Effects of High-Flow Nasal Cannula on the Work of Breathing in Patients Recovering From Acute Respiratory Failure*

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Objectives: High-flow nasal cannula is increasingly used in the management of respiratory failure. However, little is known about its impact on respiratory effort, which could explain part of the benefits in terms of comfort and efficiency. This study was designed to assess the effects of high-flow nasal cannula on indexes of respiratory effort (i.e., esophageal pressure variations, esophageal pressure-time product/min, and work of breathing/min) in adults.

Design: A randomized controlled crossover study was conducted in 12 patients with moderate respiratory distress (i.e., after partial recovery from an acute episode, allowing physiologic measurements).

Setting: Institut Universitaire de Cardiologie et de Pneumologie de Québec, QC, Canada.

Subjects: Twelve adult patients with respiratory distress symptoms were enrolled in this study.

Interventions: Four experimental conditions were evaluated: baseline with conventional oxygen therapy and high-flow nasal cannula at 20, 40, and 60 L/min. The primary outcomes were the indexes of respiratory effort (i.e., esophageal pressure variations, esophageal pressure-time product/min, and work of breathing/min). Secondary outcomes included tidal volume, respiratory rate, minute volume, dynamic lung compliance, inspiratory resistance, and blood gases.

Measurements and Main Results: Esophageal pressure variations decreased from 9.8 (5.8–14.6) cm H_2O at baseline to 4.9 (2.1–9.1) cm H_2O at 60 L/min (p = 0.035). Esophageal pressure-time product/min decreased from 165 (126–179) to 72 (54–137) cm H_2O • s/min, respectively (p = 0.033). Work of breathing/min decreased from 4.3 (3.5–6.3) to 2.1 (1.5–5.0) J/min, respectively (p = 0.031). Respiratory pattern variables and capillary blood gases were not significantly modified between experimental conditions. Dynamic lung compliance increased from 38 (24–64) mL/cm H_2O at baseline to 59 (43–175) mL/cm H_2O at 60 L/min (p = 0.007), and inspiratory resistance decreased from 9.6 (5.5–13.4) to 5.0 (1.0–9.1) cm H_2O/L/s, respectively (p = 0.07).

Conclusions: High-flow nasal cannula, when set at 60 L/min, significantly reduces the indexes of respiratory effort in adult patients recovering from acute respiratory failure. This effect is associated with an improvement in respiratory mechanics. (*Crit Care Med* 2017; 45:1981–1988)

Key Words: high-flow nasal cannula; oxygen therapy; respiratory distress; respiratory inductive plethysmography; work of breathing

The utilization of high-flow nasal cannula (HFNC) in ICUs is increasing every day. Recent clinical data support its use as a first-line strategy for the treatment and prevention of hypoxemic respiratory failure. Indeed, several high-quality trials recently demonstrated a major clinical impact of HFNC in patients with hypoxemic respiratory failure (1), after extubation in patients at risk of hypoxemia (2) or even in patients with low risk of reintubation (3), and in the postoperative period of cardiothoracic surgery (4).

Physiologically, HFNC allows a better control of delivered F_{IO_2} (5) and provides low levels of positive airway pressure (6–8) associated with increased end-expiratory lung volume and improved oxygenation (9–11). Furthermore, recent bench studies have highlighted that the continuous flow delivered in the upper airways during HFNC therapy may result in a flow-dependent anatomical dead space washout, reducing carbon dioxide rebreathing (12–15). These data are consistent with clinical findings suggesting that HFNC may lead to a reduction in respiratory rate (RR) and minute ventilation (11, 16, 17), P_{aCO_2} remaining constant or slightly reduced (2, 11, 17).

*See also p. 2103.

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High-flow nasal cannula devices and consumables were provided by Fisher & Paykel Healthcare, who had no other involvement in the study.

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Taken together, these physiologic advantages support the hypothesis that some of the benefits of HFNC in terms of comfort and efficiency might be explained by a reduction of respiratory effort (5, 18, 19). We therefore designed this study in order to evaluate the effects of HFNC on the indexes of respiratory effort in patients with acute and moderate respiratory distress (i.e., after partial recovery from an acute episode, allowing physiological measurements) and to assess whether there is a dose-response relationship between flow rates and respiratory effort.

