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Neurally adjusted ventilatory assist (NAVA) improves patient–ventilator interaction during non-invasive ventilation delivered by face mask

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Abstract Purpose: To determine if, compared to pressure support (PS), neurally adjusted ventilatory assist (NAVA) reduces patient–ventilator asynchrony in intensive care patients undergoing noninvasive ventilation with an oronasal face mask.

Methods: In this prospective interventional study we compared patient–ventilator synchrony between PS (with ventilator settings determined by the clinician) and NAVA (with the level set so as to obtain the same maximal airway pressure as in PS). Two 20-min recordings of airway pressure, flow and electrical activity of the diaphragm during PS and NAVA were acquired in a randomized order. Trigger delay (T_d), the patient's neural inspiratory time (T_{in}), ventilator pressurization duration (T_{iv}), inspiratory time in excess (T_{iex}), number of asynchrony events per minute and asynchrony index (AI) were determined. **Results:** The study included 13 patients, six with COPD, and two with mixed

pulmonary disease. T_d was reduced with NAVA: median 35 ms (IQR 31–53 ms) versus 181 ms (122–208 ms); $p = 0.0002$. NAVA reduced both premature and delayed cyclings in the majority of patients, but not the median T_{iex} value. The total number of asynchrony events tended to be reduced with NAVA: 1.0 events/min (0.5–3.1 events/min) versus 4.4 events/min (0.9–12.1 events/min); $p = 0.08$. AI was lower with NAVA: 4.9 % (2.5–10.5 %) versus 15.8 % (5.5–49.6 %); $p = 0.03$. During NAVA, there were no ineffective efforts, or late or premature cyclings. PaO_2 and $PaCO_2$ were not different between ventilatory modes. **Conclusion:** Compared to PS, NAVA improved patient–ventilator synchrony during noninvasive ventilation by reducing T_d and AI. Moreover, with NAVA, ineffective efforts, and late and premature cyclings were absent.

Keywords Patient-ventilator interaction · Patient-ventilator synchrony · Noninvasive Ventilation · Pressure support · Neurally adjusted ventilatory assist

Introduction

Noninvasive pressure support ventilation (PS-NIV) is widely used to treat acute respiratory failure of various

etiologies [1, 2] and to avoid reintubation in patients at risk of postextubation respiratory failure [3]. Because patient and ventilator respiratory profiles differ, patient–ventilator asynchronies often occur during pressure

support ventilation (PS) [4, 5]. They are particularly frequent during PS-NIV because unavoidable leaks at the patient–ventilator interface interfere with pneumatic triggering (i.e. pressure or flow triggering) and cycling-off [6]. As asynchronies are related to poor tolerance and increased risk of NIV failure [7], reducing asynchronies during NIV is a major issue. Under bench testing conditions, dedicated NIV modes decrease the number of asynchronies [8]. However, the ability of NIV modes to reduce asynchronies varies between ventilators [8], and dedicated NIV modes fail to decrease the total number of patient–ventilator asynchronies in intensive care patients [9].

Even if ventilators specially dedicated to NIV are more efficient than standard intensive care ventilators in reducing asynchronies [10], no currently available technology can prevent their occurrence during PS-NIV. However, when delivering PS-NIV through a helmet, neural triggering has been shown to improve patient–ventilator synchrony compared to pneumatic triggering [11]. As neurally adjusted ventilatory assist (NAVA) [12] uses a neural signal (the diaphragm electrical activity, or EAdi, independent from airway pressure and flow signals), to trigger and cycle-off the ventilator as well as to adapt the amount of pressure delivered, and as NAVA improves patient–ventilator interaction during invasive ventilation [13–16], we hypothesized that NAVA could improve patient–ventilator synchrony during NIV. The purpose of this study was to test this hypothesis in adult intensive care patients requiring NIV because of acute respiratory failure or because of being at risk of respiratory failure after extubation [3].

Materials and methods

This was a prospective interventional study. Patients in the intensive care units of two university hospitals (Liege and Brussels, Belgium) were included. The study protocol was approved by both ethics committee.

