# Hygrometric Performances of Different High-Flow Nasal Cannula Devices: Bench Evaluation and Clinical Tolerance

Mathieu Delorme, Pierre-Alexandre Bouchard, Serge Simard, and François Lellouche

**BACKGROUND: High-flow nasal cannula (HFNC) is increasingly used for the management of respiratory failure. Settings include $F_{IO_2}$, total gas flow, and temperature target. Resulting absolute humidity (AH) at the nasal cannula may affect clinical tolerance, and optimal settings with respect to hygrometry remain poorly documented. METHODS: A bench study was designed to assess AH delivered by 4 HFNC devices (Optiflow, Airvo 2, Precision Flow, and Hydrate) according to flow, ambient temperature, and other available settings. Clinical tolerance of different levels of hygrometry (20, 30, and 40 mg $H_2O$/L) was evaluated in 15 healthy volunteers. RESULTS: With $F_{IO_2}$ set at 1.0, normal ambient temperature, and settings made accordingly to the manufacturers' recommendations, mean ± SD AH was 42.2 ± 3.1, 39.5 ± 1.8, 35.7 ± 2.0, and 32.9 ± 2.7 mg $H_2O$/L for the Airvo 2, Optiflow, Hydrate, and Precision Flow, respectively, ($P < .001$). AH dropped from −3.5 to −10.7 mg $H_2O$/L ($P <. 001$) with high ambient temperature, except for the Precision Flow. Increasing flow did not significantly affect AH except for the Precision Flow (from 36.4 ± 1.6 to 29.8 ± 0.2 mg $H_2O$/L at 10 and 40 L/min, respectively, [$P < .001$]). The lowest AH was encountered with the Optiflow set with noninvasive ventilation (NIV) mode, without compensation algorithm, and at high ambient temperature (14.2 ± 1.5 mg $H_2O$/L). In studied subjects, AH significantly affected breathing comfort, reduced from 7.0 ± 1.0 to 3.0 ± 2.0 at 40 and 20 mg $H_2O$/L, respectively, ($P < .001$). Comfort was similar at 30 and 40 mg $H_2O$/L. CONCLUSIONS: When used according to manufacturer's recommendations and at normal ambient temperature, all the HFNC devices evaluated achieved satisfactory hygrometric output with respect to breathing comfort evaluated in healthy subjects (≥ 30 mg $H_2O$/L). Substantial differences exist between devices, and optimal knowledge of their working principles is required as inappropriate usage may dramatically alter efficacy and clinical tolerance.** *Key words: High-flow nasal cannula; humidification performances; absolute humidity; psychrometry; breathing comfort.* [Respir Care 2021;66(11):1720–1728. © 2021 Daedalus Enterprises]

## Introduction

High-flow nasal cannula (HFNC) devices have been developed and introduced in the market over the past decade.[1,2] They deliver flows up to 60 L/min, and $F_{IO_2}$ can be adjusted from 0.21 to nearly 1.0. Several large-scaled, randomized, controlled trials comparing HFNC to conventional oxygen therapy in patients with various etiologies of acute hypoxemic respiratory failure have reported conflicting results in terms of respiratory complications or survival.[3-6] However, HFNC is frequently used in the management of acute hypoxemic respiratory failure.[7-9]

The use of high flows allows better control of delivered $F_{IO_2}$,[10] but beyond this, many physiological and clinical

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benefits have been suggested.[11,12] HFNC devices have repeatedly been reported to improve comfort,[3,13-15] decrease breathing frequency[3,6,16-19] and respiratory effort[20-23] in comparison with conventional oxygen therapy. Thus, these benefits have promoted the widespread use of this therapy.

Of note, besides the well-described detrimental effects of dry and cold gas inhalation on airway mucosa,[24,25] the use of high flows has been shown to markedly affect patient breathing comfort.[26] Actually, the clinical tolerance of such flows during HFNC is allowed by the delivery of heated and humidified gas, significantly reducing mouth and throat dryness.[13,26] There is, nevertheless, a paucity of data available in the literature regarding hygrometric performances of HFNC devices, even though this aspect is likely to play a major role in patient tolerance and thus in the treatment success.

We, therefore, designed this study to evaluate the impact of different hygrometric levels on the comfort of breathing in healthy volunteers and to assess the hygrometric performances of several available HFNC devices under various conditions.

**QUICK LOOK**

**Current knowledge**

The clinical tolerance of high-flow nasal cannula (HFNC) has been repeatedly suggested to be related to adequate warming and humidification of respiratory gases, but the technical performances of available devices and clinical tolerance of different levels of hygrometry remain poorly documented. Consequently, clinical recommendations in terms of hygrometric output for HFNC are lacking.

**What this paper contributes to our knowledge**

Common HFNC devices can deliver adequate inspiratory humidity during optimal conditions, but substantial under-humidification may occur with high ambient temperature, high flows, and low target temperature. Our data suggest delivering a minimum humidity target around 30 mg $H_2O$/L during HFNC therapy.

## Methods

### Clinical Study

**Subjects.** The ethics review board of the Institut Universitaire de Cardiologie et de Pneumologie de Québec approved the study protocol (# 21115), and all subjects gave their written informed consent prior to enrollment. Eligibility was assessed by a medical questionnaire confirming the absence of any significant respiratory disease, rhinitis, or chronic medication.

