baseline condition. Panel B: Campbell diagram with volume on the Y axis and Pressure on the X axis. The area subtended by lung elastic recoil (Pel,L green line) and Pmus-Patm (black curve) to the left defines the inspiratory work of breathing in the baseline condition. The yellow line is the elastic recoil of the chest wall (Pel,cw).

**Figure 3.** Box-and-Whisker plots of the total work of breathing (done by the lung, the device and the nasal cannula) at 20 and 30 breaths/min and low, medium and high respiratory efforts for 20, 40 and 60.L/min oxygen flow across the devices. There is no data for the V500 device at 60 L/min as the highest flow achieved with it is 50 L/min. \*P<0.00005 vs Optiflow device taken as the reference. The blue lines drawn along the median values of the Optiflow device.

**Figure 4.** Box-and-Whisker plots of the resistive work of breathing done by the lung, the device and the nasal cannula at 20 and 30 breaths/min and low, medium and high respiratory efforts for 20, 40 and 60.L/min oxygen flow across the devices. There is no data for the V500 device at 60 L/min as the highest flow achieved with it is 50 L/min. \*P<0.00005 vs Optiflow device taken as the reference. The blue lines drawn along the median values of the Optiflow device.

**Figure 5.** Box-and-Whisker plots of the elastic work of breathing done by the lung, the device and the nasal cannula at 20 and 30 breaths/min and low, medium and high respiratory efforts for 20, 40 and 60.L/min oxygen flow across the devices. There is no data for the V500 device at 60 L/min as the highest flow achieved with it is 50 L/min. \*P<0.00005 vs Optiflow device taken as the reference. The blue lines drawn along the median values of the Optiflow device.

**Figure 6.** Box-and-Whisker plots of the positive end expiratory pressure (PEEP) generated at 20 and 30 breaths/min and low, medium and high respiratory efforts for 20, 40 and 60 L/min oxygen flow across the devices. There is no data for the V500 device at 60 L/min as the highest flow achieved with it is 50 L/min. \*P<0.00005 vs Optiflow device taken as the reference. The blue lines drawn along the median values of the Optiflow device. Values are median (1st-3rd quartiles) in J/min. NA: not available: this device does not generate 60 L/min oxygen flow

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## **Quick Look**

### **Current knowledge.**

High flow oxygen is increasingly used worldwide in patients with acute hypoxemic respiratory failure. In the meantime there is also a growing number of devices to deliver the treatment.

Whether or not these devices affect the work of breathing (WOB) differently has not been studied. **What This Paper Contributes To Our Knowledge**

In a bench study we measured the WOB among six devices used to deliver high flow oxygen through nasal cannula. As compared to original device, the WOB did not differ significantly with the new devices.

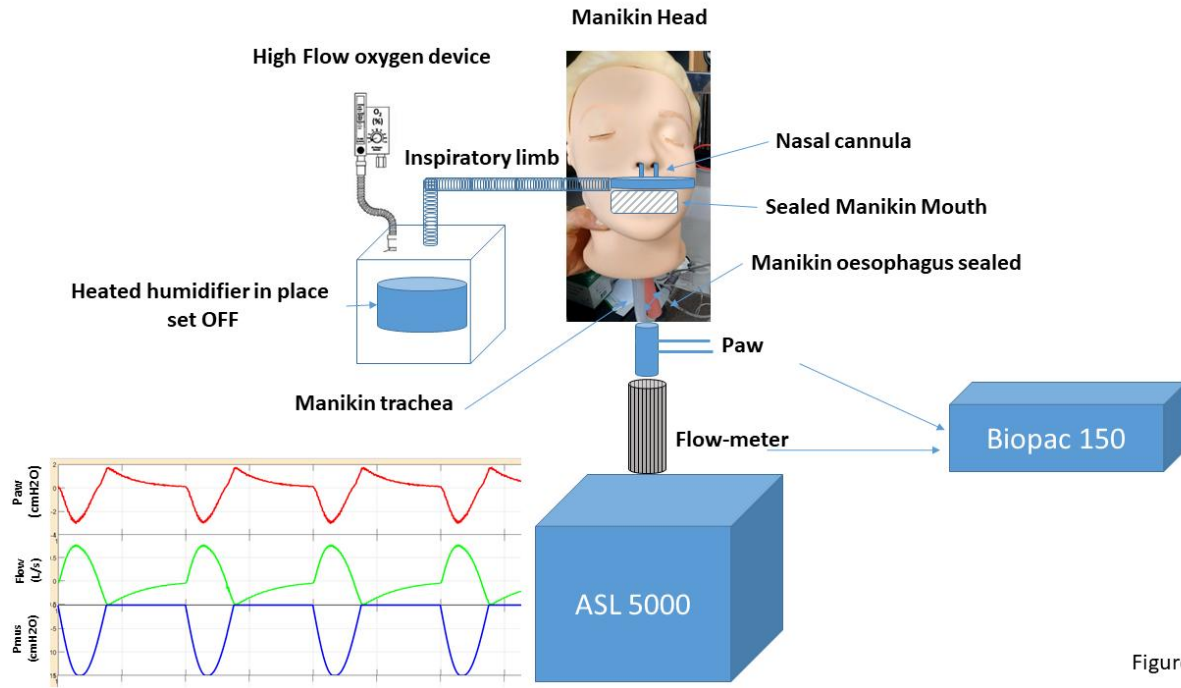


Figure 1.

