Patient-Ventilator Interaction During Noninvasive Ventilation in Subjects With Exacerbation of COPD: Effect of Support Level and Ventilator Mode

Eline Oppersma, Jonne Doorduin, Lisanne H Roesthuis, Johannes G van der Hoeven, Peter H Veltink, and Leo MA Heunks

BACKGROUND: Patient-ventilator synchrony in patients with COPD is at risk during noninvasive ventilation (NIV). NIV in neurally-adjusted ventilatory assist (NAVA) mode improves synchrony compared to pressure support ventilation (PSV). The current study investigated patient-ventilator interaction at 2 levels of NAVA and PSV mode in subjects with COPD exacerbation. METHODS: NIV was randomly applied at 2 levels (5 and 15 cm H_2O) of PSV and NAVA. Patient-ventilator interaction was evaluated by comparing airway pressure and electrical activity of the diaphragm waveforms with automated computer algorithms. RESULTS: 8 subjects were included. Trigger delay was longer in PSV high (268 ± 112 ms) than in PSV low (161 ± 118 ms, $P = .043$), and trigger delay during NAVA was shorter than PSV for both low support (49 ± 24 ms for NAVA, $P = .035$) and high support (79 ± 276 ms for NAVA, $P = .003$). No difference in cycling error for low and high levels of PSV (PSV low −100 ± 114 ms and PSV high 56 ± 315 ms) or NAVA (NAVA low −5 ± 18 ms, NAVA high 12 ± 36 ms) and no difference between PSV and NAVA was found. CONCLUSIONS: Increasing PSV levels during NIV caused a progressive mismatch between neural effort and pneumatic timing. Patient-ventilator interaction during NAVA was more synchronous than during PSV, independent of inspiratory support level. (ClinicalTrials.gov registration NCT01791335.) *Key words: noninvasive ventilation; patient-ventilator asynchrony; NAVA; COPD.* [Respir Care 2020;65(9):1315–1322. © 2020 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) improves outcomes for patients with a COPD exacerbation.[1,2] More specifically, NIV decreases work of breathing and increases alveolar ventilation by increasing tidal volume and decreasing breathing frequency.[3] In patients with COPD, NIV reduces endotracheal intubation rates and related complications compared to conventional medical therapy, thereby shortening hospital length of stay and decreasing mortality.[1,2] However, synchrony between the patient and the ventilator, defined as a match between the patient's neural inspiratory and expiratory times and the ventilator's mechanical inspiratory and expiratory times,[4] is at risk during NIV, especially in patients with COPD, due to the presence of pulmonary hyperinflation and leaks.[5]

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Dr Heunks has disclosed relationships with Maquet Critical Care, Orion Pharma, and Liberate Medical. The other authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.07159

Patient-ventilator asynchronies have been associated with failure of NIV and may eventually result in invasive mechanical ventilation.[6,7] In patients with COPD, delayed cycling, defined as prolonged pressurization by the machine into the patient's expiratory phase, can result in inadequate emptying of the lungs and dynamic hyperinflation with increasing levels of inspiratory support, increasing the trigger delay and the respiratory work load.[8,9] In neurally-adjusted ventilatory assist (NAVA) mode, the ventilator is controlled by the electrical activity of the diaphragm (EA_{di}).[10] Ventilator triggering, cycling, and the level of assist is based on EA_{di}. During invasive mechanical ventilation, high levels of inspiratory support with NAVA have significantly shorter trigger delays and fewer cycling errors compared to high levels of pressure support ventilation (PSV).[11,12] Ineffective triggering increases with the level of PSV because of the risk of dynamic hyperinflation.[4]

We previously reported that noninvasive NAVA im-proved patient-ventilator interaction relative to equal inspiratory pressures during noninvasive PSV.[13] Trigger delays were substantially longer during PSV than during NAVA. Cycling errors during NAVA were negligible, whereas PSV showed a large variability in early and late cycling.[13] Although increasing inspiratory support progressively unloads the respiratory muscles and improves gas exchange in patients with respiratory failure, the effects of increasing the level of inspiratory support on patient-ventilator interaction during noninvasive PSV and NAVA in patients with a COPD exacerbation are unknown. We hypothesized that patient-ventilator asynchrony would increase during PSV with high levels of inspiratory pressure, whereas patient-ventilator interaction during NAVA would improve independently of the level of inspiratory pressure.

