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Effect of electrical activity of the diaphragm waveform patterns on SpO2 for extremely preterm infants ventilated with neurally adjusted ventilatory assist

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Abstract

Objective

This study aimed to evaluate the association between electrical activity of the diaphragm (Edi) waveform patterns and peripheral oxygen saturation (SpO_2) in extremely preterm infants who are ventilated with neurally adjusted ventilatory assist (NAVA).

Study Design

We conducted a retrospective cohort study at a level III neonatal intensive care unit. Extremely preterm infants born at our hospital between November 2019 and November 2020 and ventilated with NAVA were included. We collected Edi waveform data and classified them into four Edi waveform patterns, including the phasic pattern, central apnea pattern, irregular low-voltage pattern, and tonic burst pattern. We analyzed the Edi waveform pattern for the first 15 hours of collectable data in each patient. To investigate the association between Edi waveform patterns and SpO_2, we analyzed the dataset every 5 minutes as one data unit. We compared the proportion of each waveform pattern between the desaturation (Desat (+)) and non-desaturation (Desat (–)) groups.

Results

We analyzed collected data for 105 hours (1260 data units). The proportion of the phasic pattern in the Desat (+) group was significantly lower than that in the Desat (–) group ($p < 0.001$). However, the proportions of the central apnea, irregular low-voltage, and tonic burst patterns in the Desat (+) group were significantly higher than those in the Desat (–) group (all $p < 0.05$).

Conclusion

Our results indicate that proportions of Edi waveform patterns have an effect on desaturation of SpO_2 in extremely preterm infants who are ventilated with NAVA.

INTRODUCTION

Recent advancement in perinatal management has improved the survival rate of extremely preterm infants. Consequently, bronchopulmonary dysplasia (BPD) has become one of the most common and severe sequelae for extremely preterm infants [1,2] and management for preventing BPD has been the focus of attention. Extremely preterm infants require mechanical ventilation for a relatively long period because of prematurity of their lungs. In such a long mechanical ventilation period, high ventilatory pressure and patient–ventilator asynchrony are important factors for BPD [3,4]. Therefore, the strategy of ventilation for extremely preterm infants has focused on minimizing inspiratory pressure and more synchronized ventilation.

Neurally adjusted ventilatory assist (NAVA) is a relatively novel mode of mechanical ventilation and provides respiratory support in response to the patient's electrical activity of the diaphragm (Edi). Compared with other patient-triggered ventilator modes, NAVA improves patient–ventilatory synchrony and reduces peak inspiratory pressure and the work of breathing without an elevated fraction of inspiratory oxygen (FiO_2) [5–9]. There has been a recent increase in reports on ventilation with NAVA for

preterm and low birth weight infants [10–13]. NAVA is expected to improve the prognosis of extremely preterm infants, especially in proceeding to BPD [14,15]. However, despite appropriate ventilatory settings, some preterm infants cannot be appropriately supported by NAVA. These infants develop an unstable respiratory condition or need to have their ventilatory mode changed from NAVA [16–18]. However, there are limited clinical indicators of whether infants can be appropriately ventilated by NAVA.

During ventilation with NAVA, respiratory support is supplied from a ventilator on the basis of the Edi waveform. Preterm infants are known to represent variable Edi waveform patterns[19,20], but there are limited data on the association between Edi waveform patterns and respiratory conditions. On the basis of our clinical experience, we consider that not only frequent central apnea, but also low inspiratory movements prevent appropriate ventilatory support by NAVA.

We hypothesize that Edi waveform patterns reflect the respiratory pattern, which affects appropriate ventilatory support by NAVA and the frequency of desaturation of peripheral oxygen saturation (SpO_2).

In this study, we evaluated the association between Edi waveform patterns and the frequency of desaturation in extremely preterm infants who are ventilated with NAVA.

MATERIALS AND METHODS

Patients

We conducted a retrospective cohort study at a single level III neonatal intensive care unit (Kyoto University Hospital, Kyoto, Japan). Extremely preterm infants of < 28 weeks gestational age who were born at our hospital between November 2019 and November 2020 and required mechanical ventilation with NAVA delivered by Servo-n® (Maquet, Critical Care AB, Solna, Sweden) were eligible for our study. Infants who needed to have their ventilation mode changed from NAVA to another mode (including those who were extubated) within 24 consecutive hours or those who did not have more than 15 hours of data collected were excluded.

Study procedure

According to our usual practice, the NAVA level was set and adjusted to maintain Edi peak < 15 μV and positive end-expiratory pressure (PEEP) was set and adjusted to maintain Edi minimum at < 5 μV. The backup support setting and apnea time were adjusted to supply proper backup ventilation to avoid desaturation. Because we

routinely adjust the NAVA ventilator settings with this procedure, the initial settings were usually the same as follows: NAVA level = 1.5 to 2 $cmH_2O/\mu V$, PEEP = 7 cmH_2O, apnea time = 2 seconds, pressure level above PEEP in backup = 10 cmH_2O, and back up respiratory rate = 40. By this procedure of adjustment, subsequent ventilator setting after the initial setting also did not vary in each patient. In accordance with the manufacturer's recommendations, proper positioning of the Edi catheter was frequently verified by attending physicians.

The waveforms of ventilator pressure, flow, and Edi were acquired from the ventilator and recorded continuously by using the software SERVO CONNECT (Fukuda Denshi Co. Ltd., Tokyo, Japan). We routinely use this software and collect data when possible.

Data collection

Demographic and clinical data of included infants were extracted from medical records. Valid data for analysis of Edi waveforms and SpO_2 were defined as when the infants had not been manipulated and the ventilator setting had not been changed at least within 3 hours, except for FiO_2. With SERVO CONNECT, Edi waveforms were

shown in one window every 10 seconds. Edi waveforms were classified into four patterns including those previously reported and a novel pattern [19,20] (Figure 1). These patterns were as follows: 1) a phasic pattern was defined as a regular increasing and decreasing pattern, 2) a central apnea pattern was defined as continuous low Edi, which induced backup mandatory ventilation, 3) a tonic burst pattern was defined as elevated tonic activity without clear phasic activity or with irregular activity, and 4) an irregular low-voltage pattern was defined as low Edi activity (Edi [peak-minimum] < 1.5 μV). Because irregular low-voltage patterns did not induce backup ventilation and generated low peak inspiratory pressure, we distinguished irregular low-voltage patterns from central apnea patterns.