Patients

Intensive care patients receiving NIV via an oronasal face mask for acute respiratory failure [17, 18] or for being at risk of postextubation respiratory failure according to previously published criteria [3] were eligible for inclusion in the study. Exclusion criteria are outlined in the Electronic Supplementary Material.

Ventilator and masks

Patients were ventilated with a Servo-i ventilator (Maquet Critical Care, Solna, Sweden) equipped with the commercially available version (v. 5.00.00) of the NAVA

software. PS and NAVA were both delivered using the invasive version of the ventilator software. Oronasal face masks (Vygon, Ecouen, France) were used to deliver NIV.

Recordings

Respiratory parameters were recorded from the ventilator using the Servo-tracker recording system. Recording methods and recorded parameters are described in the Electronic Supplementary Material.

Measurements

Trigger delay (T_d) was defined as the time difference between the initial increase in the EAdi (visually determined) and the beginning of ventilator inspiratory flow. Neural inspiratory time (T_{in}) was defined, according to previously published NAVA studies [13–15, 19], as the time difference between the initial increase and the maximal value of EAdi ($EAdi_{max}$). Details on this point are given in the Electronic Supplementary Material. Ventilator pressurization time (T_{iv}) was defined as the time difference between the beginning and the end of inspiratory flow, and inspiratory time in excess (T_{iex}) was calculated as the time difference between the end of T_{iv} and T_{in} .

From the recorded curves, the numbers of the five types of patient–ventilator asynchronies as defined by Thille et al. [5] were determined. In contrast to the study of Thille et al., EAdi was used in addition to airway pressure and flow curves to define asynchrony events [13]. This approach allows a more accurate definition of asynchrony events in relation to T_{in} and is more sensitive in detecting asynchrony events during PS. Moreover, during NAVA, we considered an additional asynchrony type as a specific type of autotriggering event. This new asynchrony, called pseudotriggering, was defined as the presence of a significant (higher than 50 % of the positive end expiratory pressure, PEEP, value) ventilator-delivered pressurization occurring in the absence of a typical concomitant EAdi signal indicating true respiratory diaphragmatic activity. Patient–ventilator asynchronies are described in detail and illustrated in the Electronic Supplementary Material. Asynchronies are expressed as the number of events per minute and as the asynchrony index (AI) as defined by Thille et al. [5], that is the number of events per minute divided by the sum of triggered and nontriggered breaths. An AI of more than 10 % was considered as severe asynchrony [5].

Leaks were defined as the difference between inspiratory tidal volume (VT_i) and expiratory tidal volume (VT_e) obtained by integration of the flow curve. VT_i , VT_e and leaks were measured for one respiratory cycle every 50 s, and are reported in fractions of VT_i and in liters per minute.

Table 1 Clinical characteristics and ventilator settings for the 13 included patients

Patient	Age (years)	Gender	Body mass index (kg/m ²)	SAPS II score	Recording	Known pulmonary disease	Reason for ICU admission	Ventilator settings							
								Inspired fraction of oxygen	Positive end expiratory pressure (cmH ₂ O)	Inspiratory trigger	Back-up trigger	PS slope (ms)	PS level (cmH ₂ O)	PS end expiratory trigger setting (%)	NAVA level (μV/cmH ₂ O)
1	62	F	20.3	33	Post-extubation	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease exacerbation	0.25	5	Flow	Flow	150	9	40	0.2
2	69	F	36.7	26	Post-extubation	Mixed disease	Pneumonia	0.30	7	Flow	Flow	150	10	30	0.6
3	70	F	22.5	31	Post-extubation	Chronic obstructive pulmonary disease	Acute bronchospasm	0.30	7	Flow	Flow	150	8	55	0.2
4	56	F	16.7	33	Post-extubation	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease exacerbation	0.30	5	Flow	Flow	150	12	45	0.2
5	64	M	22.5	54	Post-extubation	None	Acute renal insufficiency	0.50	5	Pressure	Flow	150	12	30	0.8
6	68	F	23.4	33	Acute respiratory failure	None	Asthma	0.25	9	Flow	Flow	150	9	30	0.4
7	75	M	26.1	34	Post-extubation	None	Sepsis	0.40	6	Flow	Flow	150	10	30	0.6
8	87	M	23.7	28	Post-extubation	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease exacerbation	0.23	5	Flow	Flow	150	12	30	0.8
9	72	M	40.0	29	Acute respiratory failure	Mixed disease	Chronic obstructive pulmonary disease exacerbation	0.30	7	Flow	Flow	200	12	50	0.4
10	87	M	27.7	30	Post-extubation	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease exacerbation	0.21	6	Flow	Flow	50	11	45	0.4
11	64	F	29.1	29	Acute respiratory failure	None	Cardiogenic pulmonary edema	0.40	5	Flow	Flow	200	5	50	1.0
12	79	F	28.0	30	Acute respiratory failure	Chronic obstructive pulmonary disease	Pneumonia	0.70	5	Flow	Flow	200	10	50	1.0
13	78	M	27.7	34	Acute respiratory failure	None	Drug intoxication	0.40	5	Flow	Flow	350	10	25	0.5
Median	70		26.1	31				0.30	5			150	10	40	0.5
25th centile	64		22.5	29				0.25	5			150	9	30	0.3
75th centile	78		28.0	33				0.40	7			200	12	50	0.8