Methods

The current study presents data derived from a previous explorative study by Oppersma et al.[14] Eight subjects with hypercapnic COPD exacerbation with a clinical indication for NIV in the ICU and the presence of a NAVA catheter (12 French; Maquet Critical Care, Solna, Sweden) were included. Exclusion criteria included upper airway, mouth, or face pathology; recent nasal bleeding; or preexisting muscle disease. This study was performed at the department of Intensive Care at Radboud University Medical Center, Nijmegen, The Netherlands. The protocol was approved by the Ethical Committee of the Radboud University Medical Center (NL40582.091.12) and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

QUICK LOOK

Current knowledge

During invasive mechanical ventilation, high levels of inspiratory support with neurally-adjusted ventilatory assist (NAVA) have significantly shorter trigger delays and fewer cycling errors compared to high levels of pressure support ventilation (PSV). The effects of increasing the level of inspiratory support on patient-ventilator interaction during noninvasive PSV and NAVA in patients with an exacerbation of COPD are unknown.

What this paper contributes to our knowledge

Automated analysis of patient-ventilator interaction indicated that there was a progressive mismatch between neural effort and pneumatic timing with increasing levels of PSV during NIV. During noninvasive NAVA, the patient-ventilator interaction improved as compared to PSV, independent of the level of inspiratory support.

Study Protocol

The study protocol included 4 ventilator settings: 2 levels of inspiratory support (5 and 15 cm H_2O) and 2 different ventilator modes (PSV and NAVA), which were randomly assigned with an online randomizer. A flexible video laryngoscope was inserted through the nose for acquisition of video images of the glottis, as required by the protocol of the study for which these data originally were acquired. Each ventilator setting started with a run-in period of 30 s in which the subject could become familiar with the ventilator setting, followed by data acquisition during at least 10 breaths with good-quality video recording of the glottis. The NAVA level was set to match peak pressure as delivered in PSV using manufacturer-supplied software. The rise-time in PSV was standardized at 0.05 s. Trigger sensitivity was set at 5% of peak flow during PSV and 0.5 μV for NAVA. F_{IO_2} was titrated to obtain peripheral oxygen saturation $> 95\%$ in both modes. Cycling was set at 50% of maximum flow during PSV and 70% of the maximum EA_{di} during NAVA. PEEP was kept constant at 5 cm H_2O throughout the study.

Data Acquisition and Analysis

NIV was delivered with a Servo-i ventilator (Maquet Critical Care). A total face mask (Respironics PerforMax, Philips, Best, The Netherlands) was used in all subjects. Airway flow, airway pressure, and EA_{di} were acquired ($f_s = 100$ Hz) using Servo Tracker, a software tool for the collection and presentation of performance data from the Servo-i ventilator.

Table 1. Subject Characteristics

Subject	Age, y	Body Mass Index, kg/m^2	FEV_1, % Predicted	FVC, % Predicted	FEV_1/FVC	pH at ICU Admission	pH at Study Inclusion	NIV Duration Before Study, h
1	66	34	24	63	28	7.24	7.35	8
2	59	23	24	42	45	7.30	7.41	46
3	69	19	51	74	55	7.16	7.36	12
4	52	20	27	77	29	7.32	7.35	16
5	73	35	30	45	49	7.29	7.31	4
6	78	31	39	109	29	7.26	7.32	5
7	56	20	18	71	22	7.24	7.37	23
8	66	22	17	76	16	7.26	7.24	46

Pulmonary function tests (FEV_1, FVC, and FEV_1/FVC) were at most 1 y before or after the study took place.
NIV = noninvasive ventilation