**Protocol.** Subjects underwent 3 sessions of HFNC performed under 3 randomized hygrometric conditions: 20, 30, and 40 mg $H_2O$/L of absolute humidity (AH). During every session, the flow was set at 40 L/min, and the $F_{IO_2}$ was set at 0.21. Ambient temperature in the laboratory was set at 21°C. The target values of AH of inspired gases were achieved with the use of specific settings on the MR730 heater humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) and controlled before each evaluation by psychrometric measurements (Supplemental Fig. 2) (see the supplementary materials at http://www.rcjournal.com).[27,28] Each session lasted for 10 min, with a 5-min wash-out period in between. Subjects were blinded for the tested condition.

**Measurements.** At the end of each session, subjects were asked to evaluate their breathing comfort on a 10-cm visual analog scale, ranging from 0 (extremely uncomfortable) to 10 (extremely comfortable). Subjects were also asked on a 4-point scale to score their nasal dryness (from 0 = no dryness to 3 = severe dryness) and the presence of nasal droplets (from 0 = no droplets to 3 = numerous droplets).

### Bench Study

We tested 4 devices with different working principles: Optiflow and Airvo 2 (Fisher & Paykel Healthcare, Auckland, New Zealand), Precision Flow (Vapotherm, Stevensville, Maryland), and Hydrate Omni (Hydrate, Midlothian, Virginia) (Supplemental Fig. 1). All these devices increase water content in inspiratory gases but through different technologies described in the online supplement (see the supplementary materials at http://www.rcjournal.com).

**Protocol.** HFNC devices were successively evaluated with a randomized sequence of 4 different flows (10, 20, 30, and 40 L/min for Optiflow, Precision Flow, and Hydrate; and 15, 20, 30, and 40 L/min for Airvo 2). Highest flows were also evaluated when available (ie, 50 L/min with Airvo 2 and 60 L/min for Optiflow). During each condition, $F_{IO_2}$ was set to the highest value available ($F_{IO_2}$ max, ie,

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Table 1. Devices and Conditions Evaluated During the Protocol

| Device | Flows Evaluated, L/Min | Ambient Temperature | $F_{IO_2}$* | Settings§ |
|---|---|---|---|---|
| Optiflow | 10, 20, 30, 40, 60 | 22–24°C and 28–30°C | 0.4, 0.6, 1.0 | 31°C‡, 37°C‡ |
| Airvo 2 | 15, 20, 30, 40, 50 | 22–24°C and 28–30°C | 0.21, $F_{IO_2}$ max† | 31°C, 34°C, 37°C |
| Precision Flow | 10, 20, 30, 40 | 22–24°C and 28–30°C | 1.0 | 37°C |
| Hydrate | 10, 20, 30, 40 | 22–24°C and 28–30°C | 1.0 | 37°C |

* With the Optiflow, the effects of $F_{IO_2}$ were only evaluated at 30 and 60 L/min under normal ambient temperature (22–24°C). For the Airvo 2, the effects of $F_{IO_2}$ were tested with all flows under both conditions of ambient temperatures.
† For the Airvo 2, $F_{IO_2}$ max corresponds to approximately 90%.
‡ For the Optiflow, 31°C and 37°C, respectively, refer to "noninvasive ventilation" and "invasive" modes.
§ For the Optiflow, additional measurements were performed with and without compensation algorithm activated.

approximately 100%). An evaluation of the effects of different $F_{IO_2}$ with the Optiflow and Airvo 2 is provided in the online supplement. As ambient air temperature can markedly affect hygrometric performances of heated-wire humidifiers,[29] we performed all measurements under normal (22–24°C) and high ambient temperatures (28–30°C). The target temperature on the devices was set at 37°C or "invasive" mode, as recommended by manufacturers for HFNC usage. Conditions evaluated are summarized in Table 1.

All devices evaluated propose adjustable temperature that can be modified by 1°C increments (Precision Flow, Hydrate) or be driven by "pre-settings" regulating the temperature at the outlet of the humidification chamber ("invasive" and "noninvasive ventilation" ["NIV"] modes with the Optiflow and 37°C, 34°C, and 31°C with the Airvo 2). We, therefore, performed additional measurements to evaluate these pre-settings with the Optiflow and Airvo 2 with both normal and high ambient temperatures. We also performed measurements with the Optiflow with and without compensation algorithm activated.[29] Measurements of the humidity of medical oxygen with and without cold humidification were also performed at 10 L/min with standard oxygen circuits to be used as comparison values.

**Measurements.** Hygrometric measurements were performed after 2 h of steady state using the psychrometric method on which additional information is provided in the online supplement.[27,28] Measurements were taken on the distal part of the circuit, that is, just before the nasal cannula (Supplemental Fig. 2) (see the supplementary materials at http://www.rcjournal.com). For each condition, 3 measurements were obtained on separate days, and results are given as mean ± SD.

