ORIGINAL

The effect of high-flow nasal cannula on diaphragm dysfunction including paradoxical diaphragmatic contraction in the intensive care unit

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Abstract : Background : Diaphragm dysfunction is a serious problem. However, a few management techniques exist for diaphragm dysfunction. Methods : Adult patients treated with high-flow nasal cannula (HFNC) in the intensive care unit were included in this study. The diaphragm function was evaluated using ultrasound measurement of thickening fraction before and after HFNC liberation. Normal diaphragm contraction was defined as thickening fraction ≥15% without HFNC, whereas decreased or paradoxical diaphragm contractions were 0%–15% or <0%, respectively. Results : Forty patients were enrolled, and 16 (40%) had normal diaphragm contraction, whereas 19 (48%) or 5 (13%) had decreased or paradoxical diaphragm contractions, respectively. Thickening fraction increased after HFNC liberation (27.0% ± 25.7% vs. 38.8% ± 34.5%, *p* = 0.03 in HFNC vs. no HFNC) in patients without diaphragm dysfunction. In patients with decreased diaphragm contraction, thickening fraction did not change with or without HFNC (8.9% ± 11.7% vs. 6.7% ± 5.2%, *p* = 0.35), whereas paradoxical contraction decreased with HFNC (1.0% ± 10.2% vs. –10.3% ± 2.7%, *p* = 0.04) in patients with paradoxical diaphragm contraction. Conclusions : The work of breathing decreased with HFNC in patients without diaphragm dysfunction, but did not decrease in patients with decreased diaphragm contraction. Paradoxical diaphragm contraction decreased with HFNC. J. Med. Invest. 68 : 159-164, February, 2021

Keywords : *Diaphragm, Ultrasonography, Intensive Care Unit, Respiration, Atrophy*

BACKGROUND

Patients undergoing prolonged mechanical ventilation experience diaphragm atrophy and dysfunction (1, 2). Diaphragm atrophy occurs in 63% of mechanically ventilated patients (3). Moreover, diaphragm atrophy is associated with diaphragm dysfunction, termed as *ventilator-induced diaphragm dysfunction*. Diaphragm dysfunction is defined as a loss of diaphragmatic force-generating capacity that includes paradoxical diaphragmatic contraction. Diaphragm dysfunction has been reported to worsen clinical outcomes (4).

Several strategies, such as ventilator settings, exist to prevent diaphragm atrophy and dysfunctions (5, 6). The strategy of ventilator setting is termed as *diaphragm protective ventilation*, which requires the preservation of spontaneous breathing and the reduction of excessive pressure support (7). However, only a few recommendations have been made for the management and treatment of diaphragm dysfunction. Although mechanical ventilation may be required for severe diaphragm dysfunction, high-flow nasal cannula (HFNC) may attenuate diaphragm dysfunction because it washes out carbon dioxide in anatomical dead space, increases lung volume, and decreases the work of breathing (8).

We hypothesized that HFNC could contribute to diaphragm dysfunction. Because HFNC decreases the work of breathing, it may support diaphragm dysfunction including paradoxical diaphragm contraction. However, no previous study has investigated the effect of HFNC therapy on diaphragm dysfunction. Therefore, this observational study was conducted to evaluate the effect of HFNC on diaphragm function using ultrasound, which is a validated method to assess diaphragm function (9).

METHODS

Study design

This observational study was conducted in the intensive care units (ICU) of Tokushima University Hospital between June 2018 and June 2020. This study was approved by clinical research ethics committees at Tokushima University Hospital (approval number 3299) and registered on a clinical trial (UMIN-Clinical Trials Registry : 000038082). Written informed consent was obtained at the time of enrollment from patients or their authorized surrogate decision-makers.

Study population

Adult patients who were treated with HFNC in the ICU were included in this study. The Optiflow™ system with an O_2/air blender and a heated humidifier at 40°C (MR850, Fisher & Paykel Healthcare, Auckland, New Zealand) was used. On the one hand, patients were liberated from HFNC when the HFNC setting was weaned to 30 L/min flow at F_IO_2 of 0.21–0.30. On the other hand, patients were eligible when oxygen saturation was ≥90% with respiratory rate <40/min. Exclusion criteria

List of abbreviations
ICU : intensive care unit ; HFNC : high-flow nasal cannula ; IQR : interquartile range ; CI : confidence interval ; VS : versus

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were < 18 years, trauma or chest tube at the measurement point, diagnosis of primary neuromuscular disease, suspicion of phrenic nerve palsy, pneumothorax, massive pleural effusion, and an unclear ultrasound image. If the patients met the criteria of oxygen saturation < 90% with supplemental oxygen, respiratory rate > 40/min, and increased work of breathing with dyspnea after liberation from HFNC, they were withdrawn from the study with the use of HFNC again.