Table 2. Breathing Pattern and Respiratory Drive

	PSV Low	PSV High	NAVA Low	NAVA High
Peak EA_{di}, μV	37.2 (11.8–60.4)	21.4* (8.9–46.1)	34.8 (16.2–58.2)	19.8* (8.7–42.8)
Peak airway pressure, cm H_2O	9.9 (9.3–10.1)	17.2* (16.4–19.1)	11.8 (9.5–14.1)	16.3* (15.9–18.7)
Neural breathing frequency, breaths/min	24.0 (13.5–29.5)	21.0 (15.0–27.0)	25.0 (18.5–29.5)	27.0† (2.5–31.5)

Data are presented as median (interquartile range).
* Significant difference between low and high inspiratory support.
† Significant difference between PSV and NAVA for high support.
PSV = pressure support ventilation
NAVA = neurally-adjusted ventilatory assist
EA_{di} = electrical activity of the diaphragm

Data were stored and buffered on an external hard drive and analyzed offline with Matlab R2017a (The Mathworks, Natick, Massachusetts). Peak EA_{di} and peak airway pressure were calculated from the last 30 s of each ventilator setting. Neural breathing frequency was calculated as the number of EA_{di} peaks per minute.

Patient-ventilator interaction during the last 30 s of each recording was evaluated by comparing airway pressure and EA_{di} waveforms with an automated computer algorithm.[13,15] Asynchronies, trigger delays, and cycling errors were calculated as percentages of neural inspiratory time periods and neural expiratory time periods, respectively. Synchrony was defined as $\leq$ 20% difference between pneumatic and neural timing because the incidence of wasted efforts increase after timing errors reach 20%.[13] Asynchronous breaths such as wasted efforts (ie, inspiratory efforts not rewarded by ventilatory assist), auto-triggering (ie, ventilatory assist without inspiratory effort), and multiple EA_{di} peaks during a single ventilator-assisted breath in which EA_{di} and airway pressure were completely dissociated were assigned 100% error.

Statistics

Statistical analyses were performed with OriginPro 9.1.0 (OriginLab, Northampton, Massachusetts). Descriptive subject characteristics were reported as mean $\pm$ SD, and respiratory study variables were reported as median and interquartile ranges. Repeated measures 2-way analysis of variance with post hoc Tukey test was used to assess the effect of ventilation mode (PSV and NAVA) and ventilator support level (low and high) on trigger delay and cycling error, given as mean $\pm$ SD; $P \leq .05$ was considered significant.

Results

Eight subjects (4 female/4 male) were enrolled in this study. Subject characteristics are shown in Table 1. All subjects were treated with bronchodilators, steroids and antibiotics. None of the subjects required intubation after NIV. Results for breathing pattern and respiratory drive are presented in Table 2. As dictated by the protocol, peak EA_{di} for both PSV and NAVA was comparable at low and high levels of support and decreased with increasing inspiratory support for both PSV and NAVA. Total time for data acquisition took a maximum of 30 min per subject; the duration in each mode varied between 30 s and 155 s. Data analysis was performed on the last 30 s of each recording, in which the number of events that was evaluated (supported breaths, but also wasted efforts and auto-triggers), varied between 9 and 35.

