의학박사 학위논문

이중유량 시스템: 정상인과 저산소성 호흡부전 환자들을 대상으로 한 탐색적 임상연구

Bi-level high flow system (Bi-flow) : An exploratory clinical trial for healthy subjects and hypoxemic respiratory failure patients

울 산 대 학 교 대 학 원

의 학 과

서 우 정

이중유량 시스템: 정상인과 저산소성 호흡부전 환자들을 대상으로 한 탐색적 임상연구

지 도 교 수　허 진 원

이 논문을 의학박사 학위 논문으로 제출함

2024년 2월

울 산 대 학 교 대 학 원

의 학 과

서 우 정

서우정의 의학박사학위 논문을 인준함

심사위원	김성훈	(인)
심사위원	임채만	(인)
심사위원	홍상범	(인)
심사위원	허진원	(인)
심사위원	김원영	(인)

울 산 대 학 교 대 학 원

2024년 02월

Abstract

Background: High-flow nasal cannula (HFNC) devices are widely used for oxygen supplementation. However, it supplies the same flow rate during inspiration and expiration, causing turbulence and increased respiratory resistance in the nasopharynx during expiration, leading to patient discomfort. We developed a bi-level high-flow system (Bi-flow) to improve this problem, providing additional flow during inspiration.

Objective: We investigated the physiologic effects of applying Bi-flow in healthy individuals and patients with hypoxemic respiratory failure and compared it with conventional HFNC (Uniflow) usage.

Methods: For healthy individuals, Uniflow (U30, U40, U50) and Bi-flow (basal flow 10, 20, 30L/min) modes were randomly assigned. Each mode varied the [inspiration/expiration rate] by increasing additional flow during inspiration, as follows: 30/10, 30/20, 40/10, 40/20, 40/30, 50/20, 50/30 trials. Physiologic data (respiratory rate, heart rate, transcutaneous CO_2, modified Borg scale) and lung volume (monitored through Electrical Impedance Tomography-EIT) were recorded. Nasal pressure-time product (N-PTP) was calculated as a surrogate marker for work of breathing (WOB).

In the hypoxemic patient's study, Uniflow and Bi-flow modes (BF25, BF50, BF75) were randomly allocated. Bi-flow mode maintained the same inspiratory flow as Uniflow, but supplied a portion of the total flow as additional flow (in percentage). The four modes were compared by analyzing patients' ROX index (the ratio of oxygen saturation as measured by pulse oximetry/FiO_2 to respiratory rate), lung volume, and N-PTP.

Results: The healthy individual's study included twelve healthy individuals. When Bi-flow was applied, a reduction in respiratory rates was observed compared with natural breathing. Additionally, a decrease in inspiratory and expiration N-PTP was noted with Bi-flow. For the 24 patients with hypoxic respiratory failure, there were no significant differences in the ROX index (UF: BF25: BF50: BF75; 13.2: 13.7: 13.4 13.9; p=0.98). However, there was a slight decrease in inspiratory N-PTP in the Bi-flow modes (UF: BF25: BF50: BF75; 11.2: 8.4: 6.0: 9.9; p=0.03). Lung volume data monitored through EIT did not show any significant statistical differences.

Conclusion: We applied Bi-flow to healthy individuals and patients with hypoxemic respiratory failure, and the results showed a partial decrease in N-PTP, a proxy of work of breathing. Furthermore, no significant adverse effects were observed. (KCT0006100, KCT0007352)

Contents

List of Figures

List of Tables

Introduction

Various types of oxygen supplemental devices have been used to avoid mechanical ventilation in patients with respiratory failure. Non-invasive ventilation (NIV) has proven beneficial for patients with hypercapnic respiratory failure or acute pulmonary edema. NIV comes in various interfaces, such as nasal pillows, facial masks, and helmet types, allowing flexibility based on the patient's respiratory patterns and compliance [1]. However, instances exist where patients struggle to adapt to NIV or worsening hypoxemia because of secretion [2, 3]. Recently, there has been a rapid increase in the use of high-flow nasal cannula (HFNC) in addition to conventional oxygen therapy and NIV methods. [4-7]. It offers the advantage of providing positive end-expiratory pressure (PEEP) by delivering humidified oxygen through high-flow [8, 9]. Many studies have shown that HFNC advantage has delayed mechanical ventilation in patients with coronavirus disease 2019 (COVID-19) [10, 11]. Besides differing from NIV and conventional oxygen supplemental system, HFNC has shown no significant side effects or complications, making it widely adopted globally.

Despite its many advantages, individualized flow settings are recommended depending on the course of the disease and the patients' heterogeneous lung condition [12]. Moreover, some patients using HFNC may complain of discomfort, leading to turbulence between tracheal and nasal cannula flows during expiration [13, 14]. This phenomenon can also result in increased work of breathing (WOB) during expiration due to continuous high-flow supply for patients using HFNC [15]. Taking this into consideration, the authors have devised a bi-level flow system (Bi-flow) collaboration with the cooperation of the manufacturers of HFNC. It can deliver different flow rates during inspiration and expiration, which is similar to bilevel positive airway pressure (BiPAP), which provides different pressures during inspiration and expiration [16]. BiPAP is a type of NIV; the patient's respiratory efforts trigger it, and it has been shown to improve gas exchange and decrease the WOB [17].

This study was conducted in two phases. In the first phase, Bi-flow was applied to healthy individuals to assess its feasibility and the benefit. In the second phase, it was applied to patients with hypoxemic respiratory failure, one of the indications for HFNC, to examine whether it could affect respiratory physiology and help the participant's respiratory efforts.

I. Healthy subjects

Methods

This study was conducted at Asan Medical Center (Seoul, South Korea) from April to June 2020. The study obtained informed consent from each participant and received approval from the Institutional Review Board (IRB No. 2020-1901).

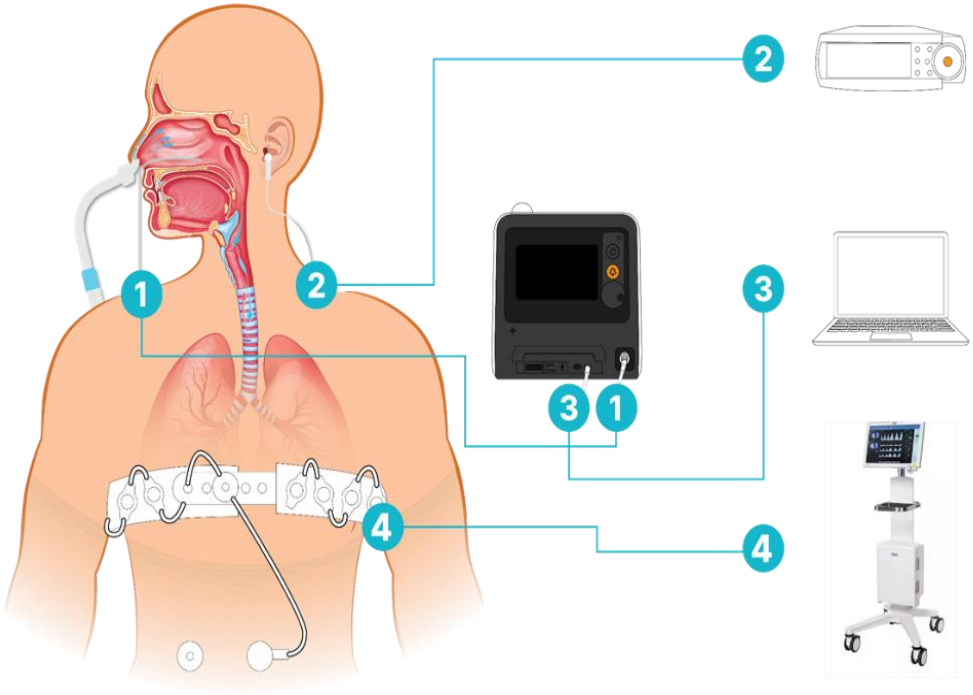
1. Data collection

During the study time, the following information was recorded from the healthy participants, as illustrated in a schematic diagram in Figure 1.

1. Respiratory data including nasopharyngeal pressure: Due to the difficulty in accurately measuring WOB, we used the nasal pressure-time product as a proxy of WOB. It was calculated by integrating *Paw* with time $\int (P\_aw - \mathrm{PEEP})\, dt$. For measuring the nasopharyngeal pressure of the participants, a thin PVC catheter (7 Fr) was placed 9 cm deep in the nostril.

   The pressure signal was stored using LabVIEW (National Instruments Co., TX, USA), and all numerical analyses were performed using the MATLAB software (Mathworks Inc, MA, USA). ΔPexp (cmH_2O) was defined as [peak pressure – baseline pressure] during expiration, and ΔPinsp (cmH_2O) as [baseline pressure – lowest pressure] during inspiration. Inspiratory, expiratory, and total nasal pressure time product (N-PTP) were obtained Figure 2 [15, 16]. Inspiration and expiration times were also measured. Relative changes (%) in inspiratory and expiratory time were referenced to natural breathing.
2. Physiologic parameters: respiratory rates (RR), inspiratory:expiratory (I:E) ratio, heart rates (HR), transcutaneous CO_2 ($tcPCO_2$), and pulse oxygen saturation (SpO_2) per minute. For evaluating subjective comfort, the researcher assessed the healthy participants using the Modified Borg Scale (MBS) at the end of each flow trial.
3. Lung volume data: Tidal impedance variation (TIV), ventral-dorsal ratio, global inhomogeneity (GI) index, and electrical impedance tomography (EIT) was obtained continuously throughout the study to compare end-expiratory lung volume (EELI). EIT generates cross-sectional images of impedance distribution within electrically conductive objects and enables semi-quantitative evaluation of static and dynamic lung volumes [18, 19].