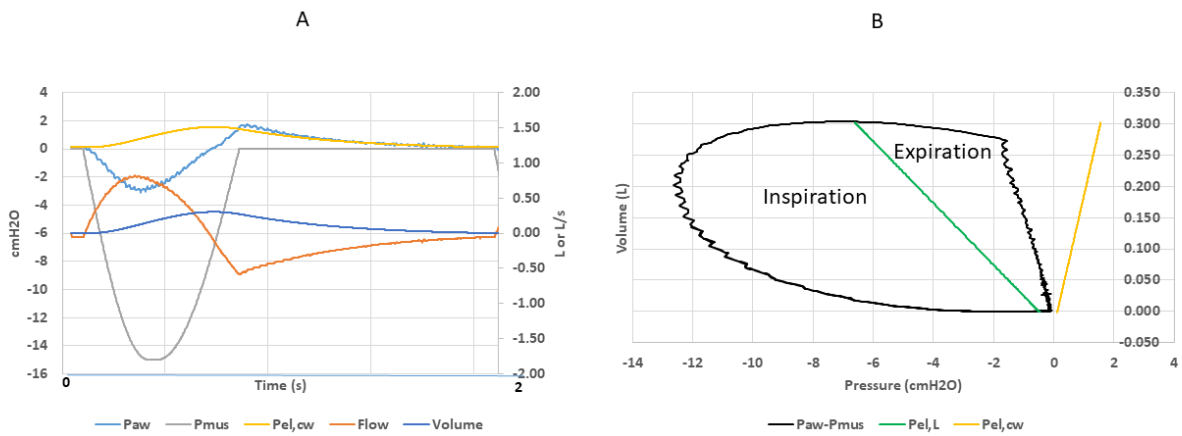


Figure 2

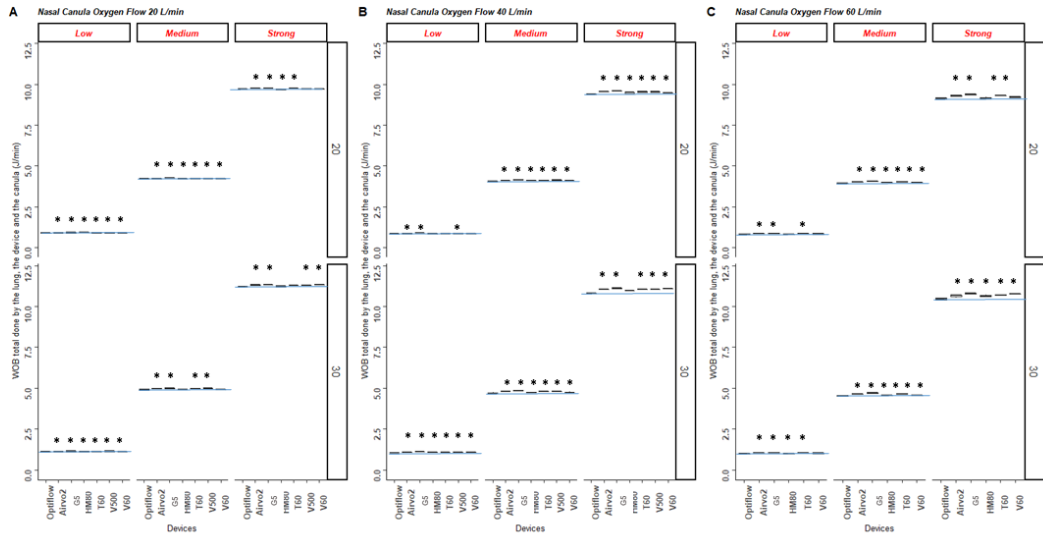


Figure 3

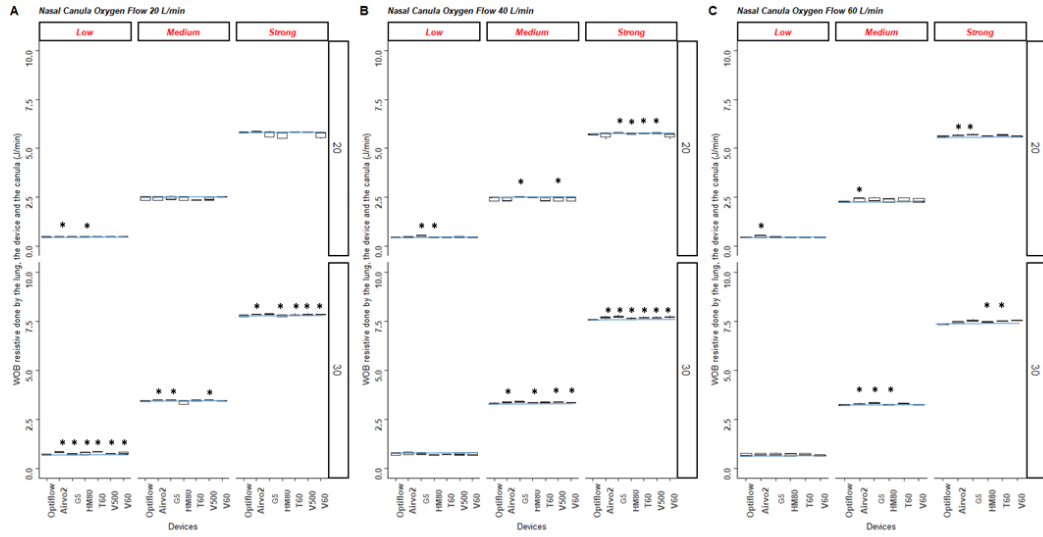