### Statistical Analysis

The clinical part of the trial consisted of subjects on HFNC randomized to 3 hygrometric conditions. A general linear mixed model using a multinomial distribution and a cumulative link function was defined to analyze their nasal dryness, nasal droplets, and their breathing comfort. The first part of the bench study was designed to evaluate 4 HFNC devices with a randomized sequence of 2 room air temperature conditions. After a room air condition was assigned to the device, the 4 different flows were applied in random order. The split-plot statistical model was performed to analyze as a crossover design for the device, and temperature was used, and flows were nested into a condition [or "trial"] using room air. Using this statistical approach, interaction factors were significant. To simplify the statistical analyses, each device was analyzed separately. This approach allowed us to analyze all the flows for Airvo 2 and Optiflow devices. The second part of the trial compared the effects of switching on and off the compensation algorithm for the Optiflow device. Crossover for flows and algorithm factors was nested within an algorithm status. Separate split-plot analyses were performed for the intubation and NIV modes, respectively. The third part of the trial was to analyze the Airvo 2 device at the different preset temperatures. Air room condition and flows were analyzed as crossed factors. The normality hypothesis was verified using the Shapiro-Wilk test using residuals from the statistical model. The results were considered significant when $P$ value was below the 5% threshold. All these statistical analyses were carried out using SAS v9.4 (SAS Institute, Cary, North Carolina).

## Results

### Clinical Study

Fifteen subjects (age 33 ± 8 y, 9 males) participated in the study. Breathing comfort was significantly lower at 20 mg $H_2O$/L compared to 30 and 40 mg $H_2O$/L, respectively, 3.0 ± 2.0 versus 7.0 ± 2.0 versus 7.0 ± 1.0 ($P < .001$) (Fig. 1). Nasal dryness sensation was more pronounced at 20 mg $H_2O$/L compared to 30 and 40 mg $H_2O$/L, respectively, 1.9 ± 1.1 versus 0.5 ± 0.8 versus 0.2 ± 0.4 ($P = .004$)

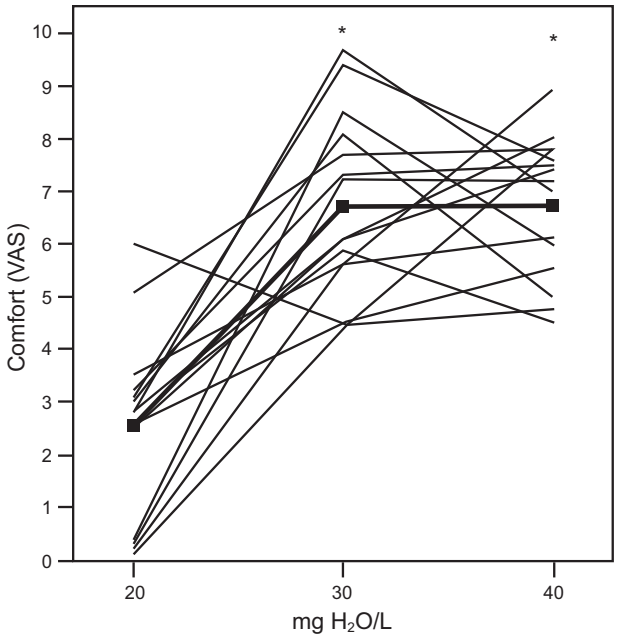


Fig. 1. Breathing comfort of healthy subjects according to the hygrometry of HFNC. *$P \geq .001$ in comparison with 20 mg $H_2O$/L. Each line represents the breathing comfort evaluated on a 10-cm visual analog scale after 10 min of HFNC set at 40 L/min with varying humidity levels for each subject (blind for the conditions). Mean breathing comfort is represented by the bold line.

(Supplemental Fig. 3) (see the supplementary materials at http://www.rcjournal.com). The presence of nasal droplets increased with hygrometric level delivered, from 0.4 ± 0.6 to 0.5 ± 0.8 and 0.8 ± 0.8 at 20, 30, and 40 mg $H_2O$/L, respectively, ($P = .25$) (Supplemental Fig. 4) (see the supplementary materials at http://www.rcjournal.com). All but one subject stated that they preferred when flow was delivered at 30 or 40 mg $H_2O$/L (respectively, 6 and 8 subjects).

## Bench Study

In total, we performed 366 hygrometric measurements, evaluating 122 different conditions of HFNC delivery that can be summarized as follows.

Conventional oxygen therapy with wall medical oxygen set at 10 L/min delivers hygrometric levels of 2.3 ± 0.3 mg $H_2O$/L and 15.9 ± 0.5 mg $H_2O$/L when administered without and with cold humidification systems, respectively. All flows combined, the highest level of hygrometry was found with the Airvo 2 set at 37°C with normal ambient temperature (41.5 ± 3.1 mg $H_2O$/L); and the lowest was found with the Optiflow set in "NIV" mode, with the compensation algorithm switched off with high ambient temperature (14.2 ± 1.5 mg $H_2O$/L).