Ventilatory settings, including the NAVA level, PEEP, backup setting, and FiO_2, were collected from the medical records. Ventilatory parameters, including Edi peak, Edi minimum, peak airway pressure, mean airway pressure, and time in backup ventilation were collected from stored data in the ventilators.

SpO_2 data were recorded by a central monitoring system (Phillips Information Management System®; Phillips Japan, Japan) every minute. We extracted these data

recorded at the same timing of ventilator waveform analysis. We defined desaturation as a decrease in SpO_2 < 85% because our setting of the lower limit of SpO_2 was routinely 85% as part of our respiratory strategy.

Data analysis

Edi waveforms every 10 seconds were assessed and classified into four patterns by only one investigator (blinded clinical data). When only one waveform pattern (e.g., phasic pattern) was shown in a window, this window was classified in this waveform pattern (e.g., phasic pattern) and counted with one point. When there were multiple patterns in one window (e.g., central apnea pattern and irregular low-voltage pattern; Figure 2 online), one point was distributed to each pattern equally (e.g., 0.5 points each in the central apnea pattern and irregular low-voltage pattern). We summed the points of each waveform pattern every 5 minutes (total of 30 points) and calculated the proportion (%) of the points (by dividing by 30). In each patient, data for the first 15 hours of data collection were analyzed.

To investigate the association between Edi waveform patterns and SpO_2, we analyzed the dataset every 5 minutes as one data unit. Some Edi waveform patterns might not affect SpO_2 immediately, but have an effect later. Therefore, the association between Edi waveform patterns and SpO_2 in 1 or 2 minutes cannot reflect the truth. One data unit of the dataset every 5 minutes included the proportion of each waveform pattern and SpO_2. There were 180 data units in each extremely preterm infant because we assessed 15 hours of data.

We divided all data units into the following two groups. The Desat (+) group was defined as when desaturation was observed in even only once. The Desat (–) group was defined as when no desaturation was observed in any time. We compared the proportion of each waveform pattern between the two groups. SpO_2 was also compared between the two groups.

In addition, to evaluate the association between the Edi waveform pattern and ventilatory parameters, we analyzed the data using another method. We calculated the median proportion of all data units in each waveform pattern. In each waveform pattern, all data units were divided into two groups as the high frequency (H-) group and the low

frequency (L-) group (e.g., H-phasic group or L-phasic group) by each median proportion. The H- group and L- group of each waveform pattern were defined as data units that were higher and lower, respectively, than the median proportion of all data units. If one data unit had a higher proportion than the median proportion in the phasic pattern, this data unit was classified as the H-phasic group. In the same data unit, if it had a lower proportion than the median proportion in the central apnea pattern, this data unit was also classified as the L-apnea group. We compared SpO_2, frequency of desaturation, and ventilatory parameters between the H- and L- groups in each waveform pattern.

The study protocol was approved by the local medical ethics committee (reference number R2154).

Statistical analysis

Statistical analysis was performed with R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) using the EZR application. Actual ventilator setting data are expressed as the mean ± standard deviation (SD). The

other data are expressed as the median (interquartile range [IQR]) and n (%). Continuous variables were analyzed using the Mann-Whitney test. We defined significant differences as $p < 0.05$.

RESULTS

Patients' characteristics

Ten extremely preterm infants were included in our study. Of these, one preterm infant was excluded because she was extubated before being ventilated with NAVA for 24 consecutive hours. Another two preterm infants were excluded because more than 15 hours of data could not be collected when they changed their ventilatory support from NAVA. Therefore, we analyzed the remaining seven preterm infants. The patients' clinical data are shown in Table 1. The preterm infants were born at 24 or 26 gestational weeks and weighed between 503 g and 1128 g. They were ventilated with NAVA at approximately 2 or 3 weeks after birth. In total, we analyzed collected data for 105 hours (1260 data units). The actual ventilatory settings for all data units are also shown in Table 1.

Edi waveform patterns and desaturation

Comparison of the proportion of each waveform pattern between the Desat (+) and (–) groups is shown in Figure 3. The Desat (+) group included 261 data units and the Desat

(–) group included 999 data units. The proportion of the phasic pattern in the Desat (+) group was significantly lower than that in the Desat (–) group ($p < 0.001$). However, the proportions of the central apnea, irregular low-voltage, and tonic burst patterns in the Desat (+) group were significantly higher than those in the Desat (–) group ($p < 0.001$, $p < 0.001$, and $p = 0.039$, respectively). SpO2 in the Desat (+) group were significantly lower than that in the Desat (-) group (Desat (+) group: 88% (86%, 89%), Desat (-) group: 95% (92%, 97%), $p<0.001$).

Edi waveform patterns and ventilatory parameters

The median proportions in all data units were 53% (42%, 71%) for the phasic pattern, 22% (12%, 37%) for the central apnea pattern, 8.9% (5%, 15%) for the irregular low-voltage pattern, and 9.4% (4.7%, 16%) for the tonic burst pattern.

In every waveform pattern, these median proportions were used as thresholds for dividing data units into the H- and L- groups. (e.g., in one unit, if the phasic pattern was 62%, the central apnea pattern was 13%, the irregular low-voltage pattern was 12%, and the tonic burst pattern was 13%, they were classified into the H-phasic group, the L-

apnea group, the H-irregular low-voltage group, and the H-tonic burst group, respectively).

SpO_2 in the H- and L- groups in each waveform pattern are shown in Table 2. SpO_2 in the H-phasic group was significantly higher than that in the L-phasic group ($p< 0.001$). However, SpO_2 was significantly lower in the H-apnea group than in the L-apnea group ($p < 0.001$) and also lower in the H-irregular low-voltage group than in the L-irregular low-voltage group ($p < 0.001$). The presence of desaturation between the H- and L-groups in each waveform pattern is also shown in Table 2. The frequency of desaturation was significantly lower in the H-phasic group than in the L-phasic group ($p < 0.001$). However, the frequency of desaturation was significantly higher in the H-apnea group than in the L-apnea group ($p < 0.001$), and higher in the H-irregular low-voltage group than in the L-irregular low-voltage group ($p < 0.001$).

