Physiologic Effects of High-Flow Nasal Cannula in Healthy Subjects

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

BACKGROUND: High-flow nasal cannula (HFNC) is increasingly used in the management of acute and chronic respiratory failure. Little is known about the optimal settings for HFNC. This study was designed to assess the dose effect of HFNC on respiratory effort indexes and respiratory patterns in spontaneously breathing adults. METHODS: A randomized controlled crossover study was conducted in 10 healthy subjects. Five experimental conditions were evaluated: baseline with no therapy; 5 L/min with conventional nasal prongs; and HFNC at 20, 40, and 60 L/min. The primary outcomes were the indexes of respiratory effort (ie, esophageal pressure swing [ΔP_{es}], esophageal pressure-time product, and work of breathing). Secondary outcomes included breathing pattern parameters and blood gases. Dead-space ventilation and washout were calculated based on minute ventilation, breathing frequency, and Radford equations. RESULTS: ΔP_{es} increased from median (interquartile range [IQR] 3.2 (2.2–3.6) cm H_2O at baseline to median (IQR) 5.7 (4.6–6.8) cm H_2O at 60 L/min ($P < .001$). Neither esophageal pressure-time product nor work of breathing were modified during the tested conditions. The minute volume was significantly reduced at 40 and 60 L/min compared with baseline ($P = .04$), mostly driven by an important and dose-dependent reduction in breathing frequency, from median (IQR) 16 (15–18) breaths/min at baseline, to median (IQR) 8 (7–10) breaths/min at 60 L/min ($P < .001$). Capillary P_{CO_2} was stable in all the tested conditions. The calculated dead-space ventilation was reduced by half with HFNC. CONCLUSIONS: HFNC did not significantly modify work of breathing in healthy subjects. However, a significant reduction in the minute volume was achieved, capillary P_{CO_2} remaining constant, which suggests a reduction in dead-space ventilation with flows > 20 L/min. (ClinicalTrials.gov registration NCT02495675). *Key words: high flow nasal cannula; dead space; work of breathing; respiratory pattern; respiratory inductive plethysmography.* [Respir Care 2020;65(9):1346–1354. © 2020 Daedalus Enterprises]

High-flow nasal cannula (HFNC) is increasingly used for the prevention and management of hypoxemic respiratory failure in patients who are critically ill.[1-5] Its widespread use in the acute setting has led to numerous studies that targeted a more-comprehensive understanding of its physiologic mechanisms of action,[6-12] and growing interest is emerging for the use of HFNC in patients with stable chronic disease, in which high oxygen flows would not be required.[13-19] Indeed, the benefits of HFNC seems to expand beyond the well-demonstrated superiority of this device to improve oxygen delivery compared with conventional oxygen therapy.[1,2,20]

The physiologic benefits of HFNC include improved gas conditioning, with adequate heating and humidification,[6,21] delivery of variable amounts of positive airway pressure

Mr Delorme is affiliated with the Université Paris-Saclay, UVSQ, ERPHAN, Versailles, France. Mr Delorme, Mr Bouchard, Dr Simon, Mr Simard, and Dr Lellouche are affiliated with the Centre de Recherche de l'Institut, Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada.

Mr Delorme discloses a relationship with ResMed. The remaining authors have disclosed no conflicts of interest.

Nasal high flow devices and consumables were provided by Fisher & Paykel Healthcare, which had no other involvement in the study.

Correspondence: François Lellouche MD, Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Sainte-Foy, G1V4G5, Québec, Québec, Canada. E-mail: francois.lellouche@criucpq.ulaval.ca.

DOI: 10.4187/respcare.07306

(which may increase dynamic lung compliance,[10-12,22,23] decrease inspiratory resistance,[6,11,24]) and anatomic dead-space washout.[24,25] Even though measuring anatomic dead space in vivo remains challenging, several bench[26-28] and clinical data[14,16,19,24] support a reduction of dead-space ventilation with HFNC. This phenomenon, which has been proposed by many researchers as a key mechanism in patients with respiratory failure[8,13,17,24,25] could reduce respiratory effort[10-12,29-31] and thus explain part of the benefits of this therapy in terms of comfort and efficiency. However, the dose-response relationship between respiratory effort and flow setting remains poorly understood. We, therefore, designed a randomized controlled crossover trial to evaluate the short-term physiologic effects of HFNC on the respiratory pattern and the indexes of respiratory effort in healthy subjects, and to investigate the effects of different flow settings on these outcomes.

QUICK LOOK

Current knowledge

High-flow nasal cannula (HFNC) is increasingly used in the management of acute and chronic respiratory failure. Little is known about the optimal settings for HFNC. This study was designed to assess the dose effect of HFNC on respiratory effort indexes and on respiratory patterns in spontaneously breathing adults.

What this paper contributes to our knowledge

In this study, HFNC had a major impact on the ventilatory pattern, with a significant decrease in minute volume, mostly driven by a dose-dependent decrease in breathing frequency (f), as low as 4 breaths/min, while increasing flow setting. P_{aCO_2} remained constant, which suggested constant alveolar ventilation flow setting. Most of the effects on dead-space washout were achieved at 20 L/min, and further reduction of dead-space ventilation encountered with higher flows was mostly due to breathing frequency reduction.