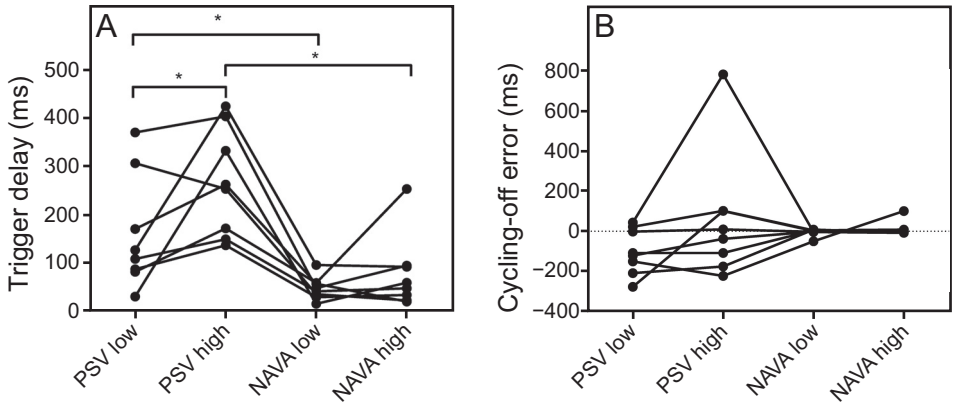

Fig. 1. A: Trigger delay and B: cycling error for the 4 ventilator settings. Positive y-axis values indicate late cycling, and negative y-axis values indicate early cycling. * $P \leq .05$. PSV = pressure support ventilation; NAVA = neurally-adjusted ventilatory assist.

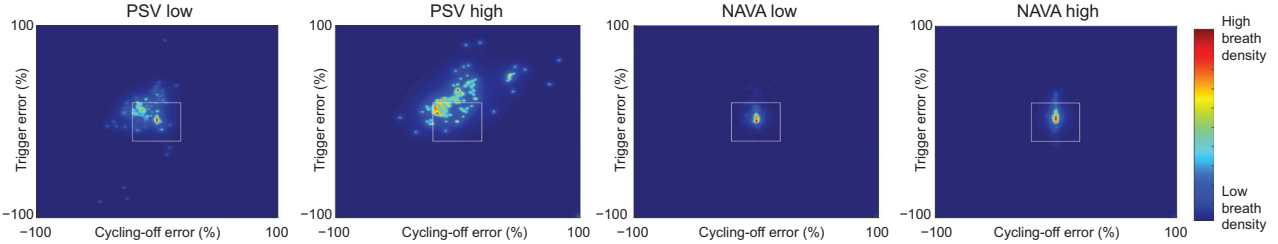

Fig. 2. Breath density graph for relative trigger and cycling errors, for all breaths in all subjects, during each ventilator setting. The white boxes indicate the limit (20%) between synchrony and dyssynchrony. PSV = pressure support ventilation; NAVA = neurally-adjusted ventilatory assist.

PSV

Figure 1 shows mean values for trigger delay (ie, delay of pneumatic timing compared to neural inspiration) and cycling error (ie, error of pneumatic timing compared to neural expiration) with each ventilator setting for all individual subjects. The mean trigger delay was longer during PSV high (268 ± 112 ms) than during PSV low (161 ± 118 ms, $P = .043$). There was no difference in mean cycling error between low and high PSV (PSV low −100 ± 114 ms and PSV high 56 ± 315 ms). Figure 2 shows a plot for all 4 ventilator settings, all breaths of all subjects, of the relative timing errors of triggering versus the relative timing error of cycling. Boxes were inserted marking synchrony as acceptable, whereas larger errors (> 20%) represent dyssynchrony. With increasing levels of PSV, incidence of dyssynchronous breaths increased. Figure 3 shows the distribution of breaths defined as synchronous, dyssynchronous, and asynchronous. Increasing the inspiratory support increases the occurrence of dyssynchronies from 33% to 54% of all breaths. Although wasted efforts were the most prevalent asynchronies, occurring in 18% of all breaths during low level PSV, during high level PSV the incidence of wasted efforts did not increase (16%). Multiple EA_{di} during assist and auto-triggering occurred in minimal percentages (≤ 3%) during PSV.