For both PS and NAVA, the measured parameters were determined over a 10-min period randomly selected from the whole recorded period.

Experimental protocol

After written informed consent had been obtained, an 8F adult NAVA nasogastric tube (16 mm interelectrode distance and 125 cm long) was positioned and checked according to the manufacturer's recommendations [20]. Approximately 30 min after placement of the nasogastric tube, two sequential 20-min periods of NIV were recorded in a randomized order, one during PS as set by the clinician in charge of the patient and one during NAVA. Because NIV modes had failed to reduce the total number of asynchrony events in a previous study [9], the dedicated NIV mode was not used by the clinicians during PS-NIV according to their usual clinical practice. Similarly, during NAVA, the invasive NAVA software (NAVA ventilation without leak compensation) was used. During PS, the PS level (PSlevel), inspiratory trigger and expiratory cycling-off criterion (expiratory trigger setting, ETS) were kept constant during the entire recording. The manufacturer's recommendations were used to standardize the NAVA level setting. The NAVA level was set so as to obtain the same peak airway pressure as the total inspiratory pressure selected by the clinician during PS. The NAVA level was kept constant during the whole recording. The NAVA trigger was set at 0.5 μV for all patients. PEEP and inspired fraction of oxygen (FIO_2) were the same during PS and NAVA. The built-in back-up security system for NAVA was set by default (PSlevel 20 cmH_2O , inspiratory flow trigger 1.2 l/min and ETS 30 %).

Statistics

PS and NAVA were compared using a paired *t*-test or a paired Wilcoxon test on ranks when required. Normality was assessed using the Shapiro-Wilk test. Statistics were computed using JMP 8.0.1 statistical package (SAS, Cary, NC). For all statistical tests, a *p* value of less than 0.05 was considered significant. Results are reported as medians (interquartile ranges, IQR) or mean \pm SD depending on the normality of their distribution.

Results

The study included 13 patients, 6 (46.2 %) with known chronic obstructive pulmonary disease and 2 (15.4 %) with mixed obstructive and restrictive pulmonary disease. Five patients (38.5 %) required NIV because of acute

respiratory failure and eight patients (61.5 %) required NIV because of being at risk of developing expiratory failure after extubation. The patients' clinical characteristics and ventilator settings are shown in Table 1. The patients' inspiratory demand and related EAdi amplitude were relatively high with a mean value of $33 \pm 17 \mu\text{V}$ during PS-NIV and $33 \pm 15 \mu\text{V}$ during NAVA-NIV. Probably because of this high EAdi amplitude, there were few artifacts in the recordings. During NAVA, EAdi was used to trigger $85 \pm 10 \%$ and to cycle-off $93 \pm 4 \%$ of breaths.