Methods

The ethics review board of the Institut Universitaire de Cardiologie et de Pneumologie de Québec approved the study protocol (project approval 21187). Healthy subjects were assessed for eligibility by completing a medical questionnaire, excluding any relevant ear, nose, and throat; digestive; cardiac; or pulmonary disease. After signing written informed consent, the subjects were invited to perform a spirometry to confirm their eligibility as healthy subjects. Individuals aged < 18 years, pregnant, or breastfeeding were not eligible for inclusion. Any contraindication for the insertion of an esophageal catheter was discarded before inclusion.

For each subject, 5 conditions were evaluated (each lasted 10 min) with the subject in a semi-recumbent position. The baseline variables were recorded during spontaneous breathing in room air. Then, 4 conditions were tested in a randomized order: 5 L/min delivered through conventional nasal prongs, and 20, 40, and 60 L/min delivered through a HFNC therapy device (Airvo2 and Optiflow nasal interface, Fisher & Paykel Healthcare, Auckland, New Zealand). All measurements were performed with F_{IO_2} of 21%, with the heater humidifier set at 37°C, and the subjects were asked to breathe with the mouth closed throughout all the tested conditions. A washout of 5 min with spontaneous breathing in room air was performed between each tested condition.

The primary outcomes of this study were the indexes of respiratory effort, including esophageal pressure swing (ΔP_{es}), esophageal pressure-time product per minute (PTP_{es})/min and work of breathing per minute (WOB)/min. Secondary outcomes included tidal volume (V_T),[32] breathing frequency, minute volume ($\dot{V}_E$), pH, capillary P_{CO_2}, V_T/inspiratory time (V_T/T_I), auto-PEEP, dynamic lung compliance, inspiratory resistance, and respiratory comfort. Variations in V_T during each tested condition was evaluated by using respiratory inductive plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, New York), as previously described.[11,33] Briefly, respiratory inductive plethysmography bands allowed for continuous recording of thoracic and abdominal excursions throughout the study protocol (and especially throughout each condition tested with HFNC, during which no direct measurements of V_T variations could be performed). At the end of each tested condition, a calibration run was performed, during which the subjects were asked to breathe through a pneumotachograph (PN279331; Hamilton Medical, Bonaduz, Switzerland) for 1 min.

A multiple linear regression model was applied to determine correlation coefficients between each respiratory inductive plethysmography band and measured V_T,[11,33] which allowed for the estimation of V_T variations during each tested condition. Respiratory flow, used to calculate respiratory effort variables, was calculated as the derivation of V_T over time. P_{es} was continuously recorded via a thin catheter with a 10-cm esophageal balloon (5 French) (Cooper Surgical, Trumbull, Connecticut) inserted through the nose to the lower third of the esophagus and connected to a differential pressure transducer (MP45 ± 2 cm H_2O; Validyne Engineering, Northridge, California). Adequate placement of the catheter was confirmed as previously described.[34,35] ΔP_{es}, esophageal pressure-time product/min, WOB/min, V_T, f, $\dot{V}_E$, V_T/T_I, auto-PEEP, dynamic lung

compliance, and inspiratory resistance were computed from respiratory flow and P_{es} variations via open-source respiratory data analysis software (RespMAT), as previously described.[11,36] Measurement and calculation of these variables were performed over at least 10 stable consecutive respiratory cycles during the last 2 min of each tested condition. The pH and capillary P_{CO_2} values were obtained from capillary blood gases sampled at the fingertip at the end of each tested condition.[37] Respiratory comfort was assessed with a 10-cm visual analog scale, whereby the subjects rated their comfort to breath at the end of each tested condition, from 0 (very uncomfortable) to 10 (very comfortable). Signals were digitized at 200 Hz and sampled by using an analogic/numeric system (MP150; Biopac Systems, Santa Barbara, California). All signal treatments and data analyses were performed with the evaluator blinded to the patient's condition.

Estimation of Dead-Space and Alveolar Ventilation

After completing enrollment of the participants in this study and after data analysis, we found relevant to perform the following analysis: (1) dead-space volume (V_D) was calculated as 2.2 mL/kg[38,39] of the predicted body weight[32]; (2) alveolar ventilation (V_A) was then calculated for each tested condition as $(V_T - V_D) \times f$ and the median value was used as a reference, assumed being constant throughout the tested conditions (as capillary P_{CO_2} was found to be stable throughout the tested conditions); (3) for all other tested conditions, anatomic dead space was calculated (in mL) as $(\dot{V}_E - V_A)/f$ (in mL), V_D/V_T as anatomic dead space/tidal volume (in percentage), dead-space ventilation as $V_D \times f$ (in mL/min), and dead-space washout/min as (baseline $V_D \times$ baseline f) – (tested condition *n* $V_D \times$ tested condition *n* f) (in mL).

Statistical Analysis

Data were expressed by using median (25th–75th interquartile range [IQR]) to summarize characteristics of the subjects unless specified otherwise. Baseline characteristic variables were analyzed by using a one-way analysis of variance, with the Satterthwaite degree of freedom. The univariate normality assumption was verified with the Shapiro-Wilk tests on the error distribution from the statistical model after a Cholesky factorization. The Brown and Forsythe variation of the Levene test statistic was used to verify the homogeneity of variances. When appropriate, some variables were log-transformed to fulfill the model assumptions, and reported *P* values were based on these transformations. To analyze respiratory data in the subjects according to the 5 tested conditions, a mixed model with interactions between subgroups and tested conditions were performed.