MATERIALS AND METHODS

The ethics review board of the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ) approved the study protocol, and written informed consent was obtained from all participants before enrollment. This study was registered with ClinicalTrials.gov (NCT02494154).

Patients

Patients were recruited between May and October 2015. They were eligible for inclusion if they presented signs of acute and/or moderate respiratory distress, defined by a RR greater than 20 breaths/min associated with either hypoxemia (pulsed oxygen saturation [Spo_2] < 90% with oxygen supplementation ≥ 3 L/min; "hypoxemic subgroup") or hypercapnia ($Paco_2$ ≥ 45 mm Hg with a respiratory acidosis [pH < 7.38]; "hypercapnic subgroup"). Subjects were not included if they had contraindications for the insertion of an esophageal catheter or if they presented severe and nonstable respiratory or cardiac disease deemed likely to be worsened by the study protocol (acute coronary syndrome, nontreated pulmonary embolism, pneumothorax). Patients at risk for imminent intubation were not included.

Protocol

Four periods of 15 minutes were successively evaluated in semi-recumbent position. First, baseline variables were recorded with conventional oxygen therapy (including patients who received HFNC before inclusion [$n = 3$]). Then, three conditions of HFNC were tested in a randomized order (20, 40, and 60 L/min). HFNC was administered via the Airvo2 (Fisher & Paykel Healthcare, Auckland, New Zealand). A washout of 10 minutes with baseline treatment was performed between each period (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C818, which describes the study protocol; **legend**, Supplemental Digital Content 2, http://links.lww.com/CCM/C819). During the whole protocol, Fio_2 was continuously adjusted in order to achieve a target Spo_2 of 90% ± 2% in hypercapnic patients and of 94% ± 2% in hypoxemic patients (20).

Physiologic Measurements

The primary outcomes of this study were the indexes of respiratory effort, including esophageal pressure variations (ΔP_{es}), esophageal pressure-time product/min (PTP_{es}/min), and work of breathing/min (WOB/min). We recognize that "PTP_{es}/min" has time units in both the numerator and denominator but have elected to express it this way to be similar in format to WOB/min. Both PTP_{es} and WOB require simultaneous recording of esophageal pressure (P_{es}) and tidal volume (Vt) variations (21–23). We used respiratory inductive plethysmography (RIP) (Respitrace; Ambulatory Monitoring, Ardsley, NY) in order to estimate variations in Vt during treatment periods. Respiratory flow was calculated as the derivation of Vt over time. A calibration of RIP bands with a pneumotachograph was performed at the end of each study period. Correlation coefficients between each RIP bands (thoracic and abdominal) and the "real" Vt were determined using a multiple linear regression model (24, 25), allowing the estimation of Vt during treatment periods ($Vt = \kappa + \tau RIP_{rib\ cage} + \alpha RIP_{abdomen}$). P_{es} was continuously recorded via a thin catheter (5 F; Cooper Surgical, Trumbull, CT) inserted, after local anesthesia, 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, CA). Additional details on the method are provided in the **supplemental data** (Supplemental Digital Content 3, http://links.lww.com/CCM/C820).

Data Analysis and Assessment of Patient's Respiratory Effort

Signals were digitized at 200 Hz and sampled using an analogic/numeric system (MP150; Biopac Systems, Santa Barbara, CA). Measurement and calculation of respiratory variables were performed over at least 10 consecutive respiratory cycles during the last 2 minutes of each study period. ΔP_{es}, PTP_{es}/min, WOB/min, Vt, RR, minute volume (MV), Vt-to-inspiratory time ratio, dynamic lung compliance (CL_{dyn}), inspiratory resistance (Res), and auto positive end-expiratory pressure (PEEP) were calculated from respiratory flow and P_{es} signals via an open-source respiratory data analysis software (RespMAT) (23). For each subject, end-expiratory esophageal pressure (EEP_{es}) was manually measured for each cycle of each study periods. The difference between mean values at baseline and at each HFNC period was calculated to assess EEP_{es} variations. All signals treatment and data analysis were performed with the evaluator blinded to patient's condition.