Figure 1. A schematic diagram of monitoring during the Bi-flow study



① Continuous monitoring of nasopharyngeal pressure using a thin PVC catheter in the nostril

② Attachment sensor for percutaneous CO_2 monitoring

③ HFT700 machine embedded Bi-flow system (respiratory parameters were analyzed through LabVIEW software)

④ Electrical impedance tomography (EIT) belt for lung volume data

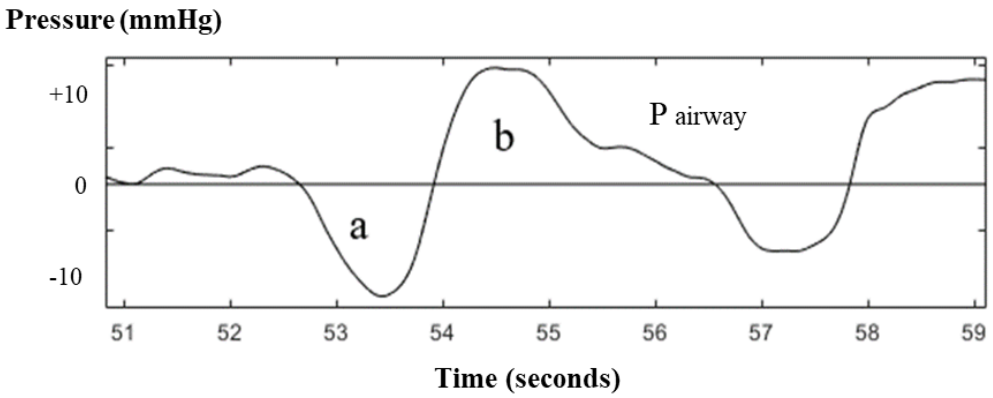


Figure 2. Respiratory parameters using nasal pressure-time product (N-PTP) in a pressure-time curve

Area (a) is inspiratory N-PTP, and area (b) is expiratory N-PTP. Total N-PTP is the sum of (a) and (b). The values of N-PTP are the average values taken of the breaths at the middle 1 min during the 3-min period.

2. Eligible participants

This study was a proof-of-concept trail for Bi-flow in healthy participants for assessing feasibility. Participants aged 18 years and above, without specific diagnosed cardiovascular diseases, and who were eligible for clinical research were recruited. Healthy individuals unable to use nasal cannula due to various reasons, such as previous facial trauma or deformities, were excluded.

3. Study design and intervention

This study was a prospective, controlled study initiated with a Uniflow or Bi-flow mode through a randomized block design with a 4:1 block. Before implementing the study protocol, spontaneous breathing was conducted for approximately 5 min for each participant; in cases starting with the Uniflow mode, the same flow was exercised for both inspiration and expiration, similar to the existing HFNC. The uniflow rates were increased to 30 L/min, 40 L/min, and 50 L/min.

For the Bi-flow mode, the basal flow started at 10 L/min, 20 L/min, and 30 L/min. Additional flow during inspiration was supplied at 20 L/min, 30 L/min, and 40 L/min, respectively, with 3 min of breathing, starting from each basal flow. The sequence of basal flow rates was randomized. Therefore, the flow settings were as follows [inspiration /expiration]: 30/10, 30/20, 40/10, 40/20, 40/30, 50/20, and 50/30 L/min. A wash-out period of 5 min, consisting of spontaneous breathing, was implemented for each mode.

In this study, a crucial step involved the machine's recognition of inspiration and expiration phase during the respiratory cycle. Inspiration and expiration were detected based on pressure changes in response to airflow variations in the nasopharynx. The transition from expiration to inspiration was determined as the point at which a drop-in pressure at baseline exceeded 0.4 cmH_2O. The transition from inspiration to expiration was determined as the point at which the flow generated from the machine exceeded 1 L/min compared with the setting flow, or when the inspiratory phase exceeded the limit for inspiratory time (6 s). The current version of the Bi-flow system failed to detect the inspiratory effort of the participant when the bias flow before inspiration was relatively low or the participant's respiratory effort was too weak. Owing to this technical limitation, the proportion of Bi-flow breaths ranged between 25% and 63% of all recorded breaths in Figure 3.

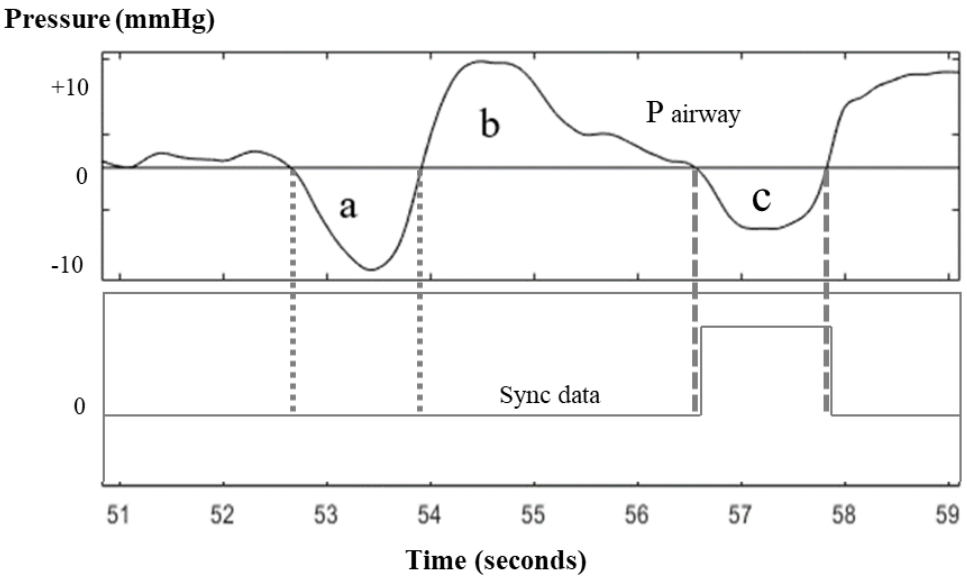


Figure 3. Airway pressure tracing (upper) and Bi-flow operating signal (lower)

During Bi-flow, breath (a) was a failed operation, and breaths (c) were successful.

4. Statistical analysis

All values are expressed as median and range (min–max) and 95% confidence interval (CI) for continuous variables or percentages for categorical variables. Wilcoxon signed-rank test was used for continuous data, and Pearson's chi-squared test or Fisher's exact test was used for categorical data. We compared the parameters of Uniflow and Bi-flow at the same inspiratory flow rate. Pooled and matched analyses were performed for the comparison of settings in Pinsp and Pexp. All p-values were two-tailed, with statistical significance set at $p < 0.05$. All statistical analyses were performed using the SPSS software (version 22.0; IBM Corporation, Somers, NY, USA).

Results

1. Baseline characteristics

We enrolled sixteen healthy participants. Among them, 12 completed the full protocol and were included in the analysis. The population comprised 58% males, and the mean age was 46.2 years. The mean BMI was 22.7 kg/m^2.

As the flow rate increased, compared with natural breathing, RR decreased during Uniflow and tended to decrease during Bi-flow. Compared with Uniflow, the decrease in RR was less pronounced with Bi-flow. As the flow rate increased during Uniflow, both inspiratory and expiratory times were prolonged. During Bi-flow, inspiratory time was prolonged, but expiratory time did not change significantly from natural breathing. Compared with Uniflow, expiratory time was shorter with Bi-flow. The I:E ratio tended to increase during Uniflow, but remained similar or decreased during Bi-flow in Table 1. HR, $tcPCO_2$, SpO_2, and MBS did not differ between Uniflow and Bi-flow at the same inspiratory flow rate in Table 2.

2. Respiratory parameters including N-PTP

Expiratory time was shorter during Bi-flow than during Uniflow in Fig 4-a. Inspiratory N-PTP and expiratory N-PTP were both lower during Bi-flow compared with Uniflow in Table 3. Total N-PTP was lower during Bi-flow than during Uniflow in Fig 4-d. The decrease in N-PTP was most prominent at B40/20 (inspiratory flow, 40 L/min, and expiratory flow, 20 L/min).

Table 1. Changes in synchronized respiratory parameters according to the flow setting

	Setting	RR (/min)	Inspiratory time (s)	Expiratory time (s)	I:E ratio
Baseline	Natural breathing	18.0 (16–22)	1.25 (1.1–1.7)	2.1 (1.6–6.1)	1.63 (1.18–3.59)
Flow30	U30	13.5* (7.0–18)	1.7* (1.4–2.7)	2.85* (1.9–5.7)	1.54 (1.25–2.48)
	B30/10	14* (7.0–27.0)	1.85* (0.9–2.5)	2.4 (1.2–5.7)	1.33* (0.68–3.35)
	B30/20	15* (12.0–21.0)	1.6 (1.0–2.3)	2.25 (1.3–2.9)	1.39 (0.93–2.15)
Flow40	U40	13* (6.0–17.0)	1.7* (1.4–2.2)	3.05* (2.1–6.8)	1.98 (1.50–3.24)
	B40/10	12.7* (10.0–20.0)	1.9* (1.1–2.9)	2.5** (1.8–3.4)	1.35*, ** (0.86–1.72)
	B40/20	17.0** (10.0–25.0)	1.5 (0.9–2.3)	2.15** (1.5–3.7)	1.57 (1.06–2.22)
	B40/30	13.5* (9.0–27.0)	1.55* (0.9–2.3)	2.95* (1.4–4.1)	1.74 (1.26–2.05)
Flow50	U50	10.5* (7.0–17.0)	1.8* (1.3–2.2)	3.75* (2.0–4.8)	2.0 (1.35–2.71)
	B50/20	14.5*, ** (10.0–22.0)	1.65 (0.9–2.3)	2.35** (1.4–3.7)	1.39** (0.45–4.11)
	B50/30	15.0*, ** (10.0–25.0)	1.7* (1.2–2.6)	2.5** (1.0–3.6)	1.34*, ** (0.77–2.08)

Data are expressed as median and range (min–max).