Table 1. Subject Baseline Characteristics

Characteristic	Overall ($N = 10$)
Men, %	40
Age, y	30 ± 7
Weight, kg*	68 ± 14
PBW, kg	65 ± 10
Height, cm	172 ± 9
BMI, kg/m^2	23 ± 3
FEV_1, L	4.0 ± 0.7
FEV_1, %	108 ± 8
FEV_1/FVC, %	81 ± 4

*PBW is calculated with the following formula: PBW = $X + 0.91 \times$ (height (in cm) – 152.4), where $X = 50$ for men and $X = 45.5$ for women (from Ref. 32).
All data are provided in mean ± SD.
PBW = predicted body weight
BMI = body mass index

In the absence of data that allowed for the estimation of the sample size at the beginning of this study, we decided arbitrarily to enroll 10 subjects in this exploratory study, with the hypothesis that this number would be sufficient to detect a significant variation in respiratory effort. The results were considered significant with $P < .05$. All analyses were conducted by using the statistical packages R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v9.4 (SAS Institute, Cary, North Carolina).

Results

Ten subjects participated in this study. Their baseline characteristics are presented in Table 1. The time course of ΔP_{es}, respiratory inductive plethysmography bands, and calculated respiratory flow over the experimental conditions in a representative subject (no. 2) are depicted in Figure 1. The ΔP_{es} swing was similar between the baseline and 5 L/min ($P = .99$), but increased linearly with an increasing flow setting of HFNC, from median (IQR) 3.2 (2.2–3.6) cm H_2O at baseline to median (IQR) 5.7 (4.6–6.8) cm H_2O at 60 L/min ($P < .001$). Neither esophageal pressure-time product nor WOB were significantly modified during the tested conditions (Table 2).

Increasing the flow setting led to a progressive and linear decrease in breathing frequency, which fell from a median (IQR) 16 (15–18) breaths/min at baseline to a median (IQR) 8 (7–10) breaths/min at 60 L/min ($P < .001$) (Fig. 2A). As shown in Figure 2A, half of the participants exhibited $f \leq 7$ breaths/min at 60 L/min (ranging from 4 to 12 breaths/min overall). This progressive reduction in breathing frequency was accompanied with an increase in V_T that reached statistical significance only with the highest flows, increasing from median (IQR) 337 (272–443) mL at baseline to median (IQR) 520 (470–626) mL at 60 L/min ($P = .005$). As a result, $\dot{V}_E$ was significantly lower compared

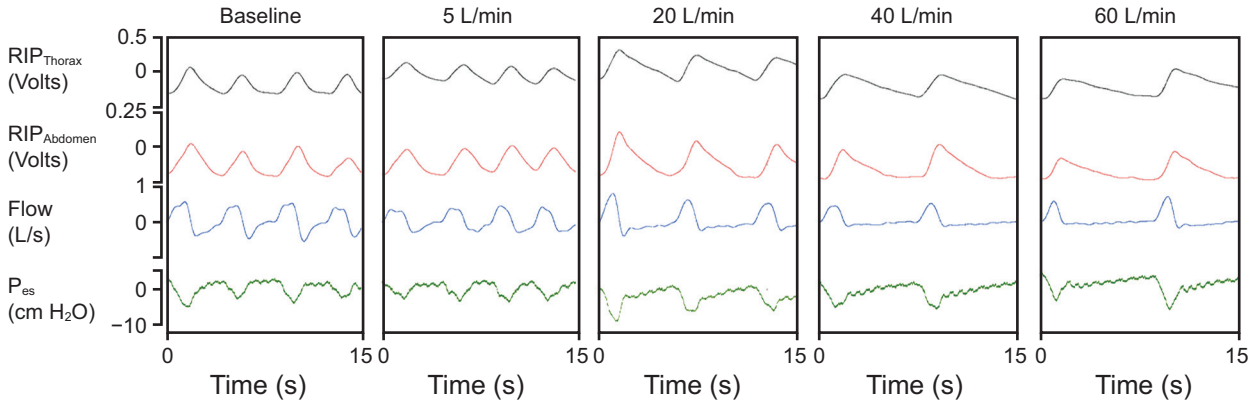

Fig. 1. The time course of study variables over the experimental conditions in a representative subject (subject no. 2). The respiratory flow is estimated from respiratory inductive plethysmography (RIP) band variations. In this subject, a marked and progressive reduction in breathing frequency occurs when increasing the flow setting, while esophageal pressure (ΔP_{es}) swings increase.