Measurements of diaphragm function

Diaphragm function was evaluated with ultrasound 30 min before and after HFNC liberation. HI VISION Preirus with a 6.5-MHz linear or 1–5-MHz convex transducer (EUP-L73S or EUP-C715, Hitachi Medical Corporation, Tokyo, Japan) was used for ultrasonography. All scanning was done in bed at an angle of 30°. Diaphragm dysfunction was decided by thickening fraction. Moreover, in thickening fraction, a linear transducer was placed perpendicular to the right chest wall at the zone of apposition with B mode, 0.5–2 cm below the costophrenic sinus, between the eighth and tenth intercostal spaces, and between the anteroaxillary and the midaxillary line (Figure 1A). The diaphragm in this area is observed as a three-layered structure consisting of the hypoechogenic muscular layer bounded by echogenic membranes of the peritoneum and diaphragmatic pleura (Figure 1B). Measurements were conducted at inspiration and end-expiration. Thickening fraction was calculated as [thickness at inspiration − thickness at expiration] / [thickness at expiration] × 100 (%). The normal range of thickening fraction is ≥ 15% during spontaneous breathing in healthy adults (4). On one hand, decreased diaphragm contraction was defined as 0%–15% without HFNC, and paradoxical diaphragm contraction was defined as < 0%. In addition to thickening fraction, diaphragm excursion was evaluated in the subcostal area with a convex transducer using *M* mode (Figure 1C). Diaphragm excursion is the distance from the lower to the upper curve of diaphragm movement (Figure 1D). The normal range of diaphragm excursion is > 1 cm. Diaphragm contraction velocity is diaphragm excursion divided by the inspiratory time, and excursion–time index is the product of diaphragm excursion and inspiratory time. Measurements were conducted three times, and the median value was used for evaluation. All measurements were performed by two ICU physicians (T.T. and N.N.). Intra- and interobserver correlations were 0.89 and 0.89 at thickening fraction and 0.90 and 0.91 at excursion, respectively. Intra- and interobserver Bland-Altman plots were 0.58 (± 1.50 ; 95% confidence interval [CI] −2.41–3.56) and −1.68 (± 1.24 ; 95% CI −4.15–0.79) at thickening fraction and −0.01 (± 0.04 ; 95% CI −0.08–0.06) and 0.05 (± 0.03 ; 95% CI −0.02–0.11) at excursion.

Statistical analysis

A feasible sample size of 40 patients was planned. Continuous data were presented as means ± standard deviation or medians (interquartile range [IQR]), whereas categorical data were expressed as numbers (in percentage). Variables obtained before and after HFNC liberation were compared by paired *t*-test. Multiple comparisons were conducted using one-way analysis of variance (ANOVA) or Kruskal–Wallis test with post hoc comparisons using Tukey-Kramer or Steel–Dwass test. Data analyses were conducted using JMP 13.1.0 (SAS Institute, Cary, NC, USA). All statistical tests were two-tailed, and a p value < 0.05 was regarded as statistically significant.

RESULTS

The characteristics of the patients are shown in Table 1. Forty patients (23 males, 17 females ; age 69 ± 16 years) were enrolled. Acute Physiology and Chronic Health Evaluation II score was 18