*$p < 0.05$ compared with natural breathing, **$p < 0.05$ compared with Uniflow.

RR, respiratory rates; I:E ratio, inspiratory to expiratory ratio; U, Uniflow; B, Bi-flow.

Table 2. Changes in physiologic variables according to the flow setting

	Setting	HR (/min)	$tcPCO_2$ (mmHg)	SpO_2 (%)	MBS
Baseline	Natural breathing	72.0 (65.8–96.3)	38.8 (24.2–43.7)	98.0 (96.0–100.0)	0
Flow30	U30	67.8 (64.0–96.0)	39.5 (23.9–42.1)	97.7 (96.0–100.0)	0 (0–3)
	B30/10	68.9 (63.7–91.3)	37.4 (23.5–42.2)	98.8 (95.7–100.0)	0.4 (0–2)
	B30/20	68.2 (63.0–93.7)	38.3 (24.4–42.4)	98.0 (96.3–100.0)	0.5 (0–3)
Flow40	U40	71.0 (65.0–96.0)	38.2 (21.9–42.8)	98.0 (96.0–100.0)	0.5 (0–3)
	B40/10	71.0 (63.3–96.7)	37.3 (21.4–41.1)	98.0 (96.0–100.0)	0.5 (0–3)
	B40/20	69.5 (63.3–93.0)	37.7 (21.5–42.1)	98.0 (96.0–100.0)	0.3 (0–2)
	B40/30	69.7 (61.7–94.7)	39.2 (22.6–41.5)	98.2 (96.0–100.0)	0.3 (0–3)
Flow50	U50	71.0 (64.7–97.7)	37.9 (21.1–43.0)	98.0 (95.7–100.0)	0.8 (0–4)
	B50/20	68.8 (61.3–93.3)	37.1 (21.2–41.9)	98.0 (95.7–100.0)	0.5 (0–3)
	B50/30	71.7 (63.0–95.7)	36.6 (21.3–42.5)	98.0 (95.7–100.0)	0.3 (0–4)

Data are expressed as median and range (min–max).

HR, heart rate; $tcPCO_2$, transcutaneous PCO_2; SpO_2, saturation pulse oxygen; MBS, modified Borg scale; U, Uniflow; B, Bi-flow.

Table 3. Changes in Pinsp and Pexp

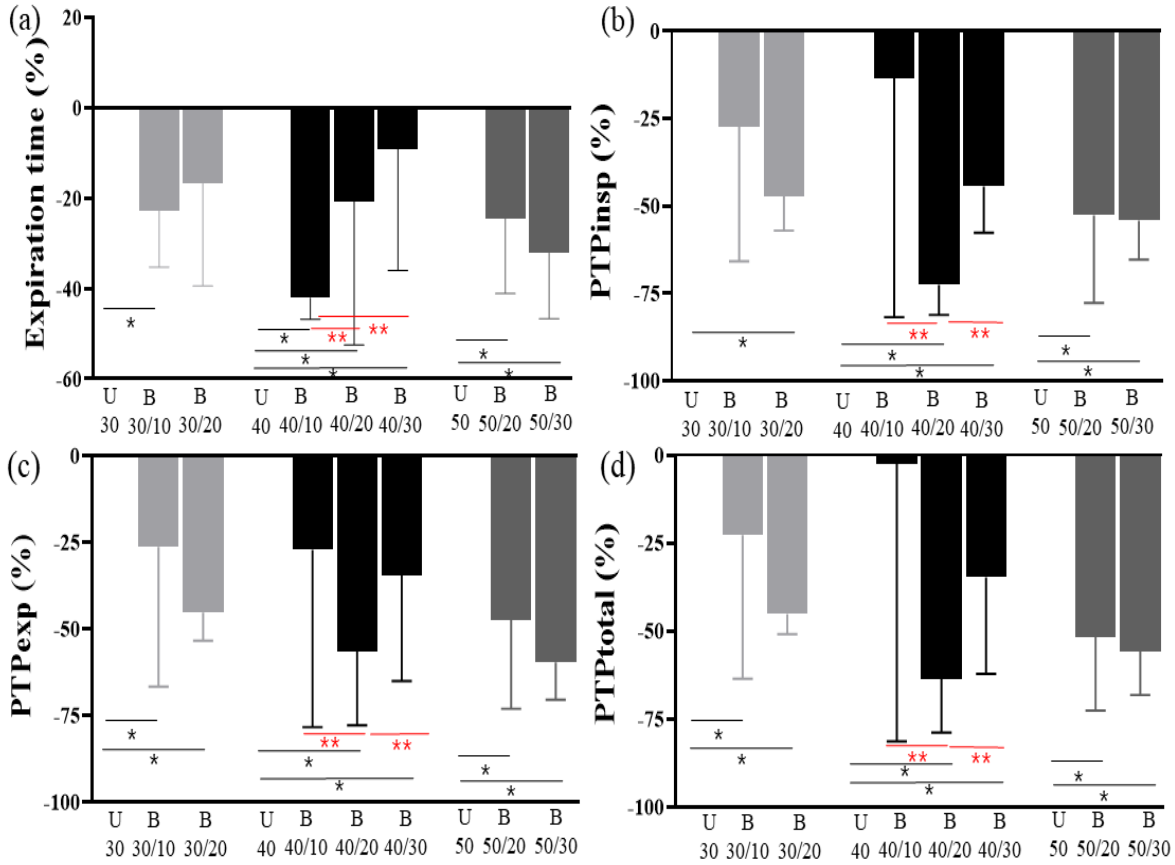
	Setting	Pinsp, %	Pexp, %
Flow30	U30	0	0
	B30/10	-27.4 (-75.7–37.7)	-22.71 (-76.92–86.13) *
	B30/20	-47.18 (-78.68–24.26) *	-45.22(-63.28–-27.74) *
Flow40	U40	0	0
	B40/10	-13.41 (-91.18–-172.97)	-27.16 (-81.08–170.23)
	B40/20	-72.61 (-89.80–-31.47) *, **	-56.43 (-89.31–-0.76) *, **
	B40/30	-44.39 (-74.18–-0.43) *, **	-34.40 (-79.32–-2.40) *, **
Flow50	U50	0	0
	B50/20	-52.65 (-86.01–0.00) *	-51.68 (-76.46–-12.46) *
	B50/30	-54.18 (-73.91–48.39) *	-55.76 (-78.17–17.08) *

Data are expressed as median and range (min–max)

*p < 0.05 compared with Uniflow, **pe of < 0.05 compared with Bi-flow.

U, Uniflow; B, Bi-flow.

Figure 4. Changes in respiratory time and N-PTP



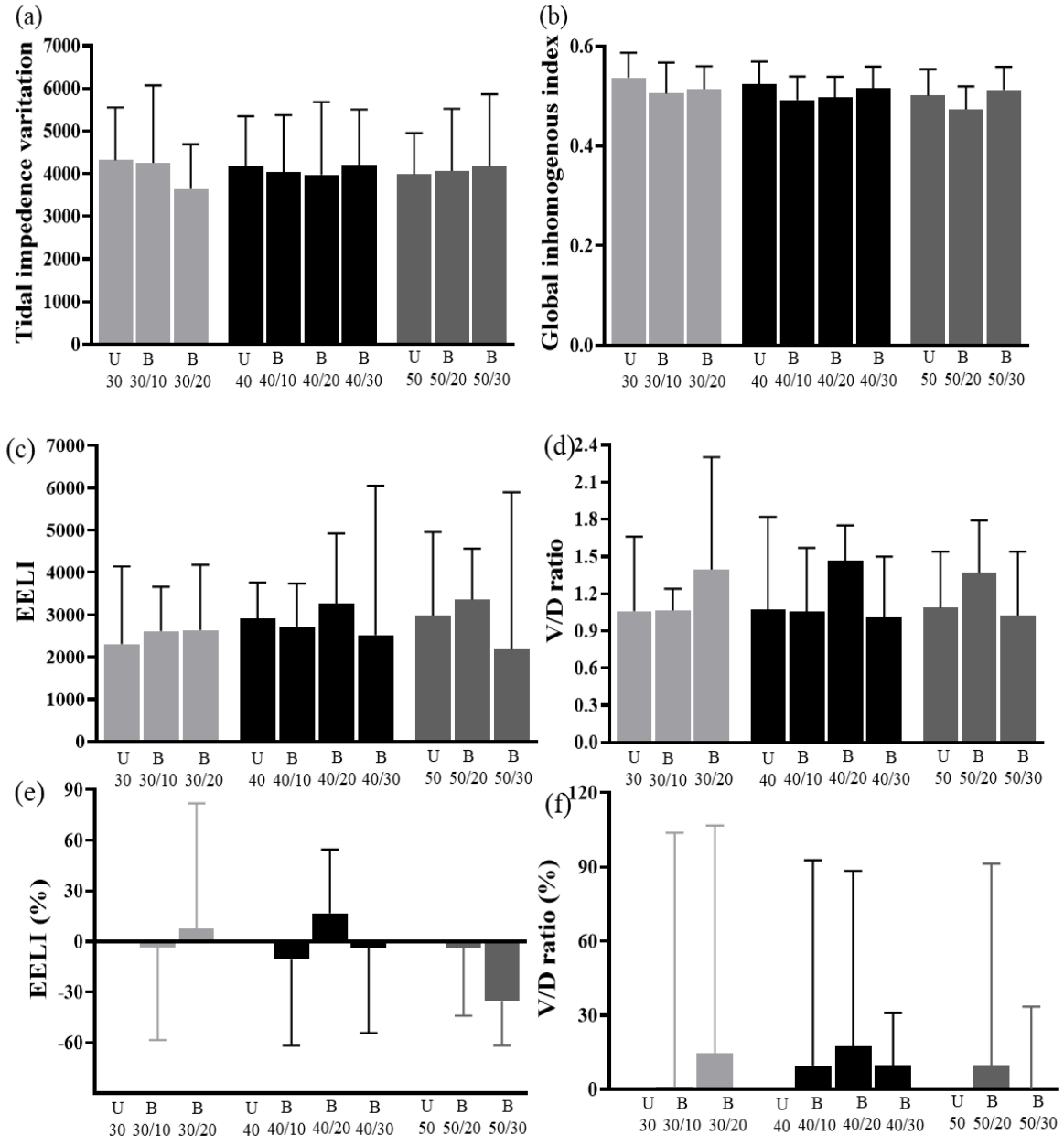
*p < 0.05 compared with Uniflow, **p < 0.05 compared with Bi-flow (in red).