Comparison of ventilatory parameters and proportions of each waveform pattern between the H- and L- groups of each waveform pattern are also shown in Table 2. Edi peak in the H-phasic group was significantly higher than that in the L-phasic group ($p < 0.001$). Time in backup ventilation in the H-phasic group were significantly lower than

those in the L-phasic group ($p < 0.001$). On the other hand, Edi peak in the H-irregular low-voltage group was significantly lower than that in the L-irregular low-voltage group ($p < 0.001$). Peak airway pressure in the H-irregular low-voltage group was significantly lower than that in the L-irregular low-voltage group ($p < 0.001$). Time in backup ventilation was not different between the H- and L-irregular low-voltage groups.

DISCUSSION

Several studies have reported characterization of breathing patterns as shown by an Edi catheter in preterm infants [19, 20]. However, the association between breathing patterns and respiratory conditions was not shown in these reports. This is the first report to evaluate the effect of Edi waveform patterns on SpO_2 and the frequency of desaturation. Our results indicated that Edi waveform patterns were associated with the frequency of desaturation. Therefore, analysis of Edi waveform patterns could be an important indicator for appropriately using NAVA in extremely preterm infants.

We found that patients had a stable SpO_2 when the phasic pattern was frequently observed. However, when an irregular low-voltage, central apnea, or tonic burst pattern was frequently observed, patients showed unstable SpO_2. These results suggest that a high frequency of an irregular low-voltage, central apnea, or tonic burst pattern is a cause of failure to ventilate with NAVA.

In this study, we defined the central apnea pattern as continuous flat Edi, which induces backup mandatory ventilation, to appropriately assess the effect of central apnea. In contrast, we defined a low Edi peak waveform as an irregular low-voltage

pattern. This waveform pattern has not been defined in previous reports. A low Edi peak waveform (Edi [peak-min] < 1.5 μV) prevents backup ventilation, but it supplies low peak inspiratory pressure [21]. Peak airway pressure supplied by NAVA is calculated according to the following formula: NAVA level ($cmH_2O/\mu V$)×(Edi peak [μV]-Edi minimum [μV])+PEEP (cmH_2O). During this study, an efficient observed peak inspiratory pressure was approximately 15 cmH_2O (IQR: 14–16 cmH_2O). Because we set the NAVA level at approximately 1.6 ± 0.4 and PEEP at 7 cmH_2O, peak airway pressure supplied by an irregular low-voltage pattern was calculated as < 10 cmH_2O (1.6×1.5+PEEP). In reality, peak airway pressure with a low Edi peak waveform observed in this study was < 10 cmH_2O. This low peak inspiratory pressure appeared to provide insufficient support. Our study indicated that a high frequency of the irregular low-voltage pattern lead to low peak airway pressure generated with low Edi peak. Our study also showed that time in backup ventilation was not different between H- and L-irregular low-voltage groups. These results indicate that the irregular low-voltage pattern may prevent backup ventilation, but supply insufficient peak airway pressure. Therefore, irregular low-voltage pattern could lead to desaturation.

In addition, a high frequency of the tonic burst pattern was associated with slightly higher peak airway pressure generated with slightly higher Edi peak. In contrast, the tonic burst pattern was more frequently observed in the Desat (+) group than in the Desat (–) group. This contradiction arose because the tonic burst pattern is an irregular waveform and is considered to be an asynchronized pattern. Therefore, the tonic burst pattern was also considered to result in desaturation. On the other hand, as tonic burst pattern was known to be an essential respiratory pattern for premature infants to recruit their lung [22,23], desaturation may lead infants to breath with tonic burst pattern. Further research about the effect of tonic burst pattern for respiratory condition would be needed.

Ventilatory parameters from the ventilator did not include information of the waveform pattern. Therefore, the ventilatory parameters especially of Edi peak and peak airway pressure could include all waveform patterns. Even if these parameters were indicated as the same value, the meaning of the value was different among the different Edi waveform patterns. When the Edi peak was 5 μV in the phasic pattern, the ventilator may provide stable support, but when that in the irregular low-voltage pattern

or tonic burst pattern the ventilator may supply ineffective or asynchronized support and cause desaturation. Therefore, desaturation could not be predicted by only using these ventilatory parameters. Consequently, the Edi waveform pattern is considered to be important for assessing desaturation.

To exclude the effect of changing the ventilator setting for the results, our data were collected when the ventilator setting had not been changed within at least 3 hours to confirm the stability of the respiratory condition with the ventilator setting at that time. In addition, because the ventilator setting did not vary much, we consider that our results did not depend on the ventilator setting, but on the variability of Edi waveform patterns instead.

There are some limitations of our study. The main limitation was the limited number of cases. Additionally, because the gestational age and duration of postconceptional age with ventilation by NAVA of the included infants had a limited range, our results might not be able to be applied for more mature infants. However, because we were able to evaluate many data units, the similarity of the patients' characteristics was a strength of this study. Further studies are required to validate our results.

In future studies, we need to identify the appropriate proportion of Edi waveform patterns that result in stable SpO_2 of infants. The criterion that indicates when the attending physician should change the ventilator mode from NAVA to another mode also needs to be investigated.

CONCLUSION

We assessed the association between Edi waveform patterns and SpO_2. Proportions of Edi waveform patterns affect SpO_2 in extremely preterm infants. Our results indicate that analysis of Edi waveform patterns is an important indicator for assessing whether preterm infants are appropriately ventilated with NAVA.

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Image legends

Figure 1. Representative waveforms for four Edi waveform patterns.

Pressure curves are shown in each upper row and Edi waveforms are shown in each lower row. A: Phasic pattern, B: central apnea pattern, C: tonic bursts pattern, D: irregular low-voltage pattern.

Figure 2. Example of one window of servo connect including multiple waveform patterns.

A pressure curve is in the upper row and an Edi waveform is in the lower row. Waveforms on the left side were classified as central apnea and waveforms on the right side were classified as an irregular low-voltage pattern. Each pattern was calculated as 0.5 points.