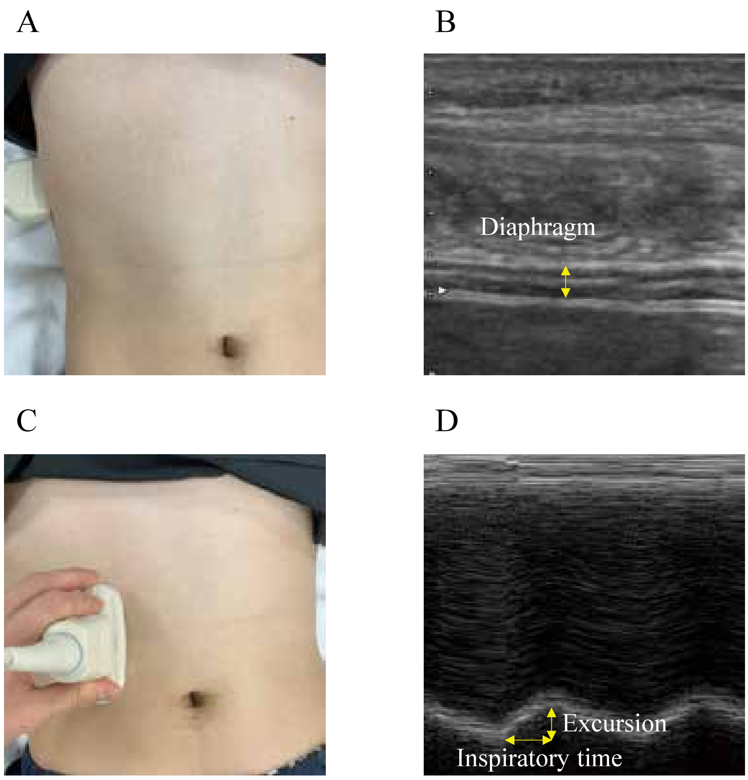

Figure 1. Ultrasound measurements of the diaphragm. A Measurement site of thickening fraction, B Ultrasound image of diaphragm thickness, C Measurement site of diaphragm excursion, and D Ultrasound image of excursion and inspiratory time.

(IQR, 12–26). The HFNC duration was 2 days (IQR, 2–3 days), which was due to post-extubation (29 patients, 73%) and respiratory failure types I (10 patients, 25%) and II (1 patient, 3%). The baseline diaphragm thickness at expiration was 1.4 (1.2–1.9) mm at the mechanical ventilation liberation. The fraction of inspired oxygen was 0.25 (0.25–0.30) before the liberation from HFNC. After HFNC liberation, 26 patients required 1–3 L/min of oxygen with a nasal cannula. The SpO_2 did not change with and without HFNC (96% ± 2% vs. 96% ± 2%, $p = 0.34$).

Sixteen (40%) patients were classified as having normal diaphragm contraction, while 19 (48%) or 5 (13%) were classified as having decreased or paradoxical diaphragm contraction, respectively. The patients in these groups significantly differed in age and sex. In post hoc analysis, patients in the paradoxical diaphragm contraction group were younger than those in the normal or decreased diaphragm contraction groups ($p = 0.02$, $p = 0.04$, respectively). The remaining parameters did not differ significantly among the three groups.

In normal diaphragm contraction, thickening fraction increased after HFNC liberation (27.0 ± 25.7 vs. 38.8 ± 34.5, $p = 0.03$ in HFNC vs. no HFNC; Figure 2). Consequently, thickening fraction did not change with or without HFNC in patients with decreased diaphragm contraction (8.9 ± 11.7 vs. 6.7 ± 5.2, $p = 0.35$). However, paradoxical contraction worsened after HFNC liberation (1.0 ± 10.2 vs. −10.3 ± 2.7, $p = 0.04$ in HFNC vs. no HFNC). Respiratory rate, excursion, contraction velocity, and excursion–time index were not different before and after HFNC liberation (Table 2).

Table 1. Patient Characteristics

Variables	Overall (n = 40)	Diaphragm contraction† Normal (n = 16 ; 40%)	Decreased (n = 19 ; 48%)	Paradoxical (n = 5 ; 13%)	*p* value
Age, years (mean [SD])	69 ± 16	74 ± 9	70 ± 17	51 ± 20‡	0.03
Sex (Male), n (%)	23 (58)	7 (44)	11 (58)	5 (100)	0.03
Body mass index, kg/m^2	21.6 (20.0–24.1)	21.4 (18.9–23.4)	22.7 (20.5–24.8)	20.0 (18.8–21.0)	0.08
APACHE II	18 (12–26)	21 (15–28)	18 (12–22)	17 (12–32)	0.32
Post-operative admission, n (%)	18 (45)	7 (44)	10 (53)	1 (20)	0.40
Length of ICU stay, days	5 (4–9)	7 (5–9)	5 (3–7)	5 (2–10)	0.11
Duration of HFNC, days	2 (2–3)	2 (2–4)	2 (1–3)	2 (2–3)	0.85
The reason of HFNC use, n (%)					
Post-extubation	29 (73)	13 (81)	13 (68)	3 (60)	
Respiratory failure Type I	10 (25)	3 (19)	6 (32)	1 (20)	0.28
Respiratory failure Type II	1 (3)	0 (0)	0 (0)	1 (20)	
Diaphragm thickness*, mm	1.4 (1.2–1.9)	1.6 (1.2–2.3)	1.3 (1.2–1.6)	1.4 (1.2–2.1)	0.57

SD = standard deviation, APACHE II = Acute Physiology and Chronic Health Evaluation II, ICU = intensive care unit, HFNC = high-flow nasal cannula

*Diaphragm thickness was measured at expiration without high-flow nasal cannula.