**Impact of device on delivered humidity.** With flows ranging from 10–15 to 40 L/min (available for all devices), normal ambient temperature (22–24°C) and settings made accordingly to the manufacturers' recommendations (ie, target temperature set at 37°C or "invasive" mode, compensation algorithm activated when available), all the devices evaluated delivered hygrometric levels close to or above 30 mg $H_2O$/L. On average, the hygrometry was higher with the Airvo 2 in comparison with the Optiflow, the Hydrate, and the Precision Flow (42.2 ± 3.1, 39.5 ± 1.8, 35.7 ± 2.0, and 32.9 ± 2.7 mg $H_2O$/L, respectively, $P < .001$). With high ambient air temperature (28–30°C), the Optiflow provided the highest humidity, followed by the Precision Flow, the Hydrate, and the Airvo 2 (35.9 ± 2.0, 34.5 ± 3.2, 32.2 ± 0.5, and 31.4 ± 3.0 mg $H_2O$/L, respectively, $P < .001$) (Fig. 2).

**Impact of ambient temperature on delivered humidity** Modification of ambient temperature (with flows ranging from 10–15 to 40 L/min) significantly modified the hygrometry delivered by the devices. From normal to high ambient temperatures, the hygrometry delivered by the Optiflow, Airvo 2, and Hydrate was reduced by 3.6, 10.7, and 3.5 mg $H_2O$/L, respectively, ($P < .001$), whereas the hygrometry delivered by the Precision Flow increased by 1.6 mg $H_2O$/L ($P = .11$) (Fig. 2). The impact of ambient temperature was similar for low flows (−3.9 mg $H_2O$/L for flows ≤ 20 L/min) and high flows (−4.0 mg $H_2O$/L for flows ≥ 30 L/min) (Supplemental Table 1) (see the supplementary materials at http://www.rcjournal.com).

**Impact of flow on delivered humidity.** The effect of flow setting differed according to the devices and the conditions evaluated. Results obtained with temperature target at 37°C or "invasive" mode (when available) and compensation algorithm activated (when available) are displayed in Table 2 for normal ambient temperatures (22–24°C) and high ambient temperatures (28–30°C). A summary of the effects of flow on hygrometry merging normal and high ambient temperature is provided in Figure 3.

**Combination of different parameters on delivered humidity.** For the Optiflow, the hygrometry delivered at normal ambient temperature was significantly lower with "NIV" mode (31°C at the humidification chamber) in comparison with "invasive" mode (37°C at the humidification chamber) (23.3 ± 2.1 mg $H_2O$/L vs 39.9 ± 1.9 mg $H_2O$/L, respectively, $P < .001$). The impact of this setting was found with low (≤ 20 L/min) and high (≥ 30 L/min) flows as well as with normal (22–24°C) and high (28–30°C) ambient temperatures (Table 3 and Supplemental Table 2) (see the supplementary materials at http://www.rcjournal.com). The maximum humidity drop was encountered with high flows and normal ambient temperature (reduction of 18.2 mg $H_2O$/L with "NIV" mode compared to "invasive" mode,

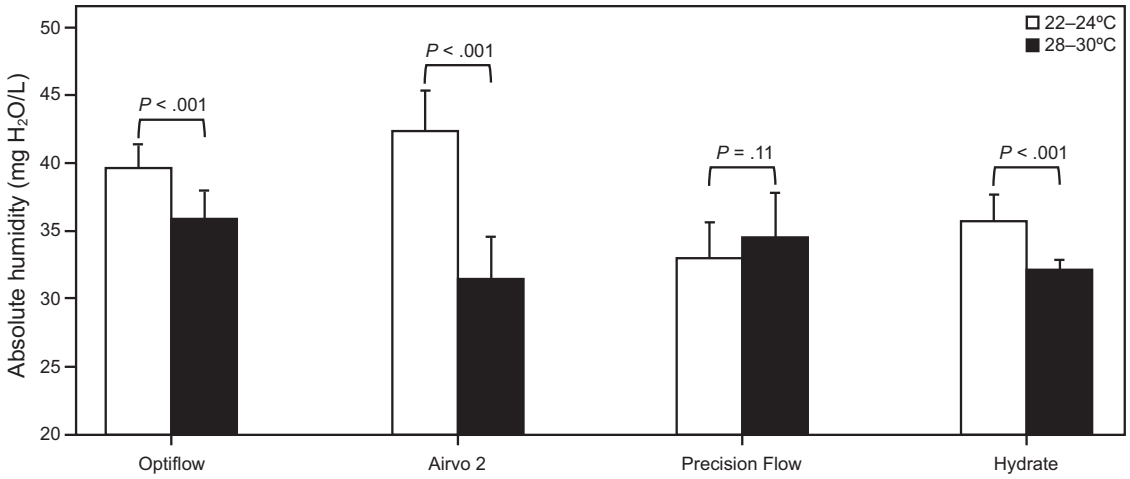


Fig. 2. Absolute humidity delivered according to device and ambient temperature. Units are expressed as mean ± SD mg $H_2O$/L (absolute humidity). The values presented are averaged from flows ranging from 15–20 L/min to 40 L/min (available for all devices) and were obtained with normal (22–24°C) and high (28–30°C) ambient temperatures, $F_{IO_2}$ set at its maximum, temperature target set at 37°C or invasive mode (when available), and compensation algorithm activated (when available).