Figure 3. Comparison of the proportions each waveform pattern between the Desaturation (+) and (-) groups.

Data are expressed as median and interquartile range. The Desat (+) group included 261 data units and the Desat (–) group included 999 data units. *, $p<0.05$.

Table 1. Patients' clinical data and ventilatory settings

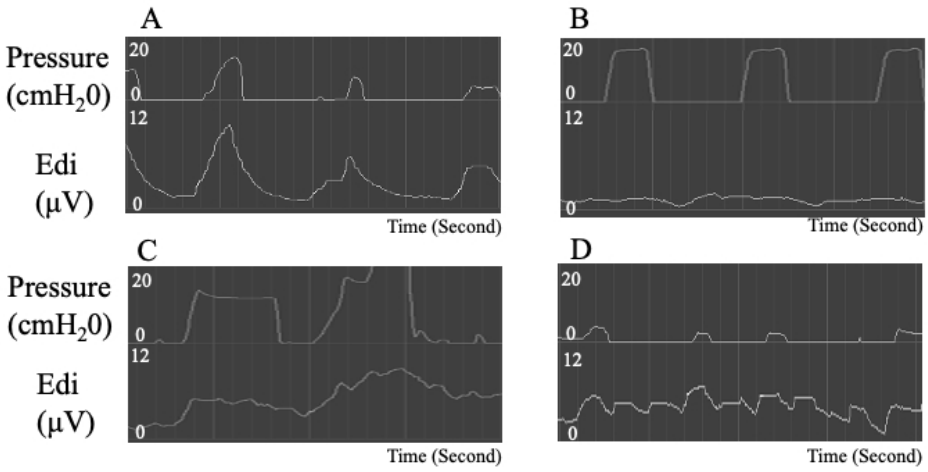
Clinical data	
Gestational Age (wks)	25.3 (24.5, 25.5)
Birth Weight (g)	626 (549, 790)
Apgar score 1 minute	4 (3, 5)
Apgar score 5 minute	7(6, 7)
DOL at NAVA started	19 (18, 20)
PCA at NAVA started (wks)	28.2 (27.4, 28.4)
Ventilator settings	
NAVA level ($cmH_2O/\mu V$)	1.6 ± 0.4
PEEP (cmH_2O)	7.2 ± 0.4
Apnea time (s)	2.0 ± 0.6
Pressure level above PEEP in backup (cmH_2O)	10 ± 1.5
Backup RR	40 ± 4.3
FiO_2 (%)	22 ± 1.4

Patients' clinical data are expressed as the median (interquartile range). Ventilator settings are presented as mean ± standard deviation. DOL, day of life; NAVA, neurally adjusted ventilatory assist; PCA, postconceptional age; PEEP, positive end expiratory pressure; RR, respiratory rate.

Table 2. Comparison between Edi waveform patterns and stability of SpO_2 and ventilatory parameters

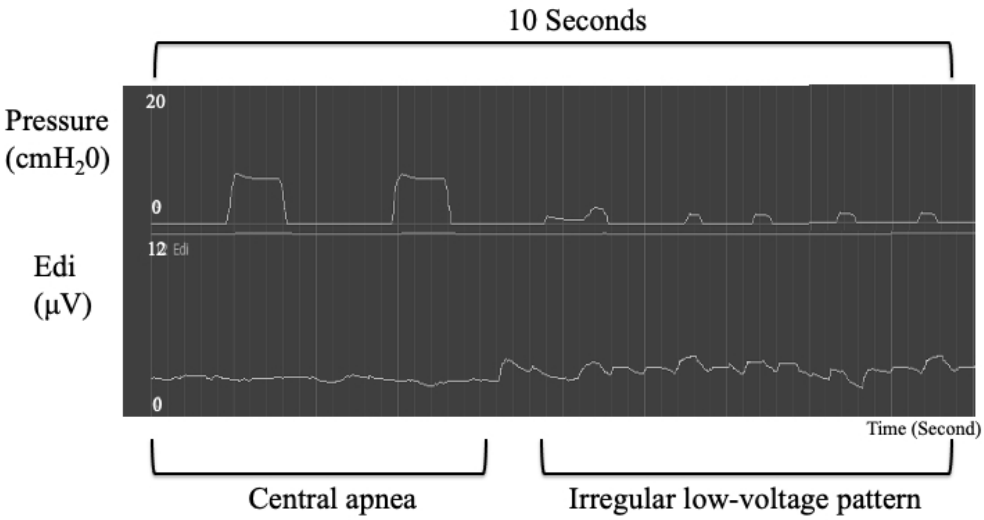
	Phasic pattern			Central apnea pattern			Irregular low-voltage pattern			Tonic burst pattern		
	H-	L-	P value	H-	L-	P value	H-	L-	P value	H-	L-	P value
SpO_2 (%)	94 (91, 97)	93 (90, 95)	<0.001	93 (90, 96)	94 (91, 96)	<0.001	93 (90, 96)	94 (91, 96)	<0.001	94 (91, 96)	93 (91, 96)	0.51
Presence of desaturation (%)	16	26	<0.001	25	17	<0.001	26	17	<0.001	22	20	0.531
Edi peak (μV)	5.2 (4.2, 6.3)	4.8 (3.8, 5.9)	<0.001	4.9 (3.9, 5.8)	5.2 (4.2, 6.4)	<0.001	4.7 (3.5, 5.7)	5.3 (4.5, 6.4)	<0.001	5.2 (4.2, 6.3)	4.9 (3.9, 5.8)	<0.001
Edi min (μV)	1.3 (1.0, 1.7)	1.4 (1.0, 1.9)	0.026	1.3 (1.0, 1.8)	1.3 (1.0, 1.8)	0.964	1.3 (0.9, 1.8)	1.4 (1.0, 1.8)	0.11	1.4 (1.1, 1.9)	1.2 (0.9, 1.7)	<0.001
Peak airway Pressure (cmH_2O)	15 (15, 16)	15 (14, 16)	0.001	15 (14, 16)	15 (14, 16)	0.47	15 (14, 16)	16 (15, 17)	<0.001	15 (14, 17)	15 (14, 16)	<0.001
Mean airway Pressure (cmH_2O)	10 (9.6, 10)	10 (9.6, 10)	0.078	10 (9.6, 10)	10 (9.6, 10)	0.34	10 (9.6, 10)	10 (9.7, 10)	<0.001	10 (9.7, 10)	10 (9.6, 10)	0.16
Time in backup (%)	14 (6.0, 28)	19 (9.0, 37)	<0.001	19 (8.7, 37)	15 (6.3, 28)	<0.001	16 (7.0, 35)	15 (6.7, 31)	0.055	15 (7.3, 30)	18 (7.7, 35)	0.028
FiO2 (%)	21 (21, 22)	21 (21, 23)	0.014	21 (21, 22)	21 (21, 22)	0.364	21 (21, 23)	21 (21, 22)	0.019	21 (21, 23)	21 (21, 22)	<0.001
Median of Phasic pattern (%)	67 (60, 76)	35 (23, 45)	<0.001	37 (23, 48)	66 (57, 76)	<0.001	43 (29, 58)	62 (47, 74)	<0.001	52 (36, 64)	54 (34, 72)	0.003
Median of Central apnea pattern (%)	13 (7.5, 19)	37 (26, 51)	<0.001	37 (28, 52)	12 (7.2, 17)	<0.001	26 (15, 41)	19 (10, 34)	<0.001	19 (11, 30)	26 (13, 45)	<0.001
Median of Irregular low-voltage pattern (%)	6.1 (3.3, 11)	13 (7.8, 21)	<0.001	11 (6.1, 18)	7.8 (3.9, 14)	<0.001	17 (13, 22)	2.0 (2.8, 7.2)	<0.001	8.9 (4.4, 15)	10 (5.0, 17)	0.026
Median of Tonic burst pattern (%)	8.9 (5.0, 13)	9.4 (4.4, 16)	0.11	7.2 (4.2, 13)	10 (5.6, 17)	<0.001	8.3 (4.4, 14)	9.4 (5.0, 16)	0.002	15 (12, 20)	5.0 (2.8, 6.7)	<0.001