Table 2. Respiratory Mechanics at the End of the Tested Conditions

Parameter	Condition					*P*
	Baseline	5 L/min	20 L/min	40 L/min	60 L/min	
ΔP_{es}, cm H_2O	3.2 (2.2–3.6)	3.2 (2.9–3.4)	4.3 (3.8–5.1)	4.9 (3.8–5.8)	5.7 (4.6–6.8)	<.001
Esophageal PTP/min, cm H_2O × s/min	71 (49–78)	65 (52–87)	70 (61–102)	72 (56–108)	84 (72–109)	.12
WOB/min, J/min	1.6 (1.0–2.5)	1.7 (1.1–2.3)	2.3 (1.2–3.3)	1.6 (1.3–2.5)	2.3 (2.0–2.9)	.18
V_T/T_I, mL/s	214 (193–253)	219 (178–258)	262 (195–310)	227 (202–246)	246 (214–255)	.50
Auto-PEEP, cm H_2O	0.1 (0.0–0.1)	0.1 (0.0–0.1)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.1 (0.0–0.3)	.01
Compliance, mL/cm H_2O	126 (118–140)	154 (105–162)	142 (106 – 181)	114 (97 – 154)	126 (116–167)	.74
Resistance, cm H_2O/L/s)	2.9 (2.5–3.8)	3.4 (2.3–4.2)	4.9 (3.9 – 6.7)	7.0 (5.1 – 8.5)	7.3 (6.6–9.6)	<.001

Data are expressed as median (25th–75th interquartile range).
ΔP_{es} = esophageal pressure variation
PTP = pressure-time product
WOB = work of breathing
V_T = tidal volume
T_I = inspiratory time
Auto-PEEP = intrinsic PEEP

with baseline at 40 L/min (*P* = .04) and 60 L/min (*P* = .04), as shown in Figure 2B and Table 3. The pH and capillary P_{CO_2} values were not significantly modified during the tested conditions (Table 3 and Fig. 2B).

Dynamic lung compliance remained stable throughout the tested conditions, whereas inspiratory resistance increased from median (IQR) 2.9 (2.5–3.8) cm H_2O/L/s at baseline to median (IQR) 7.3 (6.6–9.6) cm H_2O/L/s at 60 L/min (*P* < .001) (Table 2). Respiratory comfort was reduced at 5 L/min compared with baseline (*P* = .01). No other statistically different modification in respiratory comfort was observed with HFNC, whatever flow setting was applied (Table 3).

Estimation of Dead-Space Ventilation and V_A

In the whole group of participants, the median (IQR) predicted body weight was 64 (57–74) kg, and the median (IQR) predicted anatomic dead space was 141 (125–162) mL. The median (IQR) V_A was 3,343 (2,165–3,933) mL/min. The estimations of dead-space ventilation and dead-space washout are provided in Table 3. The evolution of these variables according to the tested conditions is displayed in Figure 3. In comparison with baseline, dead-space ventilation was reduced by 36% at 20 L/min and by 48% at 40 and 60 L/min, with a decrease of the breathing frequency by 36% at 20 L/min and by 45 and 51% at 40 and 60 L/min, respectively. V_D/V_T progressively decreased while increasing flow setting (Table 3).

Discussion

In this study, we showed that, in healthy awake subjects, HFNC did not significantly modify respiratory effort, whatever flow setting was applied. Meanwhile, the respiratory pattern changed significantly, with a linear decrease in

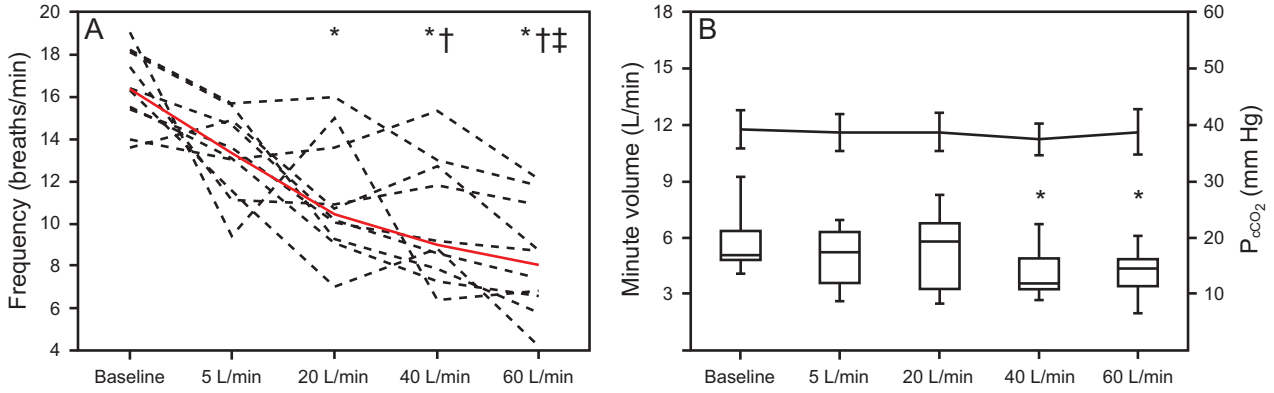

Fig. 2. Respiratory pattern and capillary P_{CO_2} variations according to the tested conditions. A: Breathing frequency (breaths/min) variations in individuals (dashed lines) and overall median breathing frequency (solid line) according to the tested conditions. B: Minute volume (L/min) (box plots) and mean ± SD capillary P_{CO_2} levels (dashed line) according to the tested conditions. Medians are expressed as horizontal bars inside the boxes, 25th–75th percentiles as the bottom and the top of the boxes, and maximum–minimum values as whiskers. * $P < .05$ versus baseline; † $P < .05$ versus 5 L/min; ‡ $P < .05$ versus 20 L/min.