Additional Measurements

Pulsed oximetry was continuously recorded, and capillary blood gases were sampled at the fingertip at the end of each study period to determine pH and $Paco_2$ (26). Respiratory comfort was assessed on a 10 cm visual analog scale and dyspnea via the modified Börg scale (27).

Statistical Analysis

Data were expressed using median (25–75th interquartile range [IQR]) to summarize characteristics of subjects unless specified otherwise. Baseline characteristic variables were analyzed using a one-way analysis of variance with the Satterthwaite's 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's variation of Levene's test statistic was used to verify the homogeneity of variances. When appropriate, some variables were log transformed to fulfill the model assumptions and report *p* values are based on these transformations. To analyze respiratory data in subjects according to the four breathing conditions, a mixed model with interaction between subgroups and breathing conditions was performed. At the early beginning of this study, no data had previously been reported regarding the effects of HFNC on the work of breathing in adults. In the absence of data allowing for the estimation of sample size, we decided arbitrarily to enroll 12 patients 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* values less than 0.05. All analyses were conducted using the statistical packages R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria.) and SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

Thirteen patients were included. One was withdrawn from the analysis because of early consent removal after the baseline period (severe discomfort after esophageal catheter insertion). All but one of the remaining 12 patients required oxygen therapy before inclusion, and three received HFNC before inclusion. Seven patients were included because of hypoxemic respiratory failure and five because of hypercapnic respiratory failure (two of them also presenting with hypoxemic criteria). Mean hospital length of stay at inclusion was 4 ± 2 days. Six patients were recruited in the ICU department of the IUCPQ and 6 patients in the pulmonology ward. Patients' characteristics are presented in **Table 1**. **Figure 1** depicts the time course of P_{es}, inductive plethysmography, and estimated respiratory flow over the experimental conditions in a representative patient.

Respiratory Effort

At baseline, median (25–75th IQR) ΔP_{es}, PTP_{es}/min, and WOB/min were respectively 9.8 (5.8–14.6) cm H_2O, 165 (126–179) cm H_2O • s/min, and 4.3 (3.5–6.3) J/min. At 20, 40, and 60 L/min, ΔP_{es} decreased to 8.6 (5.5–12.2), 7.6 (5.6–9.5), and 4.9 (2.1–9.1) cm H_2O, respectively, (p = 0.035). PTP_{es}/min decreased to 127 (95–188), 138 (81–172), and 72 (54–137) cm H_2O • s/min, respectively, (p = 0.033). WOB/min decreased to 3.7(2.3–5.4), 3.4 (2.7–5.0), and 2.1 (1.5–5.0) J/min, respectively, (p = 0.031). Pooled data for ΔP_{es}, PTP_{es}/min, and WOB/min are shown in **Figure 2, *A–C***. At 20, 40, and 60 L/min, the WOB/min was reduced compared with baseline in 58%, 67%, and 75% of the participants, respectively. The maximal reduction