Table 2. Hygrometry Delivered With Settings Made According to the Manufacturer's Recommendations

| | 10–15 L/Min | 20 L/Min | 30 L/Min | 40 L/Min | 50–60 L/Min | *P* |
|---|---|---|---|---|---|---|
| Optiflow | | | | | | |
| 22–24°C | 37.3 ± 1.3 | 38.9 ± 0.6 | 39.8 ± 0.3 | 41.8 ± 0.2 | 41.5 ± 1.1 | .008 |
| 28–30°C | 37.0 ± 3.0 | 36.0 ± 2.7* | 34.8 ± 1.4* | 35.6 ± 0.7* | 36.3 ± 0.7* | .50 |
| Airvo 2 | | | | | | |
| 22–24°C | 41.8 ± 3.9 | 44.2 ± 0.4 | 39.1 ± 3.9 | 43.6 ± 0.4 | 38.8 ± 1.0 | .009 |
| 28–30°C | 28.9 ± 2.3* | 29.9 ± 0.2* | 31.1 ± 1.0* | 35.8 ± 1.3* | 37.9 ± 0.3 | < .001 |
| Precision Flow | | | | | | |
| 22–24°C | 35.0 ± 0.8 | 35.3 ± 0.6 | 31.7 ± 2.0 | 29.6 ± 0.2 | – | < .001 |
| 28–30°C | 37.7 ± 0.3* | 36.6 ± 0.4 | 33.8 ± 0.2* | 29.9 ± 0.2 | – | < .001 |
| Hydrate | | | | | | |
| 22–24°C | 33.2 ± 0.3 | 36.0 ± 0.6 | 38.1 ± 0.4 | 35.3 ± 1.9 | – | < .001 |
| 28–30°C | 32.2 ± 0.7 | 32.1 ± 0.4* | 32.5 ± 0.6* | 32.0 ± 0.3* | – | .92 |

*$P \leq .05$ in comparison with normal ambient temperature.
Units are expressed as mean ± SD mg $H_2O$/L (absolute humidity). For all flows and devices, the values presented were obtained with normal (22–24°C) and high (28–30°C) ambient temperatures, $F_{IO_2}$ set at its maximum, temperature target set at 37°C or "invasive" mode (when available), and compensation algorithm activated (when available).
Conventional oxygen therapy with wall medical oxygen set at 10 L/min delivers hygrometric levels of 2.3 ± 0.3 mg $H_2O$/L and 15.9 ± 0.5 mg $H_2O$/L when administered without and with cold humidification systems, respectively.

P <. 001) (Supplemental Table 2) (see the supplementary materials at http://www.rcjournal.com). For the Airvo 2, decreasing temperature setting significantly decreased hygrometry at normal ambient temperature, from 41.5 ± 3.1 mg $H_2O$/L at 37°C to 28.6 ± 2.8 mg $H_2O$/L at 31°C (*P* < .001) (Table 3). The impact of this setting was found in every tested condition, and the maximum humidity drop was encountered with low flows and normal ambient temperature (reduction of 15.0 mg $H_2O$/L at 31°C compared to 37°C, *P* < .001) (Supplemental Table 2) (see the supplementary materials at http://www.rcjournal.com).

With the Optiflow, switching off the compensation algorithm with normal ambient temperature did not significantly modify the hygrometry delivered by the device, both with "invasive" and "NIV" modes. However, with high ambient temperature, switching off the compensation algorithm significantly reduced the hygrometry from 36.0 ± 1.8 mg $H_2O$/L to 33.0 ± 1.5 mg $H_2O$/L with "invasive" mode (reduction of 2.9 mg $H_2O$/L, *P* = .001) and from 23.8 ± 3.3 mg $H_2O$/L to 14.2 ± 1.5 mg $H_2O$/L with "NIV" mode (reduction of 9.7 mg $H_2O$/L, *P* < .001) (Supplemental Table 3).

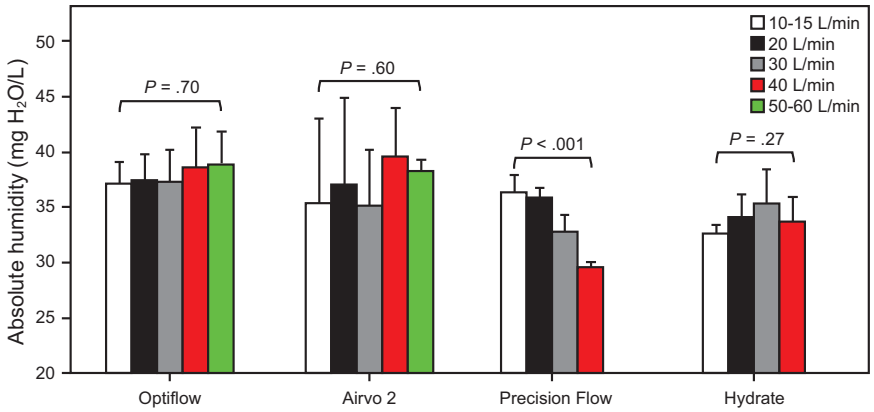


Fig. 3. Effects of flow setting on absolute humidity. Units are expressed as mean ± SD mg $H_2O$/L (absolute humidity). The values presented are averaged from measurements obtained with normal (22–24°C) and high (28–30°C) ambient temperatures, $F_{IO_2}$ set at its maximum, temperature target set at 37°C or invasive mode (when available), and compensation algorithm activated (when available).