Table 3. Respiratory Pattern Variables, Blood Gases, and Comfort at the End of the Tested Conditions

Parameters	Condition					*P*
	Baseline	5 L/min	20 L/min	40 L/min	60 L/min	
Data collected during the study, median (IQR)						
V_T, mL	337 (272–443)	358 (287–458)	448 (345–580)	450 (307–480)	520 (470–626)	.004
V_T, mL/kg*	5.2 (4.3–6.6)	5.3 (5.0–5.8)	7.1 (5.5–8.6)	6.5 (5.6–7.9)	7.9 (7.0–9.5)	.004
f, breaths/min	16 (15–18)	13 (12–15)	10 (10–13)	9 (8–12)	8 (7–10)	<.001
$\dot{V}_E$, L/min	5.1 (4.8–6.3)	5.2 (3.6–6.3)	5.8 (3.2–6.8)	3.5 (3.2–4.9)	4.4 (3.4–4.8)	.02
pH	7.40 (7.39–7.42)	7.41 (7.40–7.41)	7.41 (7.39–7.42)	7.42 (7.40–7.43)	7.41 (7.40–7.43)	.10
Capillary P_{CO_2}, mm Hg	39 (37–40)	39 (37–41)	40 (36–40)	37 (36–39)	38 (35–42)	.50
Respiratory comfort (VAS)	10 (10–10)	9 (6–10)	10 (9–10)	9 (7–10)	8 (8–9)	.009
Estimation of dead space and V_A (post hoc statistical analysis)						
V_A, mL/min	3,343	3,343	3,343	3,343	3,343	NA
V_D/V_T, %	45	39	38	34	31	.007
Dead-space ventilation, mL/min	2,431	1,823	1,546	1,276	1,276	.01
Dead-space washout, mL/min	0	863	1,140	1,191	1,160	.02

* V_T is expressed as mL/kg of predicted body weight (PBW), calculated with the following formula: PBW = X + 0.91 × (height in cm) – 152.4), where X = 50 for men and X = 45.5 for women (from Ref. 32).
IQR = interquartile range
V_T = tidal volume
f = breathing frequency
$\dot{V}_E$ = minute volume
P_{CO_2} = CO_2 partial pressure
V_A = alveolar ventilation
VAS = visual analog scale
NA = not applicable
V_D = dead-space volume

breathing frequency while increasing the flow setting. This phenomenon was only partially balanced by an increase in V_T, which led to a significant decrease in $\dot{V}_E$ at 40 and 60 L/min.

It has been repeatedly demonstrated in upper airway models that HFNC is capable of effectively washing out the upper airways and thus reducing CO_2 rebreathing with relatively low flows.[26,40] The baseline hypothesis of our study was that a reduction in dead-space ventilation, if confirmed, could lead to a reduction of the respiratory drive and the WOB in healthy awake subjects. We failed to demonstrate any reduction in respiratory effort in the present study, even

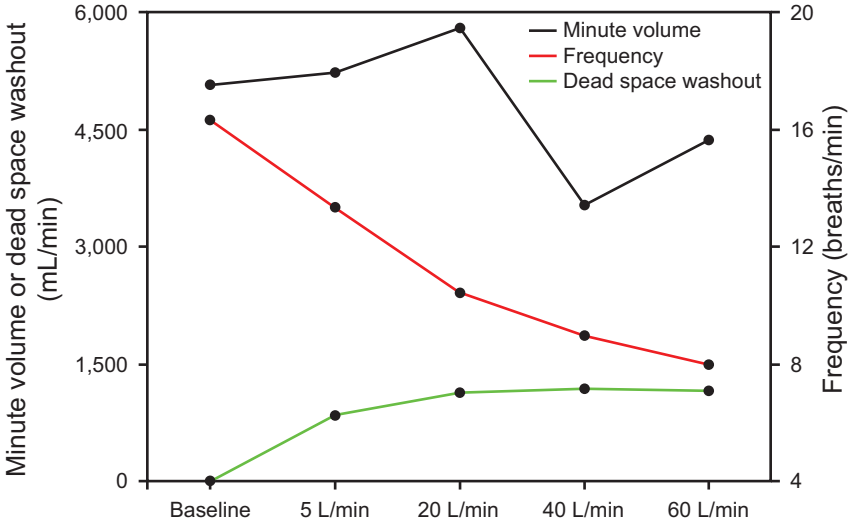

Fig. 3. Dead-space washout and respiratory pattern variations according to the tested conditions. The increase in flow setting with high-flow nasal cannula (HFNC) led to progressive decrease in dead-space ventilation. This phenomenon might be explained by both dead-space washout and breathing-frequency reduction with flows < 40 L/min, and mostly by a reduction in breathing frequency with flows ≥ 40 L/min. The dead-space washout may be subject to a plateau effect with flows ≥ 40 L/min.

though this phenomenon has previously been reported in subjects with various severity of respiratory failure.[11,29-31]

Several assumptions may explain this result. We found that inspiratory resistance significantly increased when the highest flow settings were applied. This finding conflicted with previous data obtained from measurements performed with upper-airway models[24,41] and was not expected. Our study was not designed to monitor dynamic variations of blood gases during the tested conditions, and we, therefore, could not conclude from our data about the underlying mechanisms related to this increase in inspiratory resistance. Nevertheless, it has recently been shown that end-tidal P_{CO_2} could be reduced up to 30 mm Hg when applying HFNC at 60 L/min to an experimental model that simulates normal lung with a closed mouth.[40] Such a reduction of P_{CO_2}, even transient, and, if confirmed in further studies, could explain both the absence of improvement in WOB and the increase in inspiratory resistance (accompanied by an increase in ΔP_{es}) observed in our subjects, as previously described by Jounieaux et al[42] in healthy subjects who were undergoing nasal intermittent positive-pressure ventilation. Another explanation for the absence of improvement in respiratory effort with HFNC in this population of healthy subjects was the baseline values, which were already low, in line with what is described in the literature[35,43] and, therefore, subject to minimal improvement despite significant reduction in dead-space ventilation.