TABLE 1. Patients Characteristics at Inclusion

Variables	Hypoxemic Patients (n = 7)	Hypercapnic Patients (n = 5)	Overall (n = 12)
Male (%)	86	40	67
Age (yr), mean ± SD	74 ± 13	61 ± 10	69 ± 13
Weight (kg), mean ± SD	88 ± 22	74 ± 11	82 ± 19
Height (cm), mean ± SD	169 ± 4	163 ± 9	167 ± 7
Body mass index (kg/m^2), mean ± SD	31.4 ± 7.1	27.8 ± 3.7	29.9 ± 6.0
FEV1[a] (L), mean ± SD	1.77 ± 0.78	0.78 ± 0.32	1.32 ± 0.78
FEV1[a] (%), mean ± SD	71 ± 27	30 ± 12	52 ± 29
FEV1/forced vital capacity[a] (%), mean ± SD	64 ± 12	44 ± 21	55 ± 19
Cause of respiratory distress (n)			
Pneumonia	2	2	4
Postoperative cardiac surgery	4	2	6
Pulmonary edema	1	0	1
Pulmonary embolism	0	1	1
Respiratory rate at inclusion (breaths/min), mean ± SD	25 ± 2	22 ± 3	24 ± 3
Pulsed O_2 saturation (%), mean ± SD	91 ± 2	91 ± 3	91 ± 2
F_{IO_2} (high-flow nasal cannula; n=3) (%), mean ± SD	63 ± 4	60 ± 0	62 ± 3
O_2 flow rate (nasal/mask; n = 9) (L/min), mean ± SD	7 ± 3	2 ± 2	5 ± 4
pH, mean ± SD	7.41 ± 0.07	7.34 ± 0.03	7.37 ± 0.06
$Paco_2$ (mm Hg), mean ± SD	40.4 ± 5.2	63.4 ± 11.6	53.1 ± 15.0

FEV1 = forced expiratory volume at 1 s.
[a]Baseline data before hospitalization.

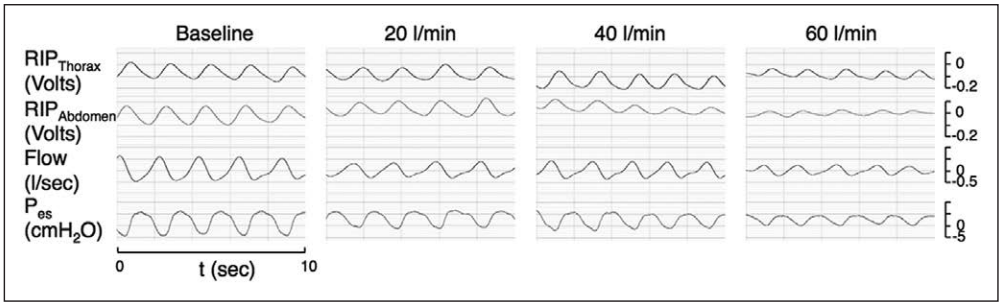

Figure 1. Time course of study variables over the experimental conditions in a representative patient (Patient number 6). The respiratory flow is estimated from respiratory inductive plethysmography (RIP) bands variations. In this patient, both esophageal pressure (P_{es}) swings and tidal volumes were reduced with the use of high-flow nasal cannula at 60 L/min while respiratory rate remained unchanged.

in respiratory effort parameters was encountered at 60 L/min with a median reduction of 27.8% (18.2–61.8%) for ΔP_{es} ($p = 0.026$), 25.6% (20.8–57.1%) for PTP_{es}/min ($p = 0.022$), and 43.3% (18.5–53.8%) for WOB/min ($p = 0.023$) (**Fig. 2, *D–F***). Most of indexes of respiratory effort at 20 and 40 L/min were reduced but not significantly different from baseline. No significant difference of respiratory effort was evidenced between flow rates of HFNC.

Respiratory Pattern and Blood Gases

Respiratory pattern parameters and capillary blood gases variations are displayed in **Table 2** (28, 29). No significant modification was evidenced between the study periods.

Respiratory Mechanics

Median auto-PEEP at baseline was 0.2 cm H_2O (0.0–1.1 cm H_2O). Neither auto-PEEP nor EEP_{es} was affected by treatment modality (**Supplemental Table 1**, Supplemental Digital Content 4, http://links.lww.com/CCM/C821). CL_{dyn} increased from 38 mL/cm H_2O (24–64 mL/cm H_2O) at baseline to 59 mL/cm H_2O (43–175 mL/cm H_2O) at 60 L/min ($p = 0.007$), and resistance decreased from 9.6 (5.5–13.4) to 5.0 (1.0–9.1) cm H_2O/L/s, respectively ($p = 0.07$) (**Fig. 3**).

Respiratory Comfort

Baseline dyspnea level assessed via the modified Börg scale was 2 (1–3)/10. No relevant modification was observed during the protocol (Supplemental Table 1, Supplemental Digital Content 4, http://links.lww.com/CCM/C821).