Data are expressed as the median (interquartile range). Edi, electrical activity of the diaphragm; H-, high frequency; L-, low frequency.



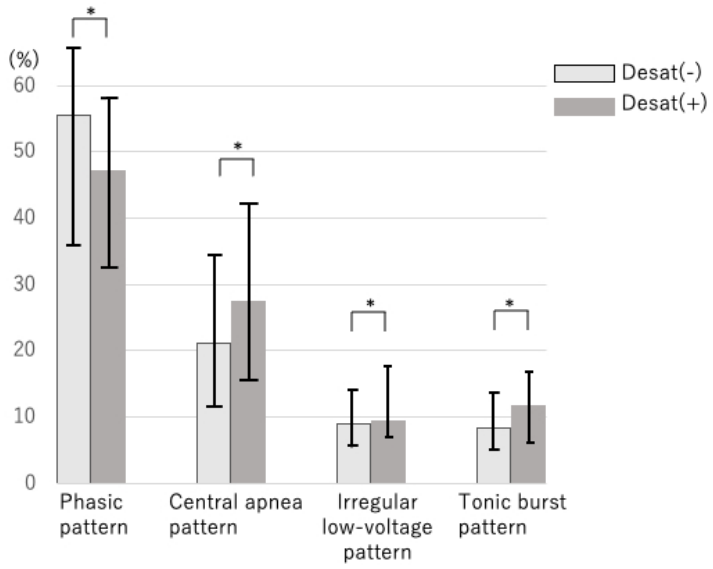
Caption: Representative waveforms for four Edi waveform patterns. Pressure curves are shown in each upper row and Edi waveforms are shown in each lower row. A: Phasic pattern, B: central apnea pattern, C: tonic bursts pattern, D: irregular low-voltage pattern.

254x190mm (72 x 72 DPI)



Caption : Example of one window of servo connect including multiple waveform patterns. A pressure curve is in the upper row and an Edi waveform is in the lower row. Waveforms on the left side were classified as central apnea and waveforms on the right side were classified as an irregular low-voltage pattern. Each pattern was calculated as 0.5 points.

254x190mm (72 x 72 DPI)



Data are expressed as median and interquartile range. The Desat (+) group included 261 data units and the Desat (−) group included 999 data units. *, $p<0.05$.

338x190mm (54 x 54 DPI)

Effect of electrical activity of the diaphragm waveform patterns on SpO2 for extremely preterm infants ventilated with neurally adjusted ventilatory assist

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Conflicts of Interest and Source of Funding: None declared.

Keywords: bronchopulmonary dysplasia; neonatal intensive care units; diaphragm; lung injury.

Abstract

Objective

This study aimed to evaluate the association between electrical activity of the diaphragm (Edi) waveform patterns and peripheral oxygen saturation (SpO_2) in extremely preterm infants who are ventilated with neurally adjusted ventilatory assist (NAVA).

Study Design

We conducted a retrospective cohort study at a level III neonatal intensive care unit. Extremely preterm infants born at our hospital between November 2019 and November 2020 and ventilated with NAVA were included. We collected Edi waveform data and classified them into four Edi waveform patterns, including the phasic pattern, central apnea pattern, irregular low-voltage pattern, and tonic burst pattern. We analyzed the Edi waveform pattern for the first 15 hours of collectable data in each patient. To investigate the association between Edi waveform patterns and SpO_2, we analyzed the dataset every 5 minutes as one data unit. We compared the proportion of each waveform pattern between the desaturation (Desat (+)) and non-desaturation (Desat (–)) groups.

Results

We analyzed collected data for 105 hours (1260 data units). The proportion of the phasic pattern in the Desat (+) group was significantly lower than that in the Desat (–) group ($p < 0.001$). However, the proportions of the central apnea, irregular low-voltage, and tonic burst patterns in the Desat (+) group were significantly higher than those in the Desat (–) group (all $p < 0.05$).

Conclusion

Our results indicate that proportions of Edi waveform patterns have an effect on desaturation of SpO_2 in extremely preterm infants who are ventilated with NAVA.