NAVA

During NAVA, the mean trigger delay, as shown in Figure 1, was the same for low and high levels of support, but shorter than both PSV with a low level of support (49 ± 24 ms for NAVA, $P = .035$) and PSV with a high level of support (79 ± 76 ms for NAVA, $P = .003$). No difference was found in mean cycling error for NAVA with low or high inspiratory support. Also, cycling error during NAVA was not different from PSV (NAVA low − 5 ± 18 ms, NAVA high 12 ± 36 ms). Figure 2 shows that with increasing levels of support in NAVA mode the percentage of dyssynchronies did not increase, and that timing of the breaths was more condensed inside the 20% box during NAVA than during both PSV with low support and PSV with high support. The distribution of breaths in Figure 3 showed relatively similar synchrony (81% of all breaths for low NAVA and 78% of all breaths for high NAVA) and dyssynchrony (13% of all breaths for low NAVA and 12% of all breaths for high NAVA). Wasted effort only occurred in 4% and 1% of all breaths during respectively low and high level

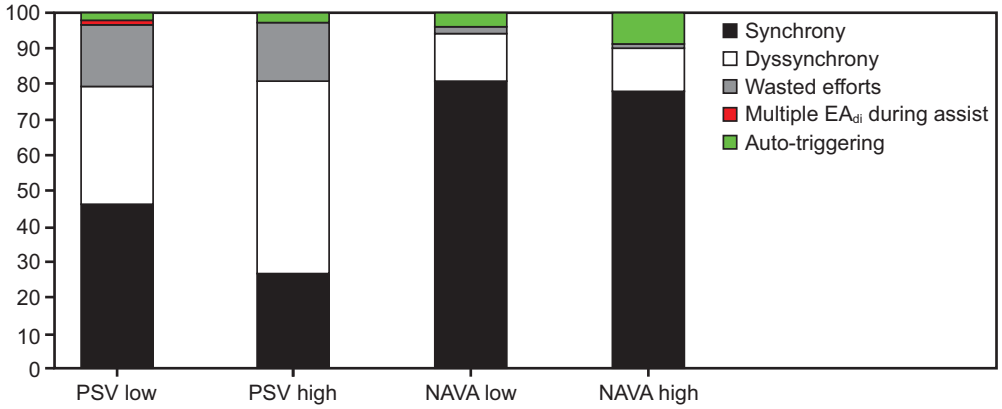

Fig. 3. Percentage of synchronous, dyssynchronous (trigger delay and cycling errors), and asynchronous (wasted efforts, auto-triggering and multiple EA_{di} during assist) breaths for the 4 ventilator settings. EA_{di} = electrical activity of the diaphragm; PSV = pressure support ventilation; NAVA = neurally adjusted ventilatory assist.

assist in NAVA mode, respectively, which is less than during both low and high PSV. However, auto-triggering increased from 4% of all breaths during low NAVA to 9% during high NAVA, which is more than during both low PSV (2%) and high PSV (3%).

Discussion

The current study provides new insights into the effects of inspiratory support levels and ventilator mode on patient-ventilator interaction during NIV in subjects with a COPD exacerbation. First, patient-ventilator synchrony worsened with increasing inspiratory pressure during PSV due to progressive incidence of trigger delays. Second, patient-ventilator interaction in NAVA mode was independent of the level of inspiratory support; no differences in trigger delay and cycling error were found with increasing level of support. Third, patient-ventilator interaction in NAVA mode was superior compared to both low and high PSV support during NIV.

Patient-Ventilator Interaction

For effective unloading of the inspiratory muscles during NIV, the ventilator should cycle in synchrony with the neural respiratory drive of the patient.[7] Previous studies have reported the presence of trigger delays and cycling errors in PSV mode and NAVA mode during NIV.[13,16,17] In those studies, inspiratory pressures were different for each subject. However, it is known that increasing the level of inspiratory assistance during invasive ventilation may worsen ineffective triggering.[4,18] To our knowledge, this is the first study to compare noninvasive PSV and NAVA both with 2 levels of inspiratory support for each subject.

PSV

We applied 2 levels (5 and 15 cm H_2O) of inspiratory pressure to all subjects. By increasing the level of assistance, the inspiratory muscles were progressively unloaded as indicated by reduced peak EA_{di}. Because of the increased inspiratory pressure support, tidal volumes may increase and the breathing frequency tends to decrease. However, increasing inspiratory assistance may also result in more leaks. Because leaks during NIV are a major contributing factor to the prevalence of patient-ventilator asynchronies by preventing the flow from reaching the preset expiratory trigger,[5] this could be an important cause of increased patient-ventilator asynchrony with increasing inspiratory support. Leaks were not quantified in this study, so this hypothesis cannot be verified.