N-PTP, nasal pressure-time product; U, Uniflow; B, Bi-flow.

3. Lung volume data using EIT

EELI was not different between Uniflow and Bi-flow in Figure 5. TIV, GI index, and ventral/dorsal ratio were not different between the modes. Figures 5-e and 5-f present percentages based on UF, with 0% as the reference.

Figure 5. Changes in TIV, global inhomogeneous index, EELI, and ventral/dorsal ratio of EIT



Data are expressed as median and range (min–max).

TIV, tidal impedance variation; EELI, end expiratory lung impedance; EIT, electrical impedance tomography; V/D ratio, ventral/dorsal ratio; U, Uniflow; B, Bi-flow.

II. Patients with hypoxemic respiratory failure

Methods

This study was conducted with a multi-center, prospective, cross-over design and was carried out at three university-affiliated hospitals: Asan Medical Center (Seoul, South Korea), Pusan National University Yangsan Hospital (Pusan, South Korea), and Ilsan Paik Hospital (Gyeonggi Province, South Korea). This study received institutional review board (IRB) approval from each institution (Asan Medical Center: 2021-1817; Pusan National University Yangsan Hospital: 03-2021-025; Ilsan Paik hospital: 2022-01-050.), and informed consent was obtained from patients or their family members. The clinical trial registration number of this study is KCT0007352.

1. Eligible patients

This study included hospitalized patients aged 19 years to 75 years, especially for mild to moderate hypoxemic respiratory failure ($100 < PaO_2/FiO_2$ ratio < 300). Excluded patients comprised of those who were incapable of nasal cannula application due to previous facial surgery, trauma, deformity, airway obstruction, or deterioration of respiratory failure requiring mechanical ventilation. This study was initially designed to enroll 24 patients with hypercapnic respiratory failure (arterial blood gas analysis showing $PaCO_2$ between 45 mmHg and 70 mmHg and pH above 7.3). However, it was discontinued due to difficulties in enrollment. Patient information is provided in the Appendix.

2. Study design and intervention

From 2022 March to 2023 February, this was a prospective, controlled study initiated with a Uniflow system; afterward, the three Bi-flow mode (Bi-flow 25, Bi-flow 50, Bi-flow 75 modes) were sequentially changed and randomly assigned by the researcher. The initial HFNC setting (UF) was determined by a physician evaluation, including the patient's clinical situation, last ABGA results, and a simple chest x-ray. Each mode was applied for 20 min, and there was a wash-out period between each mode.

1. Uniflow system (UF): Same method as existing HFNC, by supplying the same flow rate to inspiration and expiration
2. Bi-flow 25 (BF25): Supply 75% of the single flow used in UF as the base flow rate and 25% as an additional flow during inspiration
3. Bi-flow 50 (BF50): Supply 50% of the single flow used in UF as the base flow rate and 50% as an additional flow during inspiration
4. Bi-flow 75 (BF75): Supply 25% of the single flow used in UF as the base flow rate and 75% as an additional

flow during inspiration

3. Data collection

All participating institutions in this study used the same HFNC machine, the HFT700 from MEC-ICS (Paju, Gyeonggi-do, South Korea). Bi-flow was the one of the built-in modes for in the machine.

1. Patient information: age, sex, underlying diseases, administered medication by electronic medical record system (EMR) review
2. Hemodynamics: blood pressure (systolic, diastolic), HR, RR, SpO_2, arterial blood gas analysis (ABGA), percutaneous CO_2 ($tcPCO_2$)
3. Respiratory parameters: N-PTP, mouth breathing ratio, modified Borg scale (MBS) for patients (To measure N-PTP, we used a nasal cannula during study and the pressure signal was analyzed using LabVIEW (National Instruments Co., TX, USA).)
4. Lung volume data: TIV, end-expiratory lung volume analyzed as the EELI, ventral to dorsal ratio using PulmoVista500 (Drager Medical GmbH, Lubeck, Germany) during the entire study time

The primary outcome compared the ROX index between the UF and BF modes. ROX index was determined as the HFNC outcome for intubation and was calculated using this formula [20]:

$$\text{ROX index} = \frac{SpO_2/FiO_2}{respiratory\ rate}$$

Additionally, as a secondary outcome, changes in physiologic data (N-PTP, $tcPCO_2$, heart rate, respiratory rate) were compared for each mode.

4. Statistical analysis

Continuous variables were presented as median with range (minimum-maximum). Categorical variables were expressed as percentages. When we compared the data between modes, the Kruskal-Wallis test was used. All analysis were considered statistically significant at $p < 0.05$ (two-sided). All analyses were performed using Microsoft Excel 2019 and GraphPad Prism version 9.0.0 for Windows (GraphPad Software, Boston MA USA; www.graphpad.com).

Results

1. Baseline characteristics and physiologic parameters

Twenty-four patients with hypoxemic respiratory failure were included. Among the study participants, seventeen patients (70.8%) were male, with an average age of 59.1 years and a median body mass index (BMI) of 23.6 kg/m^2. The median

HFNC initial flow rate was 40 L/min, with a FiO_2 of 40%. The median respiratory rate was 19 breaths/min, and the $tcPCO_2$ was 37 mmHg. The patients' baseline data before the study are presented in Table 4.

As the primary outcome, the ROX index slightly increased in BF modes, although no statistically significant differences were observed. As a secondary outcome, the average heart rate, respiratory rate, SpO_2, and $tcPCO_2$ did not show significant differences among each mode. However, the modified Borg scale appeared to decrease slightly in the BF25 mode when compared to Uniflow in Table 5.

Table 4. Baseline characteristics and initial setting for patients with hypoxemic respiratory failure

Variables	Median (min-max)
Male	17/24 (70.83%)
Height (cm)	170 (147-182)
Weight (kg)	67 (38-95)
BMI (body mass index, kg/m^2)	23.57 (15.59-31.87)
Oxygen flow (L/min)	40 (35-45)
Fraction of inspired oxygen (FiO_2, %)	40 (30-55)
Heart rate (HR, rate/min)	86 (68-115)
Respiratory rates (RR, rate/min)	19 (8-35)
Systolic blood pressure (SBP, mmHg)	126 (90-173)
Diastolic blood pressure (DBP, mmHg)	70 (30-105)
Percutaneous CO_2 ($tcPCO_2$, mmHg)	37 (22-65)
Modified Borg scale (MBS)	1 (0-4)
ROX index (PaO_2/FiO_2/RR)	13.61 (5.49-40.83)

Data are expressed as median and range (min–max).

Table 5. Ranges of vital signs and ROX index for each mode

	UF	BF25	BF50	BF75	p-value
HR	88 (68-109.5)	88.9 (67-108.8)	88.6 (66-110)	88.6 (64.8-110.3)	0.952
RR	19.6 (8-30)	19.1 (7.8-30.8)	18.6 (7.8-30.3)	18.9 (8-32.5)	0.995
SpO_2	98 (91.5-100)	97.6 (91.3-100)	97.1 (92.8-100)	96.6 (92-100)	0.429
$tcPCO_2$	37.6 (24-65.7)	35.7 (24.2-64.3)	37.1 (23.8-65.0)	37.1 (23.6-64.8)	0.990
MBS	0.5 (0-3.5)	0.25 (0-4)	0.5 (0-4)	0.5 (0-4)	0.601
ROX index	13.2 (7.7-40.9)	13.7 (7.9-42.2)	13.4 (7.4-42.2)	13.9 (6.8-40.8)	0.987

Data are expressed as median and range (min–max).

HR, heart rate; RR, respiratory rate; SpO_2, saturation pulse oxygen; $tcPCO_2$, transcutaneous carbon dioxide; MBS, modified Borg scale; UF, Uniflow; BF, Bi-flow.

2. Respiratory parameters including N-PTP

Regarding respiratory physiologic data, Table 6 demonstrates a decreasing trend in mouth breathing ratio in a sequential order of BF25, BF50, and BF75, as the additional flow increased. The respiratory rate and I:E ratio did not significantly differ. Nasal PTP, a surrogate marker of WOB, the inspiratory PTP, and expiratory PTP show a decrease in BF mode compared with UF in Figures 6-b and 6-c. Total PTP appeared to slightly decrease at BF25 and BF50 mode, but did not show significant differences at BF75 in Figure 6-d.