Table 3. Hygrometry Delivered According to Target Temperature Setting

| | 37°C "Invasive" mode | 34°C | 31°C "NIV" mode | *P* |
|---|---|---|---|---|
| Optiflow | | | | |
| 22–24°C | 39.9 ± 1.9 | – | 23.3 ± 2.1 | < .001 |
| 28–30°C | 36.0 ± 1.8* | – | 24.2 ± 3.4 | < .001 |
| Airvo 2 | | | | |
| 22–24°C | 41.5 ± 3.1 | 29.5 ± 5.6 | 28.6 ± 2.8 | < .001 |
| 28–30°C | 32.7 ± 3.8* | 21.7 ± 3.1* | 22.3 ± 1.5* | < .001 |

*$P \leq .05$ in comparison with normal ambient temperature.
Units are expressed as mean ± SD mg $H_2O$/L (absolute humidity). The values presented are averaged from all flows evaluated for each device and obtained with normal (22–24°C) and high (28–30°C) ambient temperature, $F_{IO_2}$ set at its maximum, and compensation algorithm activated (when available).

**Impact of $F_{IO_2}$ on delivered humidity.** $F_{IO_2}$ did not significantly affect humidity delivered with Optiflow. On the contrary, with Airvo 2, the mean humidity delivered was 35.9 ± 5.3 mg $H_2O$/L with $F_{IO_2}$ set at 0.21 and 29.4 ± 7.5 mg $H_2O$/L with $F_{IO_2}$ max ($P < .001$). The effects of different $F_{IO_2}$ with Optiflow and Airvo 2 are detailed in the online supplement and presented in Supplemental Figures 5 to 7 (see the supplementary materials at http://www.rcjournal.com).

## Discussion

Our results show that when used according to manufacturer's recommendations and when ambient temperature is normal all the evaluated HFNC devices achieved satisfactory hygrometric output (≥ 30 mg $H_2O$/L) with respect to breathing comfort evaluated in healthy subjects. In the clinical evaluation in healthy subjects, inspired humidity of 30 and 40 mg $H_2O$/L was equivalent in terms of comfort but much better tolerated in comparison with 20 mg $H_2O$/L.

These data are consistent with previous bench evaluations performed by Chikata et al[30] under intermediate room air condition (25.6 ± 0.5°C) in which they found that Airvo 2 and Optiflow provided AH from 35.3 ± 2.0 to 37.6 ± 2.1 mg $H_2O$/L and 33.1 ± 1.5 to 36.2 ± 1.8 mg $H_2O$/L, with flows ranging from 20 to 50 L/min, respectively. Nevertheless, our results underline that substantial differences exist between the devices and that their inner characteristics (principles of operation, algorithms) may yield different behavior for a similar situation. For instance, all evaluated devices reduced their hygrometric performances in the condition of high ambient temperature except the Precision Flow. It can be speculated for this device that high ambient temperature reduced the temperature drop of the water circulating along the circuit, thus promoting better AH in the delivered gases compared to normal ambient temperature. Conversely, the decreased hygrometric output at 28–30°C with other devices might be explained by a downregulation of the heater plate temperature promoted by high ambient temperature, therefore reducing water vapor content in the air flow. From our results, it should be emphasized that following manufacturer's recommendations provided satisfactory performances in most situations whereas inappropriate usage may dramatically alter devices' efficacy (with humidity delivered below 15 mg $H_2O$/L), as previously reported for invasive mechanical ventilation[29,31] and NIV.[32] Several histological studies yielded consistent findings on the detrimental effects of the exposition of airway epithelium to underhumidified gases, increasing airway resistance[33] and promoting airway inflammation.[34] Models of airway mucosa exposed to levels of hygrometry below 15 mg $H_2O$/L reported mucociliary dysfunction proportional to the duration of exposure.[24] On the opposite, clinical data

suggest improved mucociliary clearance with the use of HFNC adequately heated and humidified.[35,36]

Yet, the optimal target of hygrometry of inspiratory gases delivered with HFNC is unclear. Recent guidelines recommend using humidified oxygen for patients who require high-flow oxygen systems for more than 24 h or who report upper airway discomfort due to dryness.[37] In the current study, significant and severe discomfort was achieved in healthy subjects within 10 min of usage of HFNC at 20 mg $H_2O$/L, which supports systematic humidification during HFNC.

Data obtained in healthy subjects suggested that a humidity of inspiratory gases above 15 mg $H_2O$/L could be recommended for NIV to enhance comfort and tolerance.[32] This level may not apply with HFNC as the gas is delivered continuously. Indeed, our data show extremely low tolerance of hygrometric levels of 20 mg $H_2O$/L during HFNC. This finding is in line with data previously reported during oxygen therapy with "intermediate" flows. Chanques et al[26] reported in 30 subjects undergoing oxygen therapy with median flow of 7.8 L/min that mouth and throat dryness were significantly lower using a heater humidifier (30.0 $\pm$ 1.0 mg $H_2O$/L) instead of a bubble humidifier (16.0 $\pm$ 2.0 mg $H_2O$/L). One can expect that the benefits of active humidification during oxygen therapy is even more pronounced with the use of higher flows.[13] The flows provided during HFNC are usually set much higher (20 to 60 L/min).[2] With such continuous high flows, the function of nasal mucosa in humidifying and warming inspiratory gases can be overwhelmed; and the target of humidity during HFNC probably should reach the physiological level of hygrometry at the trachea, that is, $\geq$ 30 mg $H_2O$/L,[38] as recommended for invasive ventilation.[39]