INTRODUCTION

Recent advancement in perinatal management has improved the survival rate of extremely preterm infants. Consequently, bronchopulmonary dysplasia (BPD) has become one of the most common and severe sequelae for extremely preterm infants [1,2] and management for preventing BPD has been the focus of attention. Extremely preterm infants require mechanical ventilation for a relatively long period because of prematurity of their lungs. In such a long mechanical ventilation period, high ventilatory pressure and patient–ventilator asynchrony are important factors for BPD [3,4]. Therefore, the strategy of ventilation for extremely preterm infants has focused on minimizing inspiratory pressure and more synchronized ventilation.

Neurally adjusted ventilatory assist (NAVA) is a relatively novel mode of mechanical ventilation and provides respiratory support in response to the patient's electrical activity of the diaphragm (Edi). Compared with other patient-triggered ventilator modes, NAVA improves patient–ventilatory synchrony and reduces peak inspiratory pressure and the work of breathing without an elevated fraction of inspiratory oxygen (FiO_2) [5–9]. There has been a recent increase in reports on ventilation with NAVA for

preterm and low birth weight infants [10–13]. NAVA is expected to improve the prognosis of extremely preterm infants, especially in proceeding to BPD [14,15]. However, despite appropriate ventilatory settings, some preterm infants cannot be appropriately supported by NAVA. These infants develop an unstable respiratory condition or need to have their ventilatory mode changed from NAVA [16–18]. However, there are limited clinical indicators of whether infants can be appropriately ventilated by NAVA.

During ventilation with NAVA, respiratory support is supplied from a ventilator on the basis of the Edi waveform. Preterm infants are known to represent variable Edi waveform patterns[19,20], but there are limited data on the association between Edi waveform patterns and respiratory conditions. On the basis of our clinical experience, we consider that not only frequent central apnea, but also low inspiratory movements prevent appropriate ventilatory support by NAVA.

We hypothesize that Edi waveform patterns reflect the respiratory pattern, which affects appropriate ventilatory support by NAVA and the frequency of desaturation of peripheral oxygen saturation (SpO_2).

In this study, we evaluated the association between Edi waveform patterns and the frequency of desaturation in extremely preterm infants who are ventilated with NAVA.

MATERIALS AND METHODS

Patients

We conducted a retrospective cohort study at a single level III neonatal intensive care unit (Kyoto University Hospital, Kyoto, Japan). Extremely preterm infants of < 28 weeks gestational age who were born at our hospital between November 2019 and November 2020 and required mechanical ventilation with NAVA delivered by Servo-n® (Maquet, Critical Care AB, Solna, Sweden) were eligible for our study. Infants who needed to have their ventilation mode changed from NAVA to another mode (including those who were extubated) within 24 consecutive hours or those who did not have more than 15 hours of data collected were excluded.

Study procedure

~~To properly use NAVA~~ According to our usual practice, the NAVA level was set and adjusted to maintain Edi peak < 15 μV and positive end-expiratory pressure (PEEP) was set and adjusted to maintain Edi minimum at < 5 μV. The backup support setting and apnea time were adjusted to supply proper backup ventilation to avoid desaturation.

Because we routinely adjust the NAVA ventilator settings with this procedure, the initial settings were usually the same as follows: NAVA level = 1.5 to 2 $cmH_2O/\mu V$, PEEP = 7 cmH_2O, apnea time = 2 seconds, pressure level above PEEP in backup = 10 cmH_2O, and back up respiratory rate = 40. ~~Subsequent setting with adjustment by this procedure did not vary in each patient.~~ By this procedure of adjustment, subsequent ventilator setting after the initial setting also did not vary in each patient. In accordance with the manufacturer's recommendations, proper positioning of the Edi catheter was frequently verified by attending physicians.

The waveforms of ventilator pressure, flow, and Edi were acquired from the ventilator and recorded continuously by using the software SERVO CONNECT (Fukuda Denshi Co. Ltd., Tokyo, Japan). We routinely use this software and collect data when possible.

Data collection

Demographic and clinical data of included infants were extracted from medical records. Valid data for analysis of Edi waveforms and SpO_2 were defined as when the infants had not been manipulated and the ventilator setting had not been changed at

least within 3 hours, except for FiO_2. With SERVO CONNECT, Edi waveforms were shown in one window every 10 seconds. Edi waveforms were classified into four patterns including those previously reported and a novel pattern [19,20] (Figure 1). These patterns were as follows: 1) a phasic pattern was defined as a regular increasing and decreasing pattern, 2) a central apnea pattern was defined as continuous low Edi, which induced backup mandatory ventilation, 3) a tonic burst pattern was defined as elevated tonic activity without clear phasic activity or with irregular activity, and 4) an irregular low-voltage pattern was defined as low Edi activity (Edi [peak-minimum] < 1.5 μV). Because irregular low-voltage patterns did not induce backup ventilation and generated low peak inspiratory pressure, we distinguished irregular low-voltage patterns from central apnea patterns.

Ventilatory settings, including the NAVA level, PEEP, backup setting, and FiO_2, were collected from the medical records. Ventilatory parameters, including Edi peak, Edi minimum, peak airway pressure, mean airway pressure, and time in backup ventilation were collected from stored data in the ventilators.

SpO_2 data were recorded by a central monitoring system (Phillips Information Management System®; Phillips Japan, Japan) every minute. We extracted these data recorded at the same timing of ventilator waveform analysis. We defined desaturation as a decrease in $SpO_2 < 85\%$ because our setting of the lower limit of SpO_2 was routinely 85% as part of our respiratory strategy.

Data analysis

Edi waveforms every 10 seconds were assessed and classified into four patterns by only one investigator (blinded clinical data). When only one waveform pattern (e.g., phasic pattern) was shown in a window, this window was classified in this waveform pattern (e.g., phasic pattern) and counted with one point. When there were multiple patterns in one window (e.g., central apnea pattern and irregular low-voltage pattern; Figure 2 online), one point was distributed to each pattern equally (e.g., 0.5 points each in the central apnea pattern and irregular low-voltage pattern). We summed the points of each waveform pattern every 5 minutes (total of 30 points) and calculated the

proportion (%) of the points (by dividing by 30). In each patient, data for the first 15 hours of data collection were analyzed.