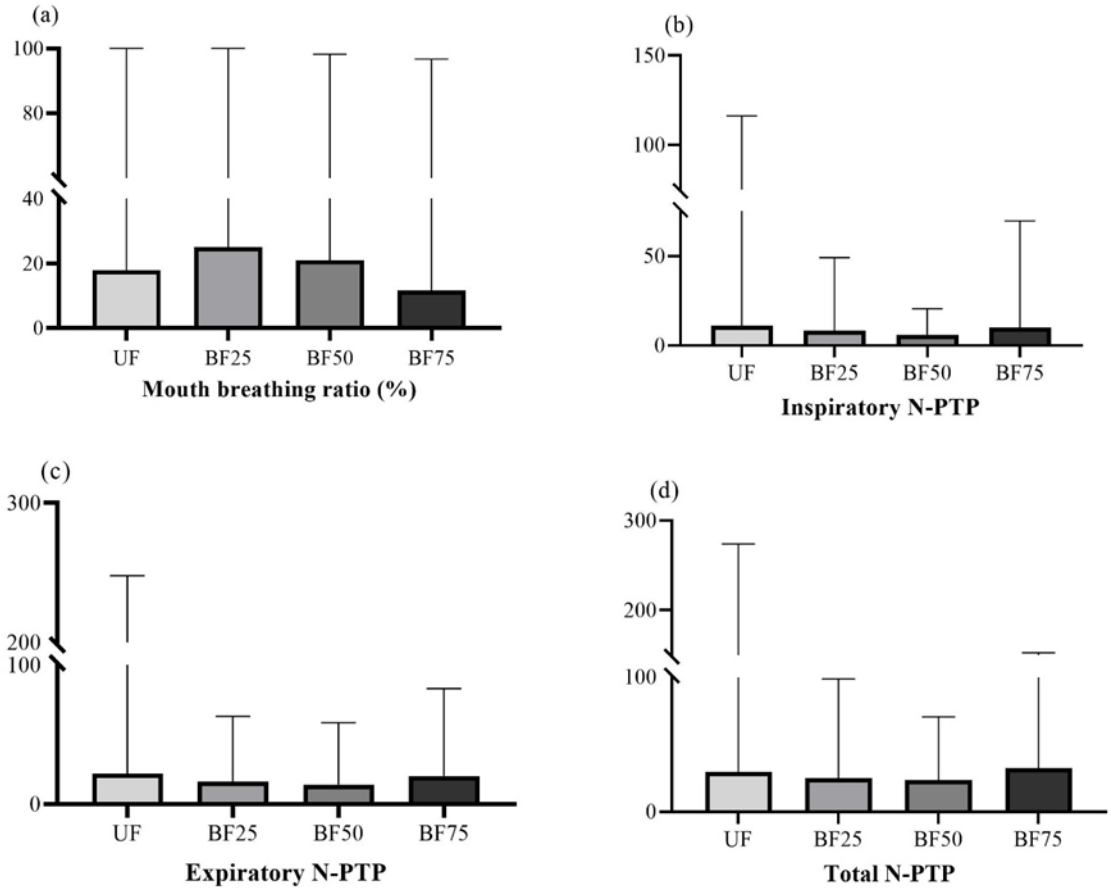
Table 6. Changes in respiratory parameters for each Bi-flow mode

	UF	BF25	BF50	BF75	p-value
Mouth breathing ratio (%)	17.9 (0-100)	25.12 (0-100)	20.97 (0-98.2)	11.12 (0-96.7)	0.439
RR	20 (9-32)	22 (9-38)	23.17 (10-53)	22 (11-32)	0.498
I:E ratio	1.5 (0.93-4.4)	1.3 (0.5-5.4)	1.4 (0.6-3.0)	1.25 (0.6-2.5)	0.194
Inspiratory N-PTP	11.2 (1.9-116.3)	8.4 (2.4-49.1)	6 (0.8-20.6)	9.9 (2.6-69.7)	0.029
Expiration N-PTP	21.9 (2-248)	16.05 (2.3-63.1)	14.1 (2.8-58.7)	20.2 (3.1-83.1)	0.256
Total N-PTP	29.4 (3.9-274)	24.8 (5.1-98.6)	23.5 (5.8-70.6)	32.6 (6.2-152.8)	0.155

Data are expressed as median and range (min-max).

UF, Uniflow; BF, Bi-flow; RR, respiratory rates; I:E ratio, inspiration:expiration ratio; N-PTP, nasal pressure-time product.

Figure 6. Respiratory data for each Bi-flow mode



Data are expressed as median and range.

N-PTP, nasal pressure-time product; UF, Uniflow; BF, Bi-flow.

3. Lung volume data using EIT

In EIT data analysis, TIV, reflecting tidal volume, did not show significant differences among the modes. EELI decreased slightly at the BF50 mode in Table 7, Figure 7-a, Figure 7-b. The ventral/dorsal (V/D) ratio and GI index did not show numerical differences in Figure 7-c, Figure 7-d.

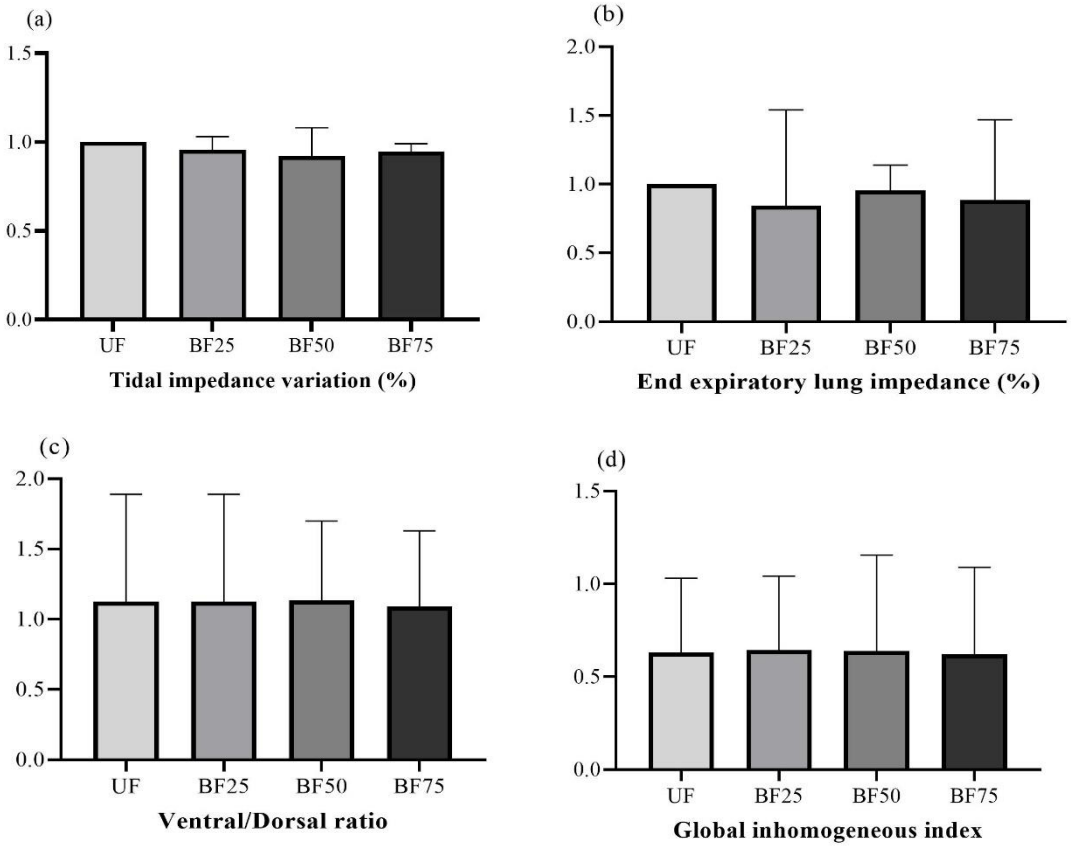
Table 7. Lung volume data for patients with hypoxemic respiratory failure in each mode

	UF	BF25	BF50	BF75
Tidal impedance variation	3195 (667.6-1113462.0)	2281.1 (783.9-54278.8)	3107.8 (390.7-74936.0)	2761.6 (421.7-141291)
EELI	1406.6 (541.0-2552157.8)	1692.0 (281.1-2372570.0)	1370.4 (474.7-2244524.2)	1755.1 (187.9-2227862.2)
GI index	0.630 (0.433-1.846)	0.6435 (0.434-1.837)	0.638 (0.438-1.837)	0.6205 (0.405-1.693)
Ventral/dorsal ratio	1.13 (0.3-4.5)	1.13 (0.3-4.5)	1.14 (0.3-4.6)	1.09 (0.3-4.2)

Data are expressed as median a range (min–max).

UF, Uniflow; BF, Bi-flow; EELI, end-expiratory lung impedance; GI index, global inhomogeneous index.