From our results, this corresponds to the "invasive" mode for Optiflow and 37°C for Airvo 2, whatever the flow set and whatever the ambient temperature, in line with manufacturer's recommendations. It is reasonable to state that this temperature setting may apply for the other devices. Lower temperature setting (31 or 34°C) might be proposed for the Airvo 2 with satisfactory hygrometry output in normal conditions (22–24°C). In the Mauri et al study,[40] conducted in patients with acute hypoxemic respiratory failure, comfort was significantly better at 31°C compared to 37°C with the Airvo 2. In this situation, with moderate $F_{IO_2}$ (around 40%), the humidity delivered was probably around 30 mg $H_2O$/L for the 31°C setting and 40 mg $H_2O$/L for the 37°C setting. In the present study, 30 and 40 mg $H_2O$/L were both well tolerated in healthy subjects. However, within a short-term exposure, there was a nonsignificant increase in nasal droplets at 40 mg $H_2O$/L, which may explain the reduced tolerance at 37°C in the Mauri study in which participants were exposed to this setting twice as long as in the current study. Along with our results, the study from Mauri et al[40] provides valuable insight for setting temperature target at patient's bedside, suggesting that a compromise between comfort and optimal delivered humidity can be found under normal ambient temperatures within the range of settings proposed in this device (31, 34, and 37°C). This may be even more relevant in the situations of long-term usage such as domiciliary HFNC.[41-43]

Our study has several limitations. First, our bench was designed to assess the hygrometry delivered by the devices on the basis of continuous unidirectional flow. In the study of Chikata et al,[30] the authors reported that when inspiratory flow was higher than HFNC flow the AH measured at the cannula was significantly reduced. This effect can be explained by room air entrainment and dilution of the inspired gases, a phenomenon that has been widely described to explain the limitations of conventional oxygen therapy in providing stable $F_{IO_2}$,[44] and consequently the added value of HFNC when set flow matches or overcomes patient's inspiratory flow.[2,11] Second, the clinical part of our study evaluated the tolerance to different hygrometric levels of healthy volunteers, and evaluation in patients may yield different results. However, the major lack of tolerance of 20 mg $H_2O$/L during a 10-min exposure to HFNC in our healthy subjects, along with the histological evidence of its detrimental effects on airway mucosa,[24,33,34] suggests similar findings may be found in subjects. Third, we did not address the effects of different interfaces that may affect droplet formation and thus clinical tolerance. Lastly, our study evaluated short duration of exposure to HFNC and, therefore, cannot apply to routine situations in which therapy is usually delivered continuously or in alternance with NIV. In the study of Cuquemelle et al,[13] the benefits of active humidification over no humidification on mouth and throat dryness during oxygen therapy increased with longer duration of exposure (up to 24 h), and we can expect that longer duration of exposure in our study would have induced larger effects in terms of comfort.

## Conclusions

We demonstrated that most common HFNC devices can deliver adequate inspiratory humidity during optimal conditions but that under-humidification may occur with high ambient temperature, high flows, and low target temperature. We propose to deliver a minimum humidity target around 30 mg $H_2O$/L during HFNC. Adequate humidification is probably the cornerstone of treatment tolerance and comfort during HFNC. Whether this translates into better clinical outcomes deserves further investigation.