†Normal, decreased, and paradoxical diaphragm contraction were defined as TF ≥ 15%, TF 0%–15%, and <0%, respectively.

Data were presented as median (interquartile range) unless otherwise indicated.

‡ Significant at $p < 0.05$ vs. normal and decreased diaphragm contraction by post hoc Steel–Dwass test.

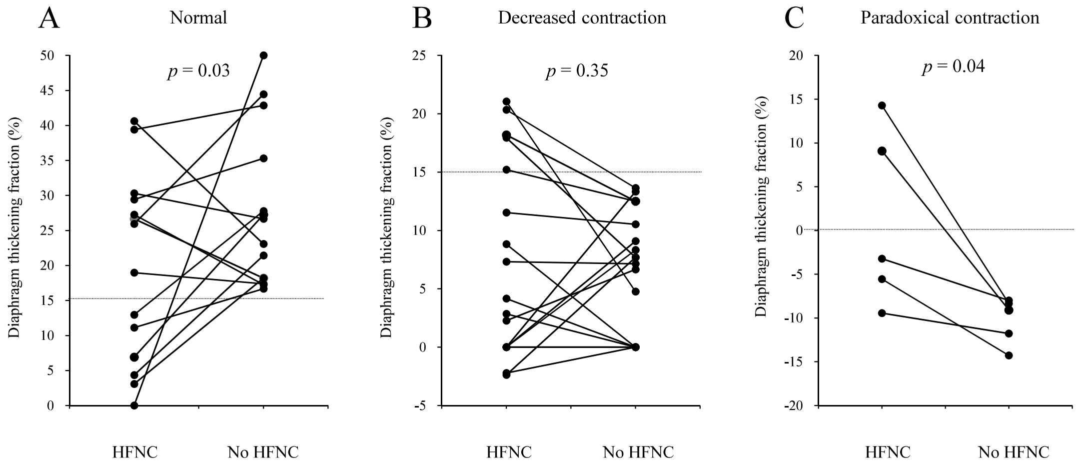

Figure 2. The change of diaphragm thickening fraction before and after HFNC liberation. A Normal diaphragm contraction; thickening fraction, 27.0% ± 25.7% vs. 38.8% ± 34.5% with HFNC vs. without HFNC ($p = 0.03$). B Decreased diaphragm contraction; thickening fraction, 8.9% ± 11.7% vs. 6.7% ± 5.2% with HFNC vs. without HFNC ($p = 0.35$). C Paradoxical diaphragm contraction; thickening fraction, 1.0% ± 10.2% vs. −10.3% ± 2.7% with HFNC vs. without HFNC ($p = 0.04$). Paired *t*-test was conducted for comparison using JMP 13.1.0 (SAS Institute, Cary, NC, USA). HFNC = high-flow nasal cannula.

Table 2. Outcomes with and without high flow nasal cannula

Variables	HFNC	No HFNC	*p* value
Normal diaphragm contraction			
Respiratory rate, breaths/min	22 ± 5	21 ± 4	0.25
Excursion, cm	1.7 ± 0.5	1.6 ± 0.6	0.68
Contraction velocity, cm/sec	2.0 ± 0.7	1.8 ± 0.6	0.38
Excursion-time index, cm-sec	1.5 ± 0.5	1.5 ± 0.8	0.82
Decreased diaphragm contraction			
Respiratory rate, breaths/min	22 ± 5	22 ± 5	0.69
Excursion, cm	1.2 ± 0.7	1.3 ± 0.9	0.33
Contraction velocity, cm/sec	1.5 ± 0.9	1.7 ± 1.2	0.53
Excursion-time index, cm-sec	1.0 ± 0.7	1.7 ± 1.2	0.23
Paradoxical diaphragm contraction			
Respiratory rate, breaths/min	18 ± 3	16 ± 3	0.19
Excursion, cm	0.9 ± 0.5	1.1 ± 0.6	0.62
Contraction velocity, cm/sec	0.9 ± 0.5	1.2 ± 0.6	0.53
Excursion-time index, cm-sec	0.9 ± 0.6	1.1 ± 0.8	0.71

HFNC = high-flow nasal cannula

DISCUSSION

HFNC did not affect decreased diaphragm contraction in this study; however, it attenuated paradoxical diaphragm contraction. The work of breathing was decreased by HFNC in patients without diaphragm dysfunction as reported (10, 11). The findings of this study suggest that HFNC may have the potential role to manage patients with paradoxical diaphragm contraction.