Figure 7. Lung volume data using EIT for each mode



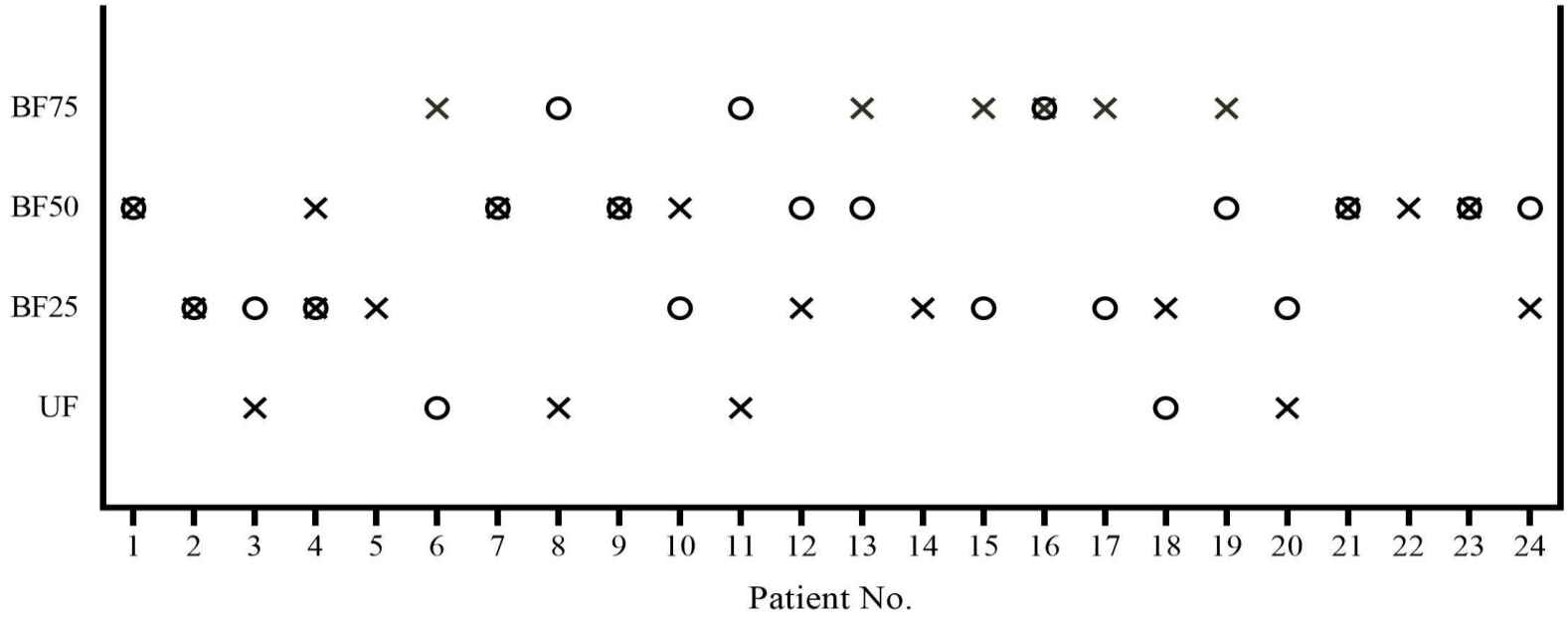
Data are expressed as median and range.

EIT, electrical impedance tomography.

4. Distribution of modes with minimum N-PTP and maximum ROX index

Figure 8 displays the distribution of modes with minimum N-PTP and maximum ROX index for each patient with hypoxic respiratory failure. The mode that frequently satisfied the minimum N-PTP value and maximum ROX index was BF50, which had the highest frequency with five patients, including patients 1, 7, 9, 21, and 23.

Figure 8. Distribution of modes with minimum total N-PTP and maximum ROX index for each patient



The X-axis represents each patient, while the Y-axis represents four modes (UF, BF25, BF50, BF75). A black circle indicates the mode with the minimum N-PTP value, and a black X mark denotes the mode with the maximum ROX index. Overlapping black circle with a black X indicates the mode with the minimum N-PTP value and the maximum ROX index matches that specific patient. If the N-PTP value for one or more modes has not been calculated in one patient, they are not presented. Modes with the same maximum ROX index were marked as duplicates in one patient.

N-PTP, nasal-pressure time product; UF, Uniflow; BF, Bi-flow.

Discussion

This study was conducted to introduce clinical application following the development of a Bi-level high-flow nasal cannula (Bi-flow; BF). This method provides additional flow during inspiration to patients. In the initial phase of this study conducted on healthy individuals, applying Uniflow (UF) and BF led to decreased respiratory rate compared to that in normal breathing. When the Bi-flow system was applied, expiratory time decreased compared to UF application, and there was a decreasing trend in N-PTP. Other physiologic data, including heart rate, $tcPCO_2$, and lung volume, did not show significant differences, and no notable side effects were observed. In the second phase of this study, when Bi-flow was applied to patients with hypoxemic respiratory failure, the ROX index numerically decreased in the BF mode compared with UF, although there was no statistically significant difference. Inspiratory PTP decreased, with more pronounced results observed in BF25 and BF50 modes. Similar to the findings in healthy individuals, other physiologic data and lung volume data did not differ.

Comparison of conventional oxygen therapy, NIV, and HFNC

Hypoxemia can lead to tissue hypoxia and organ dysfunction; oxygen therapy is essential for patients with respiratory failure [21]. Conventional oxygen therapy (COT) methods include nasal prongs, simple facial and venturi masks, and more. The choice of oxygen delivering method is determined by the clinicians' judgment, including patients' breathing pattern, oxygen demand, and minute ventilation [22]. Even while using conventional oxygen therapy, if a patient’s respiratory symptom worsens or there are issues with gas exchange, NIV should be considered before attempting mechanical ventilation. NIV mask application is an adequate oxygen supplemental device with the improvement of gas exchange, but it is often associated with facial pressure sore or patients' discomfort [23, 24]. Helmet NIV also has concerns about noise and claustrophobia, making it uncommon in use [25].

With the increasing use of HFNC, some studies have compared COT with HFNC. HFNC may decrease intubation risk in acute hypoxemia respiratory failure but not affect mortality [26]. The use of HFNC in patients with hypercapnic respiratory failure showed effectiveness in previous studies compared to COT [27]. During the COVID-19 pandemic, HFNC appeared to be clinically beneficial compared to COT [28]. However, large-scale studies are yet to be conducted, and meta-analyses still need to clearly demonstrate the efficacy of HFNC in patients with hypercapnia [29]. There is limited research with head-to-head comparision of HFNC and NIV. Previous studies suggested that HFNC could be considered as

an alternative to NIV in patients with COPD; however, currently, there is no clear evidence of its superiority [30, 31].

The efficacy and limitations of HFNC

HFNC not only improves oxygenation [32] but also decreases physiologic dead space [33, 34] and provides a PEEP effect in patients with hypoxemic respiratory failure, as evidenced in several studies [6, 34]. Compared to NIV or conventional oxygen, patients with HFNC showed comfort and tolerance to oxygen supplements [5]. For the safety issue, one of the reasons for the recent increasing use of HFNC is the ease of application without significant side effects for patients. Although concerns about delaying intubation exist [35], most medical teams believe that applying HFNC would not impact respiratory deterioration [36]. In the early days of the COVID-19 pandemic, there were concerns about the possibility of droplet distribution, but the potential was reportedly low [37]. Despite these many advantages, an increase in flow rate leads to increased resistance in the nasopharynx cavity, causing alveolar overdistension and discomfort to patients [13]. Similar to the same way that patient adaptation and comfort play a crucial role in the success of NIV, a complementary approach is needed for HFNC. For this reason, Bi-flow has been devised to reduce patient discomfort.

Most previous studies have focused on decreasing inspiratory effort using HFNC [5, 6]. The optimal flow for patients using HFNC has been a subject of ongoing discussion. A recent systemic review highlighted that as flow increases, it affects the patient's peak inspiratory flow. Therefore, individualized flow settings should be consider based on the patient's condition and the course of the disease [12]. Patients enrolled in our study also had heterogeneous diseases, such as interstitial lung disease, bronchiectasis, and lung transplantation, which might have affected the results. HFNC generally shows no significant safety and patient compliance issues, but the precise flow setting remains to be discussed depending on individual patient characteristics.

Bi-flow system for healthy individuals

In the initial phase of the study for healthy individuals, Bi-flow resulted in less bradypnea than conventional Uniflow. During bi-flow, the decrease or RR was less pronounced than in UF, and expiratory time was preserved like natural

breathing. Moreover, compared with UF, N-PTP during BF was lower for both inspiration and expiration. During BF, the lower expiratory N-PTP was attributable to the decreased expiratory time, and the lower inspiratory N-PTP was attributable to lower pressure change values during the inspiration phase. In healthy participants, Bi-flow may help the disruption of the respiratory cycle due to increased resistance caused by excessive flow persisting during expiration. The application of BF resulted in less pressure difference in the nasopharynx compared to UF. This, in turn, could be considered a reason for the reduction in N-PTP.

First phase of this study was a proof-of-concept trial for Bi-flow in healthy individuals. Although there was no difference in modified Borg scale scores between BF and UF applications, there appeared to be lesser disturbance in breathing (less bradypnea, lower N-PTP) during BF. During this study, due to technological limitations in detecting inspiration in BF, it was not accurately measured when the healthy individuals' inspiration flow was too low.

Bi-flow application for patients with hypoxemic respiratory failure

The second phase of this study aimed to elucidate the differences between Uniflow and Bi-flow in patients with diseases. To enhance the analysis compared to the first phase study with healthy individuals, the time in each mode was extended to 20 min for observing respiratory pattern changes. Furthermore, considering the substantial variation in flow settings with healthy individuals, the BF mode was simplified into three categories (BF25, BF50, and BF75).

When Bi-flow was applied to patients with hypoxemic respiratory failure, although varying by mode, BF did not show an apparent reduction in respiratory rate compared to UF, and an elongation of the I:E ratio was not pronounced. During the design of this study, we assumed that applying Bi-flow would reduce patient discomfort and nasopharyngeal resistance during the expiratory phase, leading to decreased N-PTP. However, there was a slightly reduction in expiratory N-PTP, overall inspiratory N-PTP, and total N-PTP, with a less pronounced decrease in respiratory rate. The hypothesis for these results is that, first, since respiration is a continuous process and the expiratory phase is a passive process, the decreases in expiratory WOB might have contributed to the overall reduction in inspiratory and total N-PTP. Secondly, as shown in Table 6, the decrease in respiratory rate was not prominently observed with the Bi-flow application; instead, the I: E ratio appeared shorter than the Uniflow application. Even during expiration, maintaining a high flow may cause an extended expiratory pause or a prolonged time for flow reduction. However, Bi-flow can be hypothesized to prevent I:E elongation and reduce discomfort by promoting a breathing pattern closer to normal respiration. Previous studies have investigated

the impact of inspiratory flow rate (IFR) on patients' breathing comfort. While the exact chemical and mechanical causes remain unclear, one study suggested that lower flow rates might lead to the sensation of air hunger. At the same time, higher IFR could result in upper airway discomfort [38]. Another study observed that patients with severe hypoxemia requiring FiO_2 levels of 45% or more reported greater comfort with higher flows [39]. Considering these findings, applying Bi-flow may benefit patients with mild to moderate hypoxemia or in cases where air hunger is not severe.