To investigate the association between Edi waveform patterns and SpO_2, we analyzed the dataset every 5 minutes as one data unit. Some Edi waveform patterns might not affect SpO_2 immediately, but have an effect later. Therefore, the association between Edi waveform patterns and SpO_2 in 1 or 2 minutes cannot reflect the truth. One data unit of the dataset every 5 minutes included the proportion of each waveform pattern and SpO_2. There were 180 data units in each extremely preterm infant because we assessed 15 hours of data.

We divided all data units into the following two groups. The Desat (+) group was defined as when desaturation was observed in even only once. The Desat (–) group was defined as when no desaturation was observed in any time. We compared the proportion of each waveform pattern between the two groups. SpO_2 was also compared between the two groups.

In addition, to evaluate the association between the Edi waveform pattern and ventilatory parameters, we analyzed the data using another method. We calculated the

median proportion of all data units in each waveform pattern. In each waveform pattern, all data units were divided into two groups as the high frequency (H-) group and the low frequency (L-) group (e.g., H-phasic group or L-phasic group) by each median proportion. The H- group and L- group of each waveform pattern were defined as data units that were higher and lower, respectively, than the median proportion of all data units. If one data unit had a higher proportion than the median proportion in the phasic pattern, this data unit was classified as the H-phasic group. In the same data unit, if it had a lower proportion than the median proportion in the central apnea pattern, this data unit was also classified as the L-apnea group. We compared SpO_2, frequency of desaturation, and ventilatory parameters between the H- and L- groups in each waveform pattern.

The study protocol was approved by the local medical ethics committee (reference number R2154).

Statistical analysis

Statistical analysis was performed with R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) using the EZR application. Actual ventilator setting data are expressed as the mean ± standard deviation (SD). The other data are expressed as the median (interquartile range [IQR]) and n (%). Continuous variables were analyzed using the Mann-Whitney test. We defined significant differences as $p < 0.05$.

RESULTS

Patients' characteristics

Ten extremely preterm infants were included in our study. Of these, one preterm infant was excluded because she was extubated before being ventilated with NAVA for 24 consecutive hours. Another two preterm infants were excluded because more than 15 hours of data could not be collected when they changed their ventilatory support from NAVA. Therefore, we analyzed the remaining seven preterm infants. The patients' clinical data are shown in Table 1. The preterm infants were born at 24 or 26 gestational weeks and weighed between 503 g and 1128 g. They were ventilated with NAVA at approximately 2 or 3 weeks after birth. In total, we analyzed collected data for 105 hours (1260 data units). The actual ventilatory settings for all data units are also shown in Table 1.

Edi waveform patterns and desaturation

Comparison of the proportion of each waveform pattern between the Desat (+) and (–) groups is shown in Figure 3. The Desat (+) group included 261 data units and the Desat (–) group included 999 data units. The proportion of the phasic pattern in the Desat (+) group was significantly lower than that in the Desat (–) group ($p < 0.001$). However, the proportions of the central apnea, irregular low-voltage, and tonic burst patterns in the Desat (+) group were significantly higher than those in the Desat (–) group ($p < 0.001$, $p < 0.001$, and $p = 0.039$, respectively). SpO2 in the Desat (+) group were significantly lower than that in the Desat (-) group (Desat (+) group: 88% (86%, 89%), Desat (-) group: 95% (92%, 97%), $p<0.001$).

Edi waveform patterns and ventilatory parameters

The median proportions in all data units were 53% (42%, 71%) for the phasic pattern, 22% (12%, 37%) for the central apnea pattern, 8.9% (5%, 15%) for the irregular low-voltage pattern, and 9.4% (4.7%, 16%) for the tonic burst pattern.

In every waveform pattern, these median proportions were used as thresholds for dividing data units into the H- and L- groups. (e.g., in one unit, if the phasic pattern was

62%, the central apnea pattern was 13%, the irregular low-voltage pattern was 12%, and the tonic burst pattern was 13%, they were classified into the H-phasic group, the L-apnea group, the H-irregular low-voltage group, and the H-tonic burst group, respectively).

SpO_2 in the H- and L- groups in each waveform pattern are shown in Table 2. SpO_2 in the H-phasic group was significantly higher than that in the L-phasic group ($p< 0.001$). However, SpO_2 was significantly lower in the H-apnea group than in the L-apnea group ($p < 0.001$) and also lower in the H-irregular low-voltage group than in the L-irregular low-voltage group ($p < 0.001$). The presence of desaturation between the H- and L-groups in each waveform pattern is also shown in Table 2. The frequency of desaturation was significantly lower in the H-phasic group than in the L-phasic group ($p < 0.001$). However, the frequency of desaturation was significantly higher in the H-apnea group than in the L-apnea group ($p < 0.001$), and higher in the H-irregular low-voltage group than in the L-irregular low-voltage group ($p < 0.001$).

Comparison of ventilatory parameters and proportions of each waveform pattern between the H- and L- groups of each waveform pattern are also shown in Table 2. Edi

peak in the H-phasic group was significantly higher than that in the L-phasic group ($p < 0.001$). Time in backup ventilation in the H-phasic group were significantly lower than those in the L-phasic group ($p < 0.001$). On the other hand, Edi peak in the H-irregular low-voltage group was significantly lower than that in the L-irregular low-voltage group ($p < 0.001$). Peak airway pressure in the H-irregular low-voltage group was significantly lower than that in the L-irregular low-voltage group ($p < 0.001$). Time in backup ventilation was not different between the H- and L-irregular low-voltage groups.

DISCUSSION

Several studies have reported characterization of breathing patterns as shown by an Edi catheter in preterm infants [19, 20]. However, the association between breathing patterns and respiratory conditions was not shown in these reports. This is the first report to evaluate the effect of Edi waveform patterns on SpO_2 and the frequency of desaturation. Our results indicated that Edi waveform patterns were associated with the frequency of desaturation. Therefore, analysis of Edi waveform patterns could be an important indicator for appropriately using NAVA in extremely preterm infants.

We found that patients had a stable SpO_2 when the phasic pattern was frequently observed. However, when an irregular low-voltage, central apnea, or tonic burst pattern was frequently observed, patients showed unstable SpO_2. These results suggest that a high frequency of an irregular low-voltage, central apnea, or tonic burst pattern is a cause of failure to ventilate with NAVA.