Figure 4

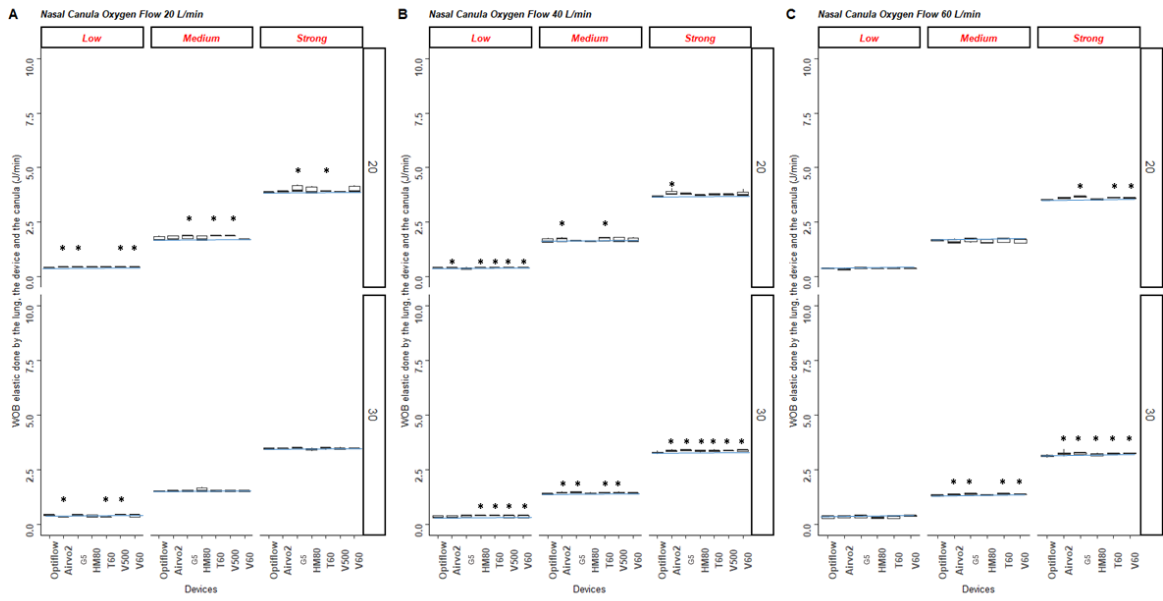


Figure 5

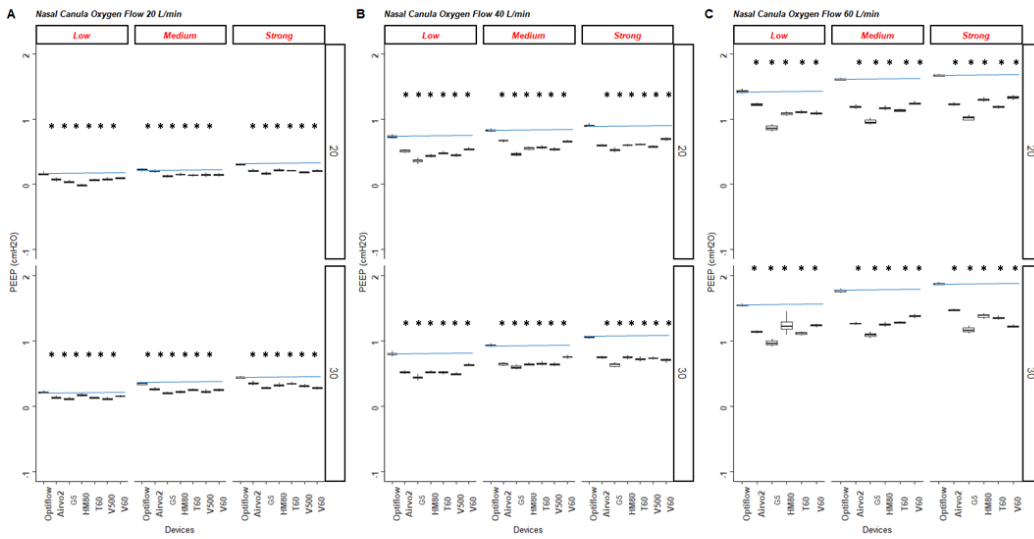


Figure 6