Figure 8 describes the most effective mode for patients, considering various parameters. For all patients, we indicated the mode with a minimum value of total N-PTP (indicating minimal WOB) and the maximum ROX index (indicating maintaining adequate oxygenation using HFNC) for every patient. The mode that satisfied two conditions, the most frequent mode, was BF50, observed in five patients. These patients had underlying diseases such as asthma, malignancy, and rheumatoid-arthritis-related interstitial lung disease (RA-ILD). Thus, their lung pathological mechanisms were not consistent. Although Bi-flow appeared closer to normal breathing than UF when indirectly measured by N-PTP, further research is needed to determine which mode might be more effective for specific types of patients.

As for the safety issue, in our study, Bi-flow could not be conducted for more than 10 min; we planned to consider it a study discontinuation for any reason. However, in the clinical trial, there were no cases where the study had to be discontinued. As none of the healthy participants or patients with hypoxemic respiratory failure complained of side effects or complications, Bi-flow may be safely used in a clinical situation.

Considerations of the Bi-flow system

One of the advantages of existing HFNC is that it can provide a high pressure in the nasopharynx and proximal trachea, mimicking the effects of PEEP, which might be decreased with the Bi-flow application. In this study, significant differences were not observed in EELI and the ventral-dorsal ratio, both indicators that could not decrease PEEP and functional residual capacity [18, 19, 40]. Furthermore, HFNC operates as an “open” respiratory system, making PEEP variation highly dependent on patients’ compliance and mouth breathing frequency [41]. The GI index quantifies the distribution of tidal volume. It calculates the pixel difference between the end-inspiration and end-expiration, serving as an indicator of uneven ventilation. A relatively low value indicates a more homogeneous distribution [42, 43]. Further, the ratio of the region of

impedance, ventral/dorsal ratio (V/D ratio), can be compared to assess the extent of lung aeration in the dependent position [44, 45]. In this study, both GI index and V/D ratio did not show changes in healthy participants and patients with hypoxemic respiratory failure. The application of Bi-flow did not result in a substantial difference in the pathological lungs of patients. However, considering the clinical trial time of around 2 h, including the wash-out period between modes, the study time needed to be longer to observe the proper effect of Bi-flow.

Future considerations about the flow differences using Bi-flow are necessary. Even in healthy individuals, when there was a significant difference in inspiratory-expiratory flow (for example, the 50/30 and 50/20 setting), patients often experienced discomfort in respiration. Patients showing increased N-PTP in the BF75 mode were occasionally observed (Table 6), indicating that applying Bi-flow with a large flow difference might cause discomfort during respiration. Moreover, HFNC has proven beneficial for patients with acute respiratory failure, but limited research focuses on patients with hypercapnic respiratory failure. Bi-flow was developed with a similar concept to BiPAP; thus, expanded research is needed to assess whether Bi-flow can be helpful for patients with hypercapnic respiratory failure.

Limitation

This study had several limitations. First, it was a concept trial for introducing Bi-flow, and the sample size of healthy individuals and patients with hypoxemic respiratory failure was small. This study was conducted as an open-label study without researcher blinding. Some results' interpretation may be subject to bias. Second, EIT data might show differences in the "open" respiratory system as it is frequently used in sedated patients with mechanical ventilation. In the case of healthy individuals, most were administered EIT in a sitting position, potentially affecting the accuracy of respiratory changes in PEEP and EELI for dependent positions. Third, the mouth opening ratio was only measured in patients with hypoxemic respiratory failure, indicating patients' compliance. Breathing with an open mouth can result in a difference between observed and actual values of N-PTP. Fourth, the parameters used in this study need improvement. The modified Borg scale, used to quantify subjective respiratory discomfort, is more commonly used in tests involving movement, such as exercise or 6-min walk tests. It might be beneficial to utilize a more numerical or finer assessment scale. Similarly, the ROX index, an indicator for predicting HFNC failure, is often used for temporal changes in the ROX index rather than a single value. Finally, some technical limitations for inspiration flow recognition were found to lack adequate accuracy. Addressing these technical deficiencies is crucial for future research.

Conclusion

This study aimed to explore the Bi-level high-flow system, which differs from conventional HFNC by regulating flow through differences in inspiration and expiration. Applying Bi-flow revealed a reduction in WOB by observing the change in N-PTP compared with that in Uniflow. Bi-flow maintained a breathing pattern similar to spontaneous respiration without significant differences in lung volume and other physiologic data. Further research with a larger sample size is necessary to investigate the effectiveness of Bi-flow and its optimal mode for each patient.

References

1. Mehta, S. and Hill, N.S., *Noninvasive ventilation.* American Journal of Respiratory and Critical Care Medicine, 2001. **163**(2): p. 540-577.
2. Carron, M., et al., *Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials.* British Journal of Anaesthesia, 2013. **110**(6): p. 896-914.
3. Ozyilmaz, E., Ugurlu, A.O., and Nava, S., *Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies.* BMC Pulmonary Medicine, 2014. **14**(1): p. 1-10.
4. Nishimura, M., *High-flow nasal cannula oxygen therapy in adults.* Journal of Intensive Care, 2015. **3**(1): p. 1-8.
5. Lee, C.C., et al., *High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: a systematic review.* Respiratory Medicine, 2016. **121**: p. 100-108.
6. Mauri, T., et al., *Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure.* American Journal of Respiratory and Critical Care Medicine, 2017. **195**(9): p. 1207-1215.
7. Rochwerg, B., et al., *The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline.* Intensive Care Medicine, 2020. **46**: p. 2226-2237.
8. Groves, N. and Tobin, A., *High flow nasal oxygen generates positive airway pressure in adult volunteers.* Australian Critical Care, 2007. **20**(4): p. 126-131.
9. Nishimura, M., *High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects.* Respiratory Care, 2016. **61**(4): p. 529-541.
10. Gürün, A., *High flow nasal cannula in COVID-19: a literature review.* Tuberk. Toraks, 2020. **68**: p. 168-174.
11. Attaway, A.H., et al., *Severe covid-19 pneumonia: pathogenesis and clinical management.* BMJ, 2021. **372**.
12. Li, J., et al., *The effects of flow settings during high-flow nasal cannula support for adult subjects: a systematic review.* Critical Care, 2023. **27**(1): p. 1-20.
13. Chang, G.Y., C.A. Cox, and T.H. Shaffer, *Nasal cannula, CPAP, and high-flow nasal cannula: effect of flow on temperature, humidity, pressure, and resistance.* Biomedical Instrumentation & Technology, 2011. **45**(1): p. 69-74.
14. Xia, J., et al., *Flow Field Analysis of Adult High-Flow Nasal Cannula Oxygen Therapy.* Complexity, 2021. **2021**: p. 1-11.
15. Adams, C.F., et al., *Modelling nasal high flow therapy effects on upper airway resistance and resistive work of breathing.* Respiratory Physiology & Neurobiology, 2018. **254**: p. 23-29.
16. Hörmann, C., et al., *Biphasic positive airway pressure (BIPAP)--a new mode of ventilatory support.* European Journal of Anaesthesiology, 1994. **11**(1): p. 37-42.
17. Kleopa, K.A., et al., *Bipap improves survival and rate of pulmonary function decline in patients with ALS.* Journal of the Neurological Sciences, 1999. **164**(1): p. 82-88.
18. Bikker, I.G., et al., *Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial.* Critical Care, 2011. **15**: p. 1-8.
19. Hsu, C.-F., et al., *Electrical impedance tomography monitoring in acute respiratory distress syndrome patients*

with mechanical ventilation during prolonged positive end-expiratory pressure adjustments. Journal of the Formosan Medical Association, 2016. **115**(3): p. 195-202.

20. Roca, O., et al., *An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy.* American Journal of Respiratory and Critical Care Medicine, 2019. **199**(11): p. 1368-1376.
21. Bateman, N. and R. Leach, *Acute oxygen therapy.* BMJ, 1998. **317**(7161): p. 798-801.
22. Siemieniuk, R.A., et al., *Oxygen therapy for acutely ill medical patients: a clinical practice guideline.* BMJ, 2018. **363**.
23. MacIntyre, N.R., *Physiologic effects of noninvasive ventilation.* Respiratory Care, 2019. **64**(6): p. 617-628.
24. Patout, M., et al., *Noninvasive ventilation (NIV) related adverse events*. 2018, European Respiratory Society, 2018.**52**: p.2378
25. Esquinas Rodriguez, A.M., et al., *Clinical review: helmet and non-invasive mechanical ventilation in critically ill patients.* Critical Care, 2013. **17**(2): p. 1-14.
26. Rochwerg, B., et al., *High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis.* Intensive Care Medicine, 2019. **45**: p. 563-572.
27. Kim, E.S., et al., *Effectiveness of high-flow nasal cannula oxygen therapy for acute respiratory failure with hypercapnia.* Journal of Thoracic Disease, 2018. **10**(2): p. 882.
28. Ospina-Tascon, G.A., et al., *Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: a randomized clinical trial.* JAMA, 2021. **326**(21): p. 2161-2171.
29. Huang, X., et al., *High-flow nasal cannula oxygen versus conventional oxygen for hypercapnic chronic obstructive pulmonary disease: A meta-analysis of randomized controlled trials.* The Clinical Respiratory Journal, 2021. **15**(4): p. 437-444.
30. Zhao, H., et al., *High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis.* Critical Care, 2017. **21**: p. 1-12.
31. Bräunlich, J., et al., *Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD.* International Journal of Chronic Obstructive Pulmonary Disease, 2019: **14** p. 1411-1421.
32. Papazian, L., et al., *Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review.* Intensive care medicine, 2016. **42**: p. 1336-1349.
33. Möller, W., et al., *Nasal high flow reduces dead space.* Journal of Applied Physiology, 2017. **122**(1): p. 191-197.
34. Lee, J.H., et al., *Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature.* Intensive Care Medicine, 2013. **39**: p. 247-257.
35. Kang, B.J., et al., *Failure of high-flow nasal cannula therapy may delay intubation and increase mortality.* Intensive Care Medicine, 2015. **41**: p. 623-632.
36. Ricard, J.-D., et al., *Use of nasal high flow oxygen during acute respiratory failure.* Intensive Care Medicine, 2020. **46**: p. 2238-2247.
37. Li, J., Fink, J.B., and Ehrmann, S., *High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion.* European Respiratory Journal, 2020. **55**(5) : 2000892
38. Manning, H.L., E.J. Molinary, and J.C. Leiter, *Effect of inspiratory flow rate on respiratory sensation and pattern*

of breathing. American Journal of Respiratory and Critical Care Medicine, 1995. **151**(3_pt_1): p. 751-757.