Paradoxical diaphragm contraction was observed in 13% of the patients in this study. The prevalence of paradoxical diaphragm contraction has not been reported previously, and it may be more prevalent in the acute phase because we investigated the prevalence in patients at the time of HFNC liberation. The mechanism of paradoxical diaphragm contraction is still unknown, and the differences in age and sex among patients require further investigation. Regarding diaphragm function, a previous study reported that the diaphragm acts as a brake during expiration to prevent lung collapse (12). HFNC maintains a positive end-expiratory pressure of 3 cmH_2O at 30 L/min (13), but the positive pressure is not provided after liberation from mechanical ventilation. This condition may cause paradoxical diaphragm contraction with thickening in the expiratory phase to prevent lung collapse. Although in previous studies paradoxical contractions were caused by spine position, phrenic nerve paralysis, and massive effusion (14-16), these conditions were excluded in the study setting. The paradoxical contraction was possibly caused by previous mechanical ventilation or some physiological conditions because this study included patients after extubation or with respiratory failure.

Contrary to thickening fraction, diaphragm excursion, velocity, and excursion–time index were not different with or without HFNC. Negative diaphragm excursion was not observed even in patients with paradoxical diaphragm contraction. The excursion is related to the inspired volume and cannot be used to assess diaphragm contraction (17-19). Therefore, these results mean that lung volume expanded even in paradoxical diaphragm function. Not only the diaphragm but also the intercostal muscles and other accessory respiratory muscles play an important role in expanding lung volume (20, 21). Thus, these respiratory muscles may have contributed to expanding lung volume. These results may have been also affected by intercostal muscles or accessory respiratory muscles although contraction velocity and excursion–time index are used to estimate diaphragm work of breathing (22, 23). Thus, these interactions of respiratory muscles may complicate the understanding of diaphragm excursion, velocity, and excursion–time index.

Decreased diaphragm contraction, defined as thickening fraction <15%, was observed in about half of the included patients. This frequent occurrence was because patients were included mostly after the use of mechanical ventilation. Indeed, the baseline diaphragm thickness was 1.4 mm, which was lower than the average 2 mm in previous studies (24, 25). Although decreased diaphragm contraction was commonly observed in this study, HFNC did not affect the diaphragm contraction in patients with decreased diaphragm contraction. Noninvasive positive pressure ventilation also might be insufficient for these respiratory supports because Marchioni *et al*. reported that decreased thickening fraction <20% indicated noninvasive ventilation failure in patients with acute exacerbations of chronic obstructive pulmonary disease (26). On the other hand, HFNC decreased the work of breathing in patients with normal diaphragm contraction defined as ≥15%. This result is consistent with that of a previous study (18). Therefore, the measurements of diaphragm function in this study are reliable.

This study has several limitations. First, no patients required HFNC after HFNC liberation although HFNC positively contributed to paradoxical diaphragm contraction. This is probably because patients whose HFNC was weaned to 30 L/min for patients' safety were included. Therefore, this study is a preliminary study suggesting the possible role of HFNC on paradoxical diaphragm contraction. HFNC may be crucial for patients with prominent paradoxical diaphragm contraction in the acute phase. Second, in this study, the observation was conducted at the time of HFNC liberation. It is desirable to observe diaphragm function at the start of HFNC, but it is unethical if treatment is delayed due to the observational study. Therefore, as a first preliminary study, the change of diaphragm function was observed at HFNC liberation. Third, this study was based on a small sample size, particularly in patients with paradoxical diaphragm contraction. Thus, further studies are required to confirm these results in a large population.

CONCLUSION

In patients without diaphragm dysfunction, work of breathing decreased with HFNC but did not decrease in patients with decreased diaphragm contraction. However, paradoxical diaphragm contraction was decreased with HFNC.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

TT and NN contributed to study design, acquisition of data, analysis of data, and drafting of the manuscript. YA analyzed the data. JO contributed to the study concept and revision of the manuscript. All authors read and approved the final manuscript.

DECLARATIONS

Ethics approval and consent to participate : Ethics approval was obtained from the clinical research ethics committee at Tokushima University Hospital (approval number 3299). Informed consent to participate in the study was also obtained from patients or from an authorized surrogate.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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