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## REFERENCES


1. Ward JJ. High-flow oxygen administration by nasal cannula for adult and perinatal patients. Respir Care 2013;58(1):98-122.
2. Papazian L, Corley A, Hess D, et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive Care Med 2016;42(9):1336-1349.
3. Frat J-P, Thille AW, Mercat A, et al. REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185-2196.
4. Hernández G, Vaquero C, González P, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. JAMA 2016;315 (13):1354-1361.
5. Futier E, Paugam-Burtz C, Godet T, et al; OPERA study investigators. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicenter randomized controlled trial (OPERA). Intensive Care Med 2016;42(12):1888-1898.
6. Azoulay E, Lemiale V, Mokart D, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. JAMA 2018;320(20):2099-2107.
7. Roca O, Masclans JR. High-flow nasal cannula oxygen therapy: innovative strategies for traditional procedures. Crit Care Med 2015;43 (3):707-708.
8. Matthay MA. Saving lives with high-flow nasal oxygen. N Engl J Med 2015;372(23):2225-2226.
9. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med 2020;48(6):e440-e469.
10. Wagstaff TAJ, Soni N. Performance of six types of oxygen delivery devices at varying respiratory rates. Anaesthesia 2007;62(5):492-503.
11. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high-flow therapy: mechanisms of action. Respir Med 2009;103(10):1400-1405.
12. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest 2015;148(1):253-261.
13. Cuquemelle E, Pham T, Papon J-F, Louis B, Danin P-E, Brochard L. Heated and humidified high-flow oxygen therapy reduces discomfort during hypoxemic respiratory failure. Respir Care 2012;57(10):1571-1577.
14. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med 2014;190 (3):282-288.
15. Spoletini G, Mega C, Pisani L, et al. High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: a pilot randomized controlled trial. J Crit Care 2018;48:418-425.
16. Sztrymf B, Messika J, Bertrand F, et al. Beneficial effects of humidified high-flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med 2011;37(11):1780-1786.
17. Fraser JF, Spooner AJ, Dunster KR, Anstey CM, Corley A. Nasal high-flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomized crossover trial. Thorax 2016;71 (8):759-761.
18. Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195(9):1207-1215.
19. Delorme M, Bouchard P-A, Simon M, Simard S, Lellouche F. Physiologic effects of high-flow nasal cannula in healthy subjects. Respir Care 2020;65(9):1346-1354.
20. Vargas F, Saint-Leger M, Boyer A, Bui NH, Hilbert G. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respir Care 2015;60(10):1369-1376.
21. Pisani L, Fasano L, Corcione N, et al. Change in pulmonary mechanics and the effect on breathing pattern of high-flow oxygen therapy in stable hypercapnic COPD. Thorax 2017;72(4):373-375.
22. Delorme M, Bouchard P-A, Simon M, Simard S, Lellouche F. Effects of high-flow nasal cannula on the work of breathing in patients recovering from acute respiratory failure. Crit Care Med 2017;45(12):1981-1988.
23. Mauri T, Alban L, Turrini C, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med 2017;43(10):1453-1463.
24. Williams R, Rankin N, Smith T, Galler D, Seakins P. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. Crit Care Med 1996;24(11):1920-1929.
25. Kilgour E, Rankin N, Ryan S, Pack R. Mucociliary function deteriorates in the clinical range of inspired air temperature and humidity. Intensive Care Med 2004;30(7):1491-1494.
26. Chanques G, Constantin J-M, Sauter M, et al. Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. Intensive Care Med 2009;35(6):996-1003.
27. Ricard JD, Le Mière E, Markowicz P, et al. Efficiency and safety of mechanical ventilation with a heat and moisture exchanger changed only once a week. Am J Respir Crit Care Med 2000;161(1):104-109.
28. Lellouche F. Main techniques for evaluating the performances of humidification devices used for mechanical ventilation. In: Esquinas AM, ed. Humidification in the Intensive Care Unit. Springer; 2012:49-63.
29. Lellouche F, Taillé S, Maggiore SM, et al. Influence of ambient and ventilator output temperatures on performance of heated-wire humidifiers. Am J Respir Crit Care Med 2004;170(10):1073-1079.
30. Chikata Y, Izawa M, Okuda N, et al. Humidification performance of two high-flow nasal cannula devices: a bench study. Respir Care 2014;59(8):1186-1190.
31. Carter BG, Whittington N, Hochmann M, Osborne A. The effect of inlet gas temperatures on heated humidifier performance. J Aerosol Med off J D 2002;15(1):7-13.
32. Lellouche F, Maggiore SM, Lyazidi A, Deye N, Taillé S, Brochard L. Water content of delivered gases during noninvasive ventilation in healthy subjects. Intensive Care Med 2009;35(6):987-995.
33. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. J Appl Physiol (1985) 1996;81(4):1739-1743.
34. Chidekel A, Zhu Y, Wang J, Mosko JJ, Rodriguez E, Shaffer TH. The effects of gas humidification with high-flow nasal cannula on cultured human airway epithelial cells. Pulm Med 2012;2012:1-8.
35. Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. Chron Respir Dis 2008;5(2):81-86.
36. Crimi C, Noto A, Cortegiani A, et al. High-flow nasal therapy use in patients with acute exacerbation of COPD and bronchiectasis: a feasibility study. COPD 2020;17(2):184-190.
37. O'Driscoll BR, Howard LS, Earis J, Mak V, British TS; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in health care and emergency settings. Thorax 2017;72(Suppl 1):ii1-ii90.
38. Chatburn RL, Primiano FP. A rational basis for humidity therapy. Respir Care 1987;32(4):249-254.
39. Ricard J-D, Dreyfuss D. Humidification. In: Tobin MJ. Principles and Practice of Mechanical Ventilation. 3rd ed. McGraw Hill; 2013.
40. Mauri T, Galazzi A, Binda F, et al. Impact of flow and temperature on patient comfort during respiratory support by high-flow nasal cannula. Crit Care 2018;22(1):120.
41. Storgaard LH, Hockey H-U, Laursen BS, Weinreich UM. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in

COPD patients with chronic hypoxemic respiratory failure. COPD 2018;Volume 13:1195-1205.
42. Nagata K, Kikuchi T, Horie T, et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease. A multicenter randomized crossover trial. Annals ATS 2018;15(4):432-439.
43. Dolidon S, Dupuis J, Molano Valencia L-C, et al. Characteristics and outcome of patients set up on high-flow oxygen therapy at home. Ther Adv Respir Dis 2019;13:175346661987979-175346661987978.
44. Bazuaye EA, Stone TN, Corris PA, Gibson GJ. Variability of inspired oxygen concentration with nasal cannulas. Thorax 1992;47(8):609-611.