Subgroup Analysis

A subgroup analysis was performed in order to assess whether hypoxemic ($n = 7$) or hypercapnic patients ($n = 5$) exhibited different response profile to HFNC in terms of respiratory effort. No significant difference was evidenced within these subgroups. Data are presented in the supplemental digital content (**Supplemental Table 2**, Supplemental Digital Content 5, http://links.lww.com/CCM/C822).

DISCUSSION

In this study, we showed that the use of HFNC in patients recovering from acute respiratory failure leads to an important and significant reduction in all the indexes of respiratory effort (i.e., ΔP_{es}, PTP_{es}/min, and WOB/min), when the flow is set at 60 L/min. We did not evidence a clear dose-response relationship between flow rates and WOB and found no significant improvement of respiratory effort with the use of flows below 60 L/min.

To date, little is known about the effects of HFNC on respiratory effort in adult patients and especially on the work of breathing. This lack of data is probably related to the technical complexity of estimating Vt during HFNC, which is required for the determination of both PTP_{es} and WOB (21–23). Here, we used RIP, which has been previously used for the same purpose in neonates (25) and adult patients (30), and has been shown to give satisfactory estimation of Vt (31, 32). Using a similar methodology, Biselli et al (30) recently reported in a subset of 6 chronic obstructive pulmonary disease (COPD) outpatients that HFNC reduced the WOB during sleep, in a greater extent than conventional oxygen therapy alone. Along with our results, this reduction of indexes of respiratory effort with HFNC corroborates clinical findings that previously suggested that part of the benefits of this therapy might be attributable to a reduction in respiratory load, as demonstrated by an improvement of supraclavicular retraction (33) or thoracoabdominal asynchrony (33, 34).

Several studies conducted among patients with high baseline RRs (25 ± 3 breaths/min) (9, 17, 19, 34–36) have shown that HFNC was likely to improve the breathing pattern. We did not find such effect in the present study, which may be explained by a relatively low RR (around 20 breaths/min) in the included patients. Furthermore, Sztrymf et al (33) showed in a study performed in critical care patients that the effects of HFNC on respiratory distress symptoms may be related to the duration of exposure, and we cannot exclude that the shortness of the study periods of our protocol may also explain the absence of effect of HFNC on respiratory pattern variables (16, 17).

Associated with lower RRs, baseline values for indexes of effort were lower in the present study than previously reported values in patients with acute respiratory distress syndrome or acute lung injury, as half of the patients in the present study were included outside ICUs (37–39). This might have limited the impact of HFNC on breathing pattern in our population and may explain that we did not observe any significant effect of lower flows (20 and 40 L/min) on respiratory effort in comparison with baseline values.

However, our results are consistent with recent data from Vargas et al (19) and Mauri et al (36) who showed in patients with acute hypoxemic respiratory failure that HFNC reduced PTP_{es} by approximately 25%, compared with conventional oxygen therapy. Interestingly, Pisani et al (40) also recently reported that HFNC could reduce transdiaphragmatic PTP