39. Mauri, T., et al., *Impact of flow and temperature on patient comfort during respiratory support by high-flow nasal cannula.* Critical Care, 2018. **22**(1): p. 1-8.
40. Bikker, I.G., et al., *Lung volume calculated from electrical impedance tomography in ICU patients at different PEEP levels.* Intensive Care Medicine, 2009. **35**: p. 1362-1367.
41. Hasan, R.A. and Habib, R.H., *Effects of flow rate and airleak at the nares and mouth opening on positive distending pressure delivery using commercially available high-flow nasal cannula systems: a lung model study.* Pediatric Critical Care Medicine, 2011. **12**(1): p. e29-e33.
42. Zhao, Z., et al., *The EIT-based global inhomogeneity index is highly correlated with regional lung opening in patients with acute respiratory distress syndrome.* BMC Research Notes, 2014. **7**(1): p. 1-7.
43. Zhao, Z., et al., *Evaluation of an electrical impedance tomography-based global inhomogeneity index for pulmonary ventilation distribution.* Intensive Care Medicine, 2009. **35**: p. 1900-1906.
44. Franchineau, G., et al., *Prone positioning monitored by electrical impedance tomography in patients with severe acute respiratory distress syndrome on veno-venous ECMO.* Annals of Intensive Care, 2020. **10**: p. 1-9.
45. Shono, A. and Kotani, T., *Clinical implication of monitoring regional ventilation using electrical impedance tomography.* Journal of Intensive Care, 2019. **7**: p. 1-10.

Appendix

Supplemental Table 1. Baseline characteristics and initial setting for patients with hypercapnic respiratory failure

Variables	Median (min-max)
Sex (male)	8/10 (80.0%)
Height (cm)	163.7 (152.4-180)
Weight (kg)	51.9 (34-70)
BMI (body mass index, kg/m^2)	20.03 (12.38-24.22)
Oxygen flow (L/min)	40 (35-40)
Fraction of inspired oxygen (FiO_2, %)	40 (30-50)
Heart rate (HR, rate/min)	90.5 (72-112)
Respiratory rate (RR, rate/min)	20.5 (14-32)
Systolic blood pressure (SBP, mmHg)	120 (90-149)
Diastolic blood pressure (DBP, mmHg)	64 (50-81)
Percutaneous CO_2 ($tcPCO_2$, mmHg)	45.05 (32.1-70)
Modified Borg scale (MBS)	0 (0-2)
ROX index (PaO_2/FiO_2/RR)	13.80 (7.92-17.86)

Data are expressed as median and range (min–max).

Supplemental Table 2. Ranges of vital signs and ROX index for each mode in patients with hypercapnia

	UF	BF25	BF50	BF75	p-value
HR	90.5 (83.3-108.8)	94 (58.5-108)	95.1 (72.3-110)	93.9 (71.5-103.5)	0.998
RR	20.63 (14.5-25.5)	20.5 (14.8-30)	21.9(14.8-30.8)	21.3 (13.8-32)	0.934
SpO_2	98.3 (92.8-100)	98.4 (93-100)	97.5 (92.8-100)	98 (92.3-100)	0.919
$tcPCO_2$	44.3 (34.9-66.4)	44.0 (34.6-62.2)	43.0(40.1-61.4)	41.6 (35.8-63.3)	0.881
MBS	0.13 (0-6)	0 (0-0.5)	0 (0-7)	0 (0-5.5)	0.834
ROX index	14.1 (8.6-19.0)	14.2 (7.8-16.8)	13.3(7.9-16.8)	13.7 (7.5-17.8)	0.919

Data are expressed as median and range (min–max).

UF, Uniflow; BF, Bi-flow; HR, heart rate; RR, respiratory rate; $tcPCO_2$, transcutaneous carbon dioxide; MBS, modified Borg scale.

Supplemental Table 3. Changes in respiratory parameters for each Bi-flow mode in patients with hypercapnia

	UF	BF25	BF50	BF75	p-value
Mouth	56.3 (0-98.6)	22.1 (0-97.6)	45.9 (0-98.5)	337 (0-99.9)	0.989
Breathing ratio (%)					
RR	19 (10-24)	17 (15-21)	19.5 (17-34)	20 (15-26)	0.297
I:E ratio	1.4 (0.9-2.4)	1.35 (0.8-2.4)	1.1 (0.3-4.7)	0.9 (0.7-2.0)	0.173
Inspiratory N-PTP	8 (0.3-69.9)	11 (1.3-25.8)	4.6 (1.8-31)	9.2 (2.4-18.3)	0.982
Expiration N-PTP	20.7(0.2-135)	20.9 (6.1-58)	4.6 (2.2-61.4)	9.3 (3.7-31)	0.129
Total N-PTP	23.8 (0.5-204.9)	33 (13.4-70.5)	7.3 (4.0-92.4)	18.5 (6.6-49.3)	0.234

Data are expressed as median and range (min-max).

UF, Uniflow; BF, Bi-flow; RR, respiratory rate; I:E ratio, inspiration:expiration ratio; N-PTP, nasal pressure-time product.

국문요약

고유량 비강 캐뉼라 시스템(High-flow nasal cannula, HFNC)는 산소 공급 장치로 널리 사용되고 있다. 그러나 흡기와 호기 시 동일한 유량을 공급하면서 호기시 비강내에서 난류를 일으켜 호흡 저항을 증가시키고 환자의 불편감을 발생시키기도 한다. 이러한 문제를 개선하기 위해 이중유량 시스템 (Bi-flow)를 개발하여 흡기마다 추가 유량을 공급하는 방식을 고안했다. 본 연구는 정상인과 저산소성 호흡 부전 환자에게서 기존의 HFNC (Uniflow; UF)와 Bi-flow를 비교하여 적용하는 두 단계의 연구로 Bi-flow의 호흡에 미치는 효과를 평가해보고자 하였다.

정상인 대상 연구의 경우 Uniflow (U30, U40, U50)와 Bi-flow 모드 (기본 유량 10, 20, 30L/min)으로 무작위 할당되었다. 각 모드에서 흡기시마다 추가 유량을 증가시켜 [흡기/호기 유량]을 각각 30/10, 30/20, 40/10, 40/20, 40/30, 50/20, 50/30으로 변화시켰다. 환자 데이터 (호흡수, 심박수, 경피적 이산화탄소 농도, Modified Borg scale)과 호흡 역학 (전기임피던스 단층 촬영)을 기록하였고, Nasal pressure time product(N-PTP)는 호흡일의 대리 지표로 계산되어 사용되었다. 저산소증 환자의 연구에서 Uniflow와 Bi-flow 모드 (BF25, BF50, BF75)가 무작위 배치되었다. Bi-flow는 흡기시에는 UF와 동일한 흡기 유량을 공급했지만 전체 유량의 일부가 호기시 유량, 나머지가 흡기마다 추가 유량으로 공급되었다. 환자의 ROX 지수 및 N-PTP를 계산하여 네 가지 모드를 비교했다.

정상인 대상 연구에서 12명의 피험자가 연구를 종료했다. 자발적 호흡과 비교하여 UF, Bi-flow 적용시 호흡수의 감소가 관찰되었다. 또한 Bi-flow 적용시 흡기 및 호기의 N-PTP가 감소하였다. 24명의 저산소성 호흡부전 환자들의 경우에는 ROX 지수에는 차이를 보이지 않았다 (UF: BF25: BF50: BF75; 13.2: 13.7: 13.4 13.9, p-value=0.98). Bi-flow를 적용했을 때 흡기 N-PTP는 감소했으나(UF: BF25: BF50: BF75; 11.2: 8.4: 6.0: 9.9, p-value=0.03), EIT로 확인한 호흡 역학은 유의한 통계적인 차이를 보이지 않았다.

본 연구는 새롭게 도입된 Bi-level high flow 비강 캐뉼라 시스템 (Bi-flow)에 대한 탐색적인 임상 시험으로 수행되었다. 건강한 자원자와 저산소성 호흡부전 환자들을 대상으로 Bi-flow 를 적용해 보았으며, 결과적으로 호흡일의 대리 지표로 사용된 N-PTP가 부분적으로 감소하는 것으로 나타났다. 그러나 환자에게서 ROX지수, 호흡수 및 EIT 데이터는 크게 차이를 보이지 않았으며 각 환자에 따른 Bi-flow의 효과 및 최적의 모드를 확인하려면 더 큰 표본을 이용한 추가적인 연구가 필요할 것으로 생각된다.