Indeed, the respiratory pattern of the subjects enrolled in this study was substantially modified according to the flow setting applied, and we, therefore, decided to perform a post hoc analysis that deserves several comments. First, HFNC, being an open system generating continuous flow, we were not able to perform dead-space measurements with the reference methods derived from analysis of CO_2 content in exhaled gases.[44,45] This limitation needs to be taken into account in the following conclusions. However, with assuming stable CO_2 production and stable respiratory ratio relative to the short duration of the tested conditions, it seems reasonable to state that the absence of modification of capillary P_{CO_2} at the end of each tested condition was associated with stable V_A throughout the study.

Analysis of our data, therefore, suggested that the reduction of $\dot{V}_E$ observed at 40 and 60 L/min, associated with stable V_A (ie, stable capillary P_{CO_2}), is the in vivo expression of a reduction in dead-space ventilation related to a major decrease in breathing frequency and a washout of the anatomic dead space. This observation was in line with previous data obtained on the bench with upper-airway models,[26,40] which demonstrated that HFNC was capable of effectively washing out the upper airways and thus reducing CO_2 rebreathing with relatively low flows. As a result of this dead-space washout, HFNC with flow that ranged from 20 to 40 L/min may reduce P_{CO_2} in the clinical setting, as recently evidenced by Bräunlich et al[19] in stable subjects with COPD. In addition, Möller et al[25] showed that, in healthy volunteers, the upper-airway washout that resulted from HFNC was flow and time dependent, as demonstrated by a significant improvement in halftime clearance of an inhaled radiotracer when the flow setting was increased from 15 to 45 L/min while the participants were asked to hold their breath. From these results, the researchers speculated that long end-expiratory pauses may enhance the clearance efficiency of HFNC[25] (ie, that a substantial reduction in breathing

frequency may increase the efficiency of upper-airway washout with HFNC).

Of note, we found that the impact of HFNC on dead-space washout was proportional to the flow setting applied, with a maximum reduction encountered at 20–40 L/min and a potential plateau effect beyond this flow. These data were in line with several recent physiologic data, analysis of which suggested that most of the $\dot{V}_E$ reduction is already obtained with flows $\leq$ 30 L/min.[12,25,40,46] It should be noted here that the highest CO_2 reductions with HFNC reported in the literature were not seen with the highest flow settings.[17]

By definition, in patients spontaneously breathing and during HFNC, the dead-space ventilation is directly related to the anatomic V_D and to the breathing frequency. The reduction of dead-space ventilation may be related both to a reduction in anatomic dead space owing to the nasopharyngeal washout during expiration[25,26,40] and to a reduction of the breathing frequency. In the current subjects, the impact of HFNC on breathing frequency was major, with a mean reduction by 2-fold in agreement to previously published data by other teams in similar settings.[24,47] This substantial reduction in breathing frequency, even though observed in healthy subjects, may apply to some patients in the field of anesthesia, an area in which HFNC is increasingly used.[48]

Such reduction of breathing frequency with high flows may, in some cases, promote anxiety that could be prevented by appropriately warning the patient about this potential effect. The impact on V_D was less marked. Most of the effects of HFNC on dead-space washout were achieved at 20 L/min. However, further reduction in dead-space ventilation occurred at 60 L/min, because of further reduction of breathing frequency rather than further washout of anatomic dead space. Analysis of this finding, in agreement with most of the studies performed in the clinical setting,[12,23,24] suggested that reduction in dead-space ventilation during HFNC while increasing the flow setting might be (1) with flows $<$ 40 L/min, due to both dead-space washout and breathing frequency reduction, and (2) with flows $\geq$ 40 L/min, mainly attributable to breathing frequency reduction, the former being subject to a plateau effect, as discussed above. The following conclusions deserve to be specifically evaluated in further studies, but we believe that, from the findings of our study, one can speculate that, when no additional reduction in breathing frequency is encountered with flows $\geq$ 40 L/min, no reduction in dead-space ventilation should be expected.

Analysis of these data have an important clinical impact when searching for the optimal flow setting to apply to specifically increase CO_2 clearance. From physiologic and clinical data now available in the literature, one can argue that, when the target is to decrease CO_2 level, flows of ~30-40 L/min may allow reaching most of the expected effects. However, when targeting improvement in the P_{aO_2}/F_{IO_2},[1,12,49] providing some level of PEEP effect and increasing expiratory lung volume,[12,22,50] or reducing the WOB,[11,12,31] a linear model is more likely to apply and the highest flow settings may be required.