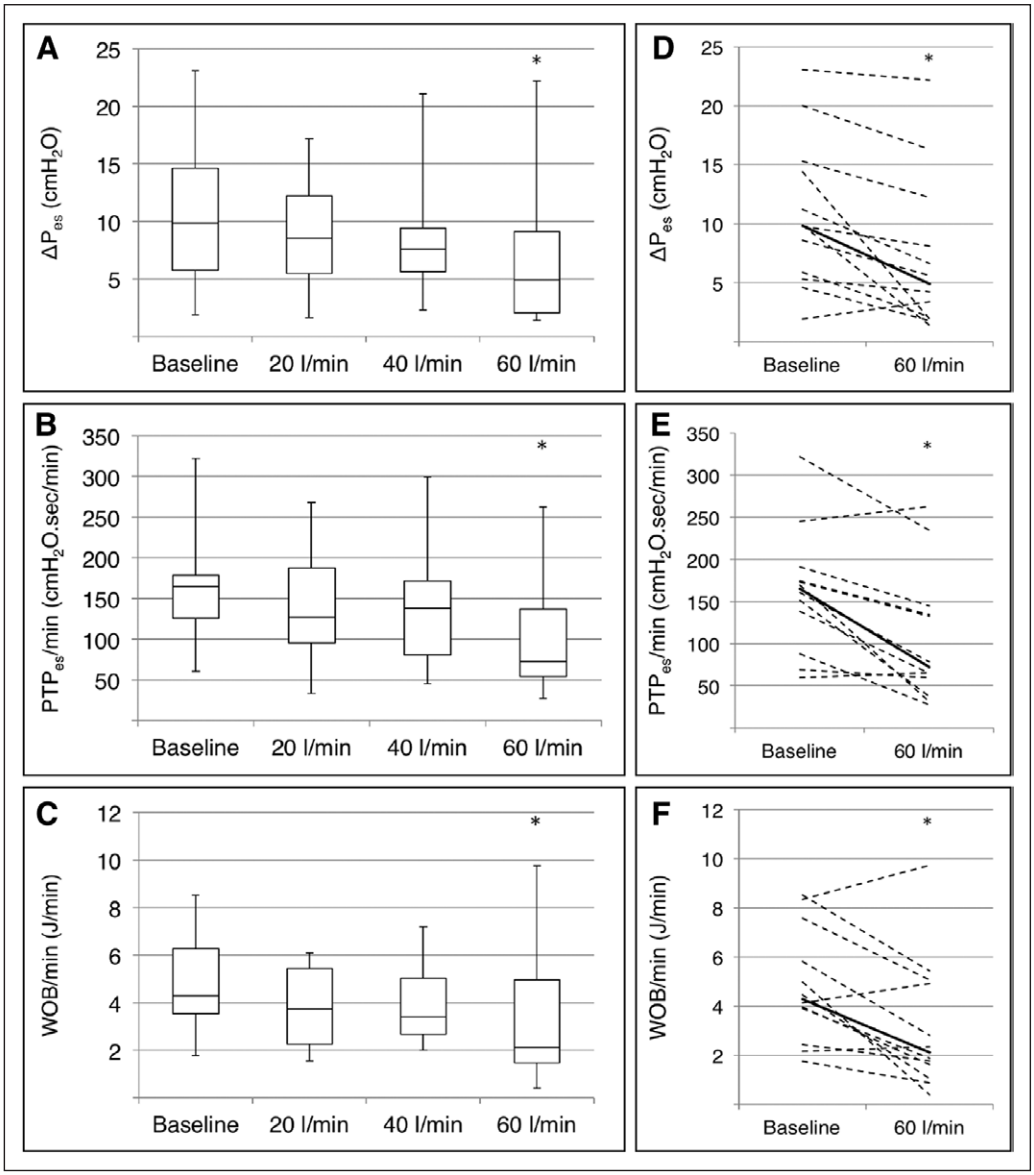

Figure 2. Indexes of respiratory effort in the tested conditions. Pooled data for esophageal pressure variations (ΔP_{es}) (cm H_2O) (**A**), esophageal pressure-time product/min (PTP_{es}/min) (cm H_2O s/min) (**B**), and work of breathing/min (WOB/min) (J/min) (**C**) are reported in the left panels. Medians are expressed as *horizontal bars* inside the boxes, 25–75th percentiles as the *bottom* and the *top of the boxes*, and maximal-minimal values as *whiskers*. The right panels display individual data (*dashed lines*) and median (*solid line*) for ΔP_{es} (cm H_2O) (**D**), PTP_{es}/min (cm H_2O s/min) (**E**), and WOB/min (J/min) (**F**) at baseline and with high-flow nasal cannula at 60 L/min. *$p < 0.05$ versus baseline.

of positive airway pressure (6, 8, 43). This pressure depends on the mouth position (open or closed) (6, 8, 43), on the flow rate (7, 8), and reaches its highest value at the beginning of expiration (8, 41). Interestingly, in the study of Vargas et al (19), HFNC set at 60 L/min was as effective as a continuous positive aiirway pressure set at 5 cm H_2O in reducing respiratory effort. Nevertheless, the clinical relevance of this PEEP effect remains uncertain (42), and we believe it is unlikely that the PEEP effect by itself plays a major role in the reduction of respiratory effort.