Although dyssynchronies increased from 33% to 54%, incidence of wasted efforts did not increase with increasing inspiratory pressure. Increasing inspiratory pressure during invasive ventilation induces more wasted efforts, mainly as a result of a decrease in respiratory drive and an increase in tidal volume resulting in hyperinflation, which makes it harder to reach the preset trigger.[18] The respiratory drive in this study, represented by a median peak EA_{di} of 21.4 μV, was not associated with more wasted efforts, whereas an increase of asynchronies and wasted efforts was shown previously, even with a comparable median peak EA_{di} of 25.6 μV.[13] The increase in asynchronies from low to high PSV support in our study was thus mainly caused by increased trigger delay, which may be the result of more leakages, reduced emptying of the lungs, and increased hyperinflation.

One subject exhibited a remarkably high cycling delay during high support PSV (Fig. 1). Because COPD is characterized by obstructive lung mechanics and elevated compliance, expiration requires relatively more time than

inspiration. The rise of the inspiratory flow should be fast to avoid hyperinflation and increasing intrinsic PEEP.[19] By increasing the inspiratory pressure and thus inspiratory flow during PSV, with equal compliance, this subject did not receive the extra time needed to inhale, which resulted in increased cycling delays during high-support PSV.

NAVA

NAVA was applied with 2 levels of support, matching peak pressure as delivered in PSV. Similar to PSV, increasing the level of assistance resulted in more unloading of the inspiratory muscles and the peak EA_{di} decreased. Both trigger delays and cycling errors during NAVA were in a comparable range with previous findings,[13,16,17] without distinction between low and high inspiratory support.

One subject in this study exhibited a high trigger delay during NAVA with a high level of support (Fig. 1). This subject had an irregular EA_{di} pattern, with many small peaks between breaths, probably resulting from inadequate EA_{di} signal analysis by the ventilator software.[20] This EA_{di} pattern caused the ventilator to switch to backup PSV mode, thus decreasing the synchrony. For this subject, NAVA was probably not the appropriate mode of support.

Compared to PSV, the mean trigger delay was shorter during NAVA for both low and high inspiratory support, in a range comparable with previous studies on noninvasive NAVA.[13,16,21] Cycling error was not significantly different for both modes and levels of noninvasive ventilation. Although the incidence of dyssynchronies is lower with both levels of NAVA than with both levels of PSV, auto-triggering during NAVA occurs slightly more frequently than during PSV, increasing from 4% to 9% from low to high NAVA support. Auto-triggering is a known phenomenon, especially with NAVA.[16] The ventilator will cycle on with even a small increase in EA_{di}, including increases due to signal artifacts or any subrespiratory diaphragmatic activity. However, because the peak EA_{di} is relatively low, the ventilator will promptly cycle off and its detrimental effect on the patient's respiratory pattern will be limited.[16] It should be noted that the median neural breathing frequency with high NAVA support was higher than that with high PSV support (Table 2), which supports the conclusion that regulation of breathing frequency is more complex than just changing the level of pressure support.[22] Although the goal was to provide similar levels of assist during high PSV support and high NAVA support, during NAVA a lower level of support was provided and therefore the neural breathing frequency was higher. The lower level of support is explained by the different methods of pressure delivery in PSV and NAVA: during PSV, the pressure wave is shaped as a rectangle, whereas the more physiological assist during NAVA provides a triangular shape of inspiratory pressure. Although peak airway pressure was similar in both modes, the mean airway pressure was lower during high NAVA support than during high PSV support to maintain adequate minute ventilation.