In this study, we also found that V_T increased progressively while increasing the flow setting. This finding was in line with data reported by other teams in similar settings,[24,51] was consistent with the increase in ΔP_{es} variations observed in our subjects, and was also in agreement with data reported in patients in various settings in which V_T increased with HFNC.[16,31,52] Nevertheless, conflicting results have also been reported in healthy awake subjects,[52] no change in V_T has been evidenced in subjects with acute hypoxemic respiratory failure,[10,12] and the opposite results have been evidenced during sleep.[24,30] The clinical relevance of this finding, therefore, deserves further investigation and should be interpreted with caution because HFNC, unlike noninvasive ventilation, does not provide inspiratory pressure support.[53]

This study had several limitations, the first one being that no pressure measurements at the airway opening were performed. The study protocol instrumentation was already quite cumbersome for the subjects, and we believed that additional catheter inserted into the pharynx would have induced major discomfort in our subjects as well as modified their respiratory pattern by itself. This limit may have biased several respiratory mechanics measurements (eg, compliance and resistance). Also, we overcame the challenging measurement of V_T by using respiratory inductive plethysmography, which is not the standard reference. In previous studies, the accuracy of this methodology has been estimated to be $\pm$10%,[33,54,55] and we performed repeated calibrations after all the conditions to reduce this bias. V_T was within the expected values, ranging from 5.2 to 8.0 mL/kg of predicted body weight, as expected in spontaneously breathing healthy subjects. Consequently, several measurements that took into account the volumes may be interpreted cautiously. Also, we reported here short-term data in healthy awake subjects. It should be noted that these results apply to the tested condition and that long-term effects in patients with impaired pulmonary mechanics or in subjects who were sleepy could be substantially different [24,30] and deserve further investigation.

Conclusions

HFNC did not significantly modify WOB in healthy awake subjects. However, a significant reduction in $\dot{V}_E$ could be achieved with flows $\geq$ 40 L/min and capillary P_{CO_2} remaining constant, which suggested a reduction in anatomic dead-space ventilation. This effect was accompanied by a major reduction of the breathing frequency, which

may explain part of the benefits of HFNC on comfort in the clinical setting.

ACKNOWLEDGMENTS

The authors thank all the participants who accepted being enrolled as healthy subjects in this study, and Quang-Thang Nguyen PhD, OxyNov, France, Louis Mayaud PhD, Mensia Technologies, France, and Bruno Louis PhD, INSERM U 955 Eq13 – CNRS ERL 7240, France, for their valuable contributions to the methodology of signals analysis.

REFERENCES

1. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, 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.
2. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185-2196.
3. Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al; BiPOP Study Group. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. JAMA 2015;313 (23):2331-2339.
4. Messika J, Ben Ahmed K, Gaudry S, Miguel-Montanes R, Rafat C, Sztrymf B, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: a 1-year observational study. Respir Care 2015;60(2):162-169.
5. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, 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.
6. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med 2009;103(10):1400-1405.
7. Ricard JD. High flow nasal oxygen in acute respiratory failure. Minerva Anestesiol 2012;78(7):836-841.
8. 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.
9. Papazian L, Corley A, Hess D, Fraser JF, Frat JP, Guitton C, et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive Care Med 2016;42(9):1336-1349.
10. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, Pesenti A. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195 (9):1207-1215.
11. Delorme M, Bouchard PA, 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.
12. Mauri T, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, 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.
13. Nilius G, Franke KJ, Domanski U, Rühle KH, Kirkness JP, Schneider H. Effects of nasal insufflation on arterial gas exchange and breathing pattern in patients with chronic obstructive pulmonary disease and hypercapnic respiratory failure. Adv Exp Med Biol 2013;755:27-34.
14. 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 randomised crossover trial. Thorax 2016;71(8):759-761.
15. Pisani L, Vega ML. Use of nasal high flow in stable COPD: rationale and physiology. COPD 2017;14(3):346-350.
16. Bräunlich J, Köhler M, Wirtz H. Nasal highflow improves ventilation in patients with COPD. Int J Chron Obstruct Pulmon Dis 2016;11:1077-1085.
17. Bräunlich J, Wirtz H. NHF and hypercapnia: how brief can you look? Respirology 2017;22(6):1049-1050.
18. 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. Int J Chron Obstruct Pulmon Dis 2018;13:1195-1205.
19. Bräunlich J, Mauersberger F, Wirtz H. Effectiveness of nasal highflow in hypercapnic COPD patients is flow and leakage dependent. BMC Pulm Med 2018;18(1):14.
20. Goligher EC, Slutsky AS. Not just oxygen? Mechanisms of benefit from high-flow nasal cannula in hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195(9):1128-1131.
21. Rea H, McAuley S, Jayaram L, Garrett J, Hockey H, Storey L, et al. The clinical utility of long-term humidification therapy in chronic airway disease. Respir Med 2010;104(4):525-533.
22. Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 2011;107(6):998-1004.
23. Parke RL, Bloch A, McGuinness SP. Effect of very-high-flow nasal therapy on airway pressure and end-expiratory lung impedance in healthy volunteers. Respir Care 2015;60(10):1397-1403.
24. Mündel T, Feng S, Tatkov S, Schneider H. Mechanisms of nasal high flow on ventilation during wakefulness and sleep. J Appl Physiol (1985) 2013;114(8):1058-1065.
25. Möller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, et al. Nasal high flow reduces dead space. J Appl Physiol (1985) 2017;122(1):191-197.
26. Möller W, Celik G, Feng S, Bartenstein P, Meyer G, Oliver E, et al. Nasal high flow clears anatomical dead space in upper airway models. J Appl Physiol (1985) 2015;118(12):1525-1532.
27. Spence CJT, Buchmann NA, Jermy MC. Unsteady flow in the nasal cavity with high flow therapy measured by stereoscopic PIV. Exp Fluids 2012;52(3):569-579.
28. Van Hove SC, Storey J, Adams C, Dey K, Geoghegan PH, Kabaliuk N, et al. An experimental and numerical investigation of co2 distribution in the upper airways during nasal high flow therapy. Ann Biomed Eng 2016;44(10):3007-3019.
29. 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.
30. Biselli PJ, Kirkness JP, Grote L, Fricke K, Schwartz AR, Smith P, Schneider H. Nasal high-flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: a prospective observational study. J Appl Physiol (1985) 2017;122(1): 82-88.
31. Pisani L, Fasano L, Corcione N, Comellini V, Musti MA, Brandao M, 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.
32. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301-1308.