Second, several bench studies have reported that a significant washout of nasopharyngeal dead space might occur during HFNC with proportional impact of the flow used (12–15). This dead space washout could explain in part the reduction of the indexes of respiratory effort. Indeed, it has been demonstrated in subjects undergoing mechanical ventilation that the reduction of instrumental dead space significantly reduced the work of breathing (44–46). It is therefore possible that a reduction of physiologic dead space during HFNC might contribute to decreasing the work of breathing (5, 18). Our data do not support this hypothesis, even though we observed a nonsignificant decrease in $Paco_2$ levels for similar MVs. Here again, our sample size was probably too small to shed a light on this mechanism.

in stable hypercapnic COPD patients, within similar proportions. We decided in our study to enroll both hypoxemic and hypercapnic patients, assuming that different underlying physiopathology might lead to different response patterns. However, we failed to demonstrate significant differences between these subgroups, as our sample size was probably too small to draw a conclusion. Several underlying mechanisms might explain the reduction of respiratory effort we observed in our study.

First, the "PEEP effect" described with high flow is part of the discussed beneficial effects of HFNC (5, 8, 41, 42). It has been shown for a long time that HFNC generates low levels

Third, the reduction of indexes of effort might also be explained by an improvement in respiratory mechanics, as demonstrated by an increase in CL_{dyn} and a nonsignificant reduction in Res. Our data are in agreement with the findings of Mauri et al (36), who showed in patients with acute hypoxemic respiratory failure that CL_{dyn} was significantly increased with HFNC. Indeed, it has been previously reported by several authors that HFNC increased end-expiratory lung

TABLE 2. Respiratory Pattern and Blood Gases at the End of the Tested Conditions

Variables	Baseline	20 L/min	40 L/min	60 L/min	*p*
Vt (mL)	265 (228–337)	287 (228–313)	280 (211–322)	289 (198–349)	0.97
Vt (mL/kg[a])	4.2 (3.7–5.9)	4.6 (3.3–5.5)	4.5 (3.4–5.5)	4.6 (3.1–6.2)	
Respiratory rate (breaths/min)	20 (18–25)	20 (16–24)	23 (16–26)	19 (15–24)	0.43
Minute volume (L/min)	5.7 (4.6–7.1)	5.3 (4.5–6.6)	5.6 (5.0–6.7)	5.5 (5.0–6.3)	0.68
Pulsed o_2 saturation (%)	93 (89–94)	92 (89–92)	92 (90–92)	92 (90–93)	0.02
F_{IO_2} (%)[b]	40 (35–60)	46 (29–64)	40 (27–46)	40 (26–45)	0.003
pH	7.42 (7.36–7.42)	7.42 (7.37–7.43)	7.42 (7.37–7.45)	7.42 (7.38–7.45)	0.11
$Paco_2$ (mm Hg)	52.1 (40.8–61.3)	47.2 (40.6–62.7)	43.9 (38.9–59.6)	43.9 (39.2–61.4)	0.31
Vt/inspiratory time (mL/s)	256 (243–286)	243 (207–277)	240 (219–269)	262 (210–322)	0.89

Vt = tidal volume.

[a]Tidal volume is expressed as mL per kilograms of predicted body weight (PBW). PBW is calculated with the following formula: PBW = X + (0.91 × height [cm] − 152.4) where X = 50 for men and X = 45.5 for women (from [28]).

[b]For patients with conventional O_2 flow at baseline, F_{IO_2} was estimated as previously described in reference (29).