This study reports a higher incidence of dyssynchronies than a previous study by our group.[13] The current study noted 33% dyssynchronies for low PSV support and 54% for high PSV support, whereas the previous study showed 30.5% dyssynchronies during PSV. During low and high levels of NAVA support, 13% and 12% of breaths were dyssynchronous, respectively, compared to 3.3% in the previous study. The difference between the current study and the previous study by our group[13] may be explained by subject selection. The previous study included 4 subjects (out of a total of 12 subjects) with other indications for NIV than COPD exacerbation. More important, mean arterial blood pH was 7.38, whereas mean arterial blood pH at time of inclusion of the subjects in the current study was 7.34. Although the arterial blood pH was already increased by supported breathing during NIV from the time of admission to the ICU to the moment of study inclusion in the current study (Table 1), these subjects were still in an acute phase of their exacerbation and in need of NIV. We noted reduced patient-ventilator synchrony in this study compared to previous research by our group in subjects with more stable COPD, which could have been caused by intrinsic PEEP and the resulting ineffective trigger that frequently occurs during a COPD exacerbation.[23] Other plausible explanations could be the presence of the video-laryngoscope, a different interface (total face mask vs oronasal mask), and the difference in inspiratory pressure and PEEP. In the current study, the inspiratory pressures were 5 and 15 cm H_2O for all subjects, whereas the mean inspiratory pressure in the previous study was 6.9 cm H_2O (SD 1.8 cm H_2O). Whereas PEEP was not changed in the current study, mean PEEP in the previous study was 6.1 cm H_2O (SD 1.2 cm H_2O). Because increasing inspiratory pressure could increase the risk of leaks and leaks might induce patient-ventilator asynchrony, these factors could explain the difference in asynchrony between these 2 studies.

Methodological Considerations

It should be noted that data discussed here were acquired for other purposes, as mentioned in the Methods section, for which a fiberoptic flexible bronchoscope (Pentax EB-1170 (11 Fr)) was inserted via the nose and positioned ± 2 cm cranial to the vocal cords. The presence of the scope might have influenced the interaction between the subject and the ventilator by reflexive mechanisms resulting from contact of the scope with, for example, epiglottic tissue. This study provides no data recorded without the scope in situ to support this.

Although leakage is associated with NIV, the precise estimation of leakage requires additional techniques that

were not available for this study. However, independent of severity of leaks, NIV with NAVA mode is expected to improve patient-ventilator interaction.

Patient-ventilator interaction was quantified with an automated method, allowing the detection of dyssynchronies (eg, trigger delays and cycling errors) and asynchronies (eg, wasted efforts, auto-triggering, and multiple EA_{di} during assist) in a standardized manner.[13,15] This method might provide a future clinical tool to monitor patient-ventilator asynchrony, and more importantly, to analyze whether patient-ventilator asynchrony occurs more often in severely ill patients, or whether patient-ventilator asynchrony itself is responsible for the poor prognosis.[24] It should be noted that the last 30 s of each dataset were used for the automated analysis of patient-ventilator interaction. This is a shorter time period than in previous studies,[4,13,15] and therefore this study should be considered as a physiological evaluation on the effects of inspiratory support level and mode on patient-ventilator interaction. Whether these observed effects remain after longer duration of mechanical ventilation remains to be investigated. Importantly, periods with multiple asynchronies may alternate with periods with almost no asynchronies.[25] Although this might induce bias in our observations, this relatively short period of data acquisition is not considered a major limitation because analysis of the incidence of patient-ventilator interaction was not the goal of this study.

The proportion of synchronous and dyssynchronous breaths is affected by the applied criterion. A previous study by our group defined 20% of relative inspiratory and expiratory neural time to be synchronous,[13] whereas another study defined 33% to be synchronous.[15] Because the wasted efforts increase after timing errors reach 20%, the current study adhered to this criterion, but it should be noted that this definition influences the percentages in Figure 3.

Conclusions

Automated analysis of patient-ventilator interaction revealed a progressive mismatch between neural effort and pneumatic timing with increasing levels of PSV during NIV. During noninvasive NAVA, the patient-ventilator interaction improved as compared to PSV, independent of the level of inspiratory support.

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