33. Loveridge B, West P, Anthonisen NR, Kryger MH. Single-position calibration of the respiratory inductance plethysmograph. J Appl Physiol Respir Environ Exerc Physiol 1983;55(3):1031-1034.
34. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 1982;126(5):788-791.
35. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, et al; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 2014;189(5):520-531.
36. Mayaud L, Lejaille M, Prigent H, Louis B, Fauroux B, Lofaso F. An open-source software for automatic calculation of respiratory parameters based on esophageal pressure. Respir Physiol Neurobiol 2014;192:1-6.
37. Zavorsky GS, Cao J, Mayo NE, Gabbay R, Murias JM. Arterial versus capillary blood gases: a meta-analysis. Respir Physiol Neurobiol 2007;155(3):268-279.
38. Radford EP Jr, Ferris BG Jr, Kriete BC. Clinical use of a nomogram to estimate proper ventilation during artificial respiration. N Engl J Med 1954;251(22):877-884.
39. Nunn JF, Campbell EJ, Peckett BW. Anatomical subdivisions of the volume of respiratory dead space and effect of position of the jaw. J Appl Physiol 1959;14(2):174-176.
40. Onodera Y, Akimoto R, Suzuki H, Okada M, Nakane M, Kawamae K. A high-flow nasal cannula system with relatively low flow effectively washes out CO_2 from the anatomical dead space in a sophisticated respiratory model made by a 3D printer. Intensive Care Med Exp 2018;6(1):7.
41. Adams CF, Geoghegan PH, Spence CJ, Jermy MC. Modelling nasal high flow therapy effects on upper airway resistance and resistive work of breathing. Respir Physiol Neurobiol 2018;254:23-29.
42. Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein DO. Effects of nasal positive-pressure hyperventilation on the glottis in normal awake subjects. J Appl Physiol (1985)1995;79(1):176-185.
43. Mancebo J, Isabey D, Lorino H, Lofaso F, Lemaire F, Brochard L. Comparative effects of pressure support ventilation and intermittent positive pressure breathing (IPPB) in non-intubated healthy subjects. Eur Respir J 1995;8(11):1901-1909.
44. Fowler WS. Lung function studies; the respiratory dead space. Am J Physiol 1948;154(3):405-416.
45. Fletcher R, Jonson B, Cumming G, Brew J. The concept of deadspace with special reference to the single breath test for carbon dioxide. Br J Anaesth 1981;53(1):77-88.
46. Biselli P, Fricke K, Grote L, Braun AT, Kirkness J, Smith P, et al. Reductions in dead space ventilation with nasal high flow depend on physiological dead space volume: metabolic hood measurements during sleep in patients with COPD and controls. Eur Respir J 2018;51(5). pii: 1702251.
47. Plotnikow GA, Thille AW, Vasquez DN, Pratto RA, Quiroga CM, Andrich ME, et al. Effects of high-flow nasal cannula on end-expiratory lung impedance in semi-seated healthy subjects. Respir Care 2018;63(8):1016-1023.
48. Ricard J-D, et al. Nasal high-flow therapy in specific conditions and diseases. In: Bräunlich J, Battilana M, Corley A, Coudroy R, Delorme M, Franklin D, et al. Basics and modern practice of nasal high-flow therapy. 1st edition. Bremen: UNI-MED Science; 2019:75-86.
49. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. Respir Care 2010;55(4):408-413.
50. Riera J, Pérez P, Cortés J, Roca O, Masclans JR, Rello J. Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. Respir Care 2013;58(4):589-596.
51. Okuda M, Tanaka N, Naito K, Kumada T, Fukuda K, Kato Y, et al. Evaluation by various methods of the physiological mechanism of a high-flow nasal cannula (HFNC) in healthy volunteers. BMJ Open Respir Res 2017;4(1):e000200.
52. Bräunlich J, Beyer D, Mai D, Hammerschmidt S, Seyfarth HJ, Wirtz H. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. Respiration 2013;85(4):319-325.
53. Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care 2013;58(10):1621-1624.
54. Tobin MJ, Jenouri G, Lind B, Watson H, Schneider A, Sackner MA. Validation of respiratory inductive plethysmography in patients with pulmonary disease. Chest 1983;83(4):615-620.
55. Gonzalez H, Haller B, Watson HL, Sackner MA. Accuracy of respiratory inductive plethysmograph over wide range of rib cage and abdominal compartmental contributions to tidal volume in normal subjects and in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1984;130(2):171-174.