Data are expressed as median (25–75th interquartile range).

volume (9, 11). This mechanism is likely to lead subjects to breath in a more compliant part of the pressure-volume curve, thus improving respiratory efficiency (47). Interestingly, in the study of Biselli et al (30) conducted in stable COPD patients, no significant improvement of CL_{dyn} was evidenced with HFNC despite a similar reduction in WOB. This suggests that the different mechanisms described above are probably involved in the reduction of respiratory effort with different ponderations according to the underlying physiopathology (i.e., hypercapnic or hypoxemic patients). Our study was not sufficiently powered to state about this issue, and further studies could help understanding the respective role of each of these mechanisms in different physiopathologic situations. Finally, although nonsignificant, we also observed a decrease in Ress, consistent with previous data reported by Mundel et al (16) in a nasal cavity model. As previously suggested by several authors (5, 18, 47), this decrease in Res might predominantly occur in the nasopharynx, but further studies are needed to address this specific issue.

This study has several limitations. The measurement of Vt was indeed a difficult aspect of the methods in the situation of HFNC, as the reference technique with direct measurements of the respiratory flows cannot be used. The RIP used to measure respiratory flows is a validated technique but may be inaccurate. In previous studies, the accuracy was estimated to ±10% (24, 31, 32), and we performed repeated calibrations after all conditions to reduce this bias. WOB being computed from Vt variations, we cannot exclude that a lack of accuracy in Vt estimation might have lead to errors in WOB calculation. However, other indexes of effort independent of the Vt measurements were reduced in the same proportion than WOB.

Furthermore, we do not clearly explain that we observed an increase in CL_{dyn} despite absence of significant modifications in EEP_{es}. As we performed our recordings without gastric pressure measurements, the end-expiratory pressure (EEP) may not have been accurate due to potential expiratory muscles activity (contraction or relaxation). This phenomenon may modify the pleural pressure curve in the very specific point of time of end expiration, and it is therefore possible that we underestimated the modifications of EEP.

Last, as recently suggested, Patient-Self Inflicted Lung Injury (P-SILI) may occur in spontaneously breathing patients with respiratory failure, while high respiratory drive promotes highly negative pleural pressures and consequently high transpulmonary pressures and high Vts (48). By reducing pleural pressure variations and consequently transpulmonary pressure, HFNC may thus limit the risk of P-SILI.

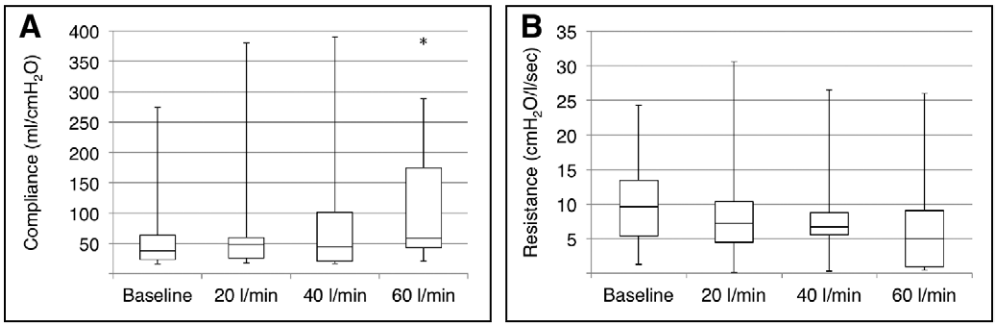

Figure 3. Respiratory mechanics in the tested conditions. Dynamic lung compliance (L/cm H_2O) (**A**) and resistance (cm H_2O/L/s) (**B**) according to tested conditions. Medians are expressed as *horizontal bars* inside the boxes, 25–75th percentiles as the *bottom* and the *top of the boxes*, and maximal-minimal values as *whiskers*. *$p < 0.05$ versus baseline.

CONCLUSION

In conclusion, HFNC significantly reduces the indexes of respiratory effort in subjects recovering from acute respiratory failure. This effect is associated with an improvement in

respiratory mechanics. Our results, along with those regarding PEEP effect and dead space washout, strongly suggest using the highest flow when initiating HFNC in patients with acute and moderate respiratory failure. Indeed, 60 L/min was usually the most efficient flow to reduce respiratory effort, especially in hypoxemic patients. Further studies are warranted to determine objective criteria that could help clinicians in flow titration at patient's bedside.

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