In this study, we defined the central apnea pattern as continuous flat Edi, which induces backup mandatory ventilation, to appropriately assess the effect of central apnea. In contrast, we defined a low Edi peak waveform as an irregular low-voltage

pattern. This waveform pattern has not been defined in previous reports. A low Edi peak waveform (Edi [peak-min] < 1.5 μV) prevents backup ventilation, but it supplies low peak inspiratory pressure [21]. Peak airway pressure supplied by NAVA is calculated according to the following formula: NAVA level ($cmH_2O/\mu V$)×(Edi peak [μV]-Edi minimum [μV])+PEEP (cmH_2O). During this study, an efficient observed peak inspiratory pressure was approximately 15 cmH_2O (IQR: 14–16 cmH_2O). Because we set the NAVA level at approximately 1.6 ± 0.4 and PEEP at 7 cmH_2O, peak airway pressure supplied by an irregular low-voltage pattern was calculated as < 10 cmH_2O (1.6×1.5+PEEP). In reality, peak airway pressure with a low Edi peak waveform observed in this study was < 10 cmH_2O. This low peak inspiratory pressure appeared to provide insufficient support. Our study indicated that a high frequency of the irregular low-voltage pattern lead to low peak airway pressure generated with low Edi peak. Our study also showed that time in backup ventilation was not different between H- and L-irregular low-voltage groups. These results indicate that the irregular low-voltage pattern may prevent backup ventilation, but supply insufficient peak airway pressure. Therefore, irregular low-voltage pattern could lead to desaturation.

In addition, a high frequency of the tonic burst pattern was associated with slightly higher peak airway pressure generated with slightly higher Edi peak. In contrast, the tonic burst pattern was more frequently observed in the Desat (+) group than in the Desat (–) group. This contradiction arose because the tonic burst pattern is an irregular waveform and is considered to be an asynchronized pattern. Therefore, the tonic burst pattern was also considered to result in desaturation. On the other hand, as tonic burst pattern was known to be an essential respiratory pattern for premature infants to recruit their lung [22,23], desaturation may lead infants to breath with tonic burst pattern. Further research about the effect of tonic burst pattern for respiratory condition would be needed.

Ventilatory parameters from the ventilator did not include information of the waveform pattern. Therefore, the ventilatory parameters especially of Edi peak and peak airway pressure could include all waveform patterns. Even if these parameters were indicated as the same value, the meaning of the value was different among the different Edi waveform patterns. When the Edi peak was 5 μV in the phasic pattern, the ventilator may provide stable support, but when that in the irregular low-voltage pattern

or tonic burst pattern the ventilator may supply ineffective or asynchronized support and cause desaturation. Therefore, desaturation could not be predicted by only using these ventilatory parameters. Consequently, the Edi waveform pattern is considered to be important for assessing desaturation.

To exclude the effect of changing the ventilator setting for the results, our data were collected when the ventilator setting had not been changed within at least 3 hours to confirm the stability of the respiratory condition with the ventilator setting at that time. In addition, because the ventilator setting did not vary much, we consider that our results did not depend on the ventilator setting, but on the variability of Edi waveform patterns instead.

There are some limitations of our study. The main limitation was the limited number of cases. Additionally, because the gestational age and duration of postconceptional age with ventilation by NAVA of the included infants had a limited range, our results might not be able to be applied for more mature infants. However, because we were able to evaluate many data units, the similarity of the patients' characteristics was a strength of this study. Further studies are required to validate our results.

In future studies, we need to identify the appropriate proportion of Edi waveform patterns that result in stable SpO_2 of infants. The criterion that indicates when the attending physician should change the ventilator mode from NAVA to another mode also needs to be investigated.

CONCLUSION

We assessed the association between Edi waveform patterns and SpO_2. Proportions of Edi waveform patterns affect SpO_2 in extremely preterm infants. Our results indicate that analysis of Edi waveform patterns is an important indicator for assessing whether preterm infants are appropriately ventilated with NAVA.

Acknowledgment

We thank Ellen Knapp, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

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Image legends

Figure 1. Representative waveforms for four Edi waveform patterns.

Pressure curves are shown in each upper row and Edi waveforms are shown in each lower row. A: Phasic pattern, B: central apnea pattern, C: tonic bursts pattern, D: irregular low-voltage pattern.

Figure 2. Example of one window of servo connect including multiple waveform patterns.

A pressure curve is in the upper row and an Edi waveform is in the lower row. Waveforms on the left side were classified as central apnea and waveforms on the right side were classified as an irregular low-voltage pattern. Each pattern was calculated as 0.5 points.

Figure 3. Comparison of the proportions each waveform pattern between the Desaturation (+) and (-) groups.

Data are expressed as median and interquartile range. The Desat (+) group included 261 data units and the Desat (–) group included 999 data units. *, $p<0.05$.

RESPONSES TO THE REVIEWERS' COMMENTS

We thank the reviewers for reviewing our manuscript. We have carefully considered the comments made by the reviewers and have revised our manuscript accordingly. We believe that our revised manuscript has been improved because of the reviewer's comments. We hope that our revisions and responses to the reviewers' comments are satisfactory.

Reviewer: 2

Comments to the Author
The manuscript has been improved and I only have minor suggestions:
- Abstract line 30 : we conducted a retrospective cohort study at a level 3...

Response: We thank the reviewer for the comment. We revised the manuscript.

- PAge 8, study procedure, line 46, please replace "To properly use NAVA", by something like " According to our usual practice,"...

Response: We thank the reviewer for the comment. We revised the manuscript as suggested.

-page 9, line 17 : I do not understand the sentence " Subsequent setting with adjustment by this procedure did not vary in each patient"... please rephrase.

Response: We rephrased the sentence, as suggested. We thank the reviewer for the suggestion.

- Figure 3: please indicate in the Figure the interquartile ranges (if the bars represent the median values) on the bars... (or the SD if the bars represent the mean values). Please also provide the number of periods in each desat group in the legend. Also, indicate in the legend which measures are illustrated (median or mean).

Response: We thank the reviewer for the comment. We revised the figure 3 and the legend as suggested.