Leaks

Leaks were not different between PS and NAVA: 14 % VT_i (IQR 10–21 % VT_i) versus 15 % VT_i (IQR 10–24 % VT_i), corresponding to 2.9 ± 3 l/min during PS and 2.7 ± 1.6 l/min during NAVA (*p* = 0.89).

T_d and T_{iex}

T_d and T_{iex} for all patients are shown in Fig. 1. As shown in Table 2, median T_d was significantly reduced during NAVA. T_d was 5 % (IQR 4–6 %) of T_{in} during NAVA and 26 % (22–27 %) during PS. Median T_{iex} was not different between the two modes. During PS, negative T_{iex} values related to premature cycling were between –440 and –10 ms. Positive T_{iex} values related to prolonged ventilator pressurization were between +10 and +2,170 ms.

Asynchronies

Individual results for asynchrony events and AI are given in Fig. 1. The total number of asynchrony events tended to be reduced during NAVA compared to PS: median 4.4 events/min (IQR 0.9–12.1) during PS versus 1.0 events/min (IQR 0.5–3.1) during NAVA (*p* = 0.08). AI was significantly lower during NAVA with a median value of 4.9 % (IQR 2.5–10.5 %) versus 15.8 % (5.5–49.6 %) during PS (*p* = 0.03). AI was higher than 10 % in 9 of 13 patients (69.2 %) during PS and only in 3 of 13 patients (23.1 %) during NAVA.

During NAVA, we observed no ineffective efforts, delayed cyclings or premature cyclings.

Other respiratory parameters

T_{in} was not different between PS and NAVA: median 698 ms (IQR 589–874 ms) during PS and 718 ms (IQR 572–882 ms) during NAVA (*p* = 0.19). Minute ventilation, VT_i , ventilator respiratory rate, mean airway pressure, EAdi_{max} and blood gas values were the same for both modes (Table 3).

Discussion

Our study showed that NAVA improved patient–ventilator synchrony during NIV by reducing T_d and severe asynchrony compared with PS. Additionally, there were no ineffective efforts, no delayed cycling and no premature cycling during NAVA. These results are consistent with improved synchrony demonstrated in animals [21] and in low-birth-weight infants (using a single nasal prong interface) [22] with NAVA-NIV in comparison to PS-NIV as well as with improved synchrony recently demonstrated with helmet NAVA-NIV in comparison to helmet PS-NIV [23].

Before discussing the results, several limitations of the study must be addressed. First, during PS-NIV, the dedicated NIV mode was not activated. This could potentially have increased the beneficial effect of NAVA on patient–ventilator synchrony as compared to PS-NIV. However, as shown in a previous study, NIV modes do not succeed in reducing the total number of patient–ventilator asynchronies [6]. Second, as the presence of a nasogastric tube can potentially worsen leaks, this could theoretically have adversely influenced patient–ventilator synchrony during PS. However, in our patients, leak volume during PS

(2.9 ± 3 l/min) was lower than previously reported values for PS-NIV [6, 9], despite the presence of NAVA nasogastric tubes. Third, since during PS-NIV settings were defined by the clinicians according to their usual procedures, the optimization of expiratory trigger, PSlevel and pressurization ramp can be questioned. According to previous reports, this could have influenced patient–ventilator synchrony during PS-NIV [24, 25]. However, as the median PSlevel was relatively low (median 10 cmH₂O, IQR 9–12 cmH₂O), over-assist and possibly related asynchronies would have been very unlikely. Additionally, the expiratory trigger was set at 45 % (IQR 41–49 %) in the subgroup of patients with known obstructive pulmonary disease, which is in line with published recommendations [25]. The ramp was determined pragmatically aiming at the most rapid pressurization tolerated while avoiding excessive face leaks and patient discomfort. According to Prinianakis et al., such ramps settings (maximum 350 ms in 1 of 13 patients) have a limited effect on T_i and intrinsic PEEP [26]. Fourth, despite having set the NAVA level according to the manufacturer’s procedure and because of very different airway pressure profiles during PS and NAVA [13], the comparability of assistance levels in PS and

Fig. 1 Various parameters of patient–ventilator synchrony in all patients. PS pressure support, NAVA neurally adjusted ventilatory assist, *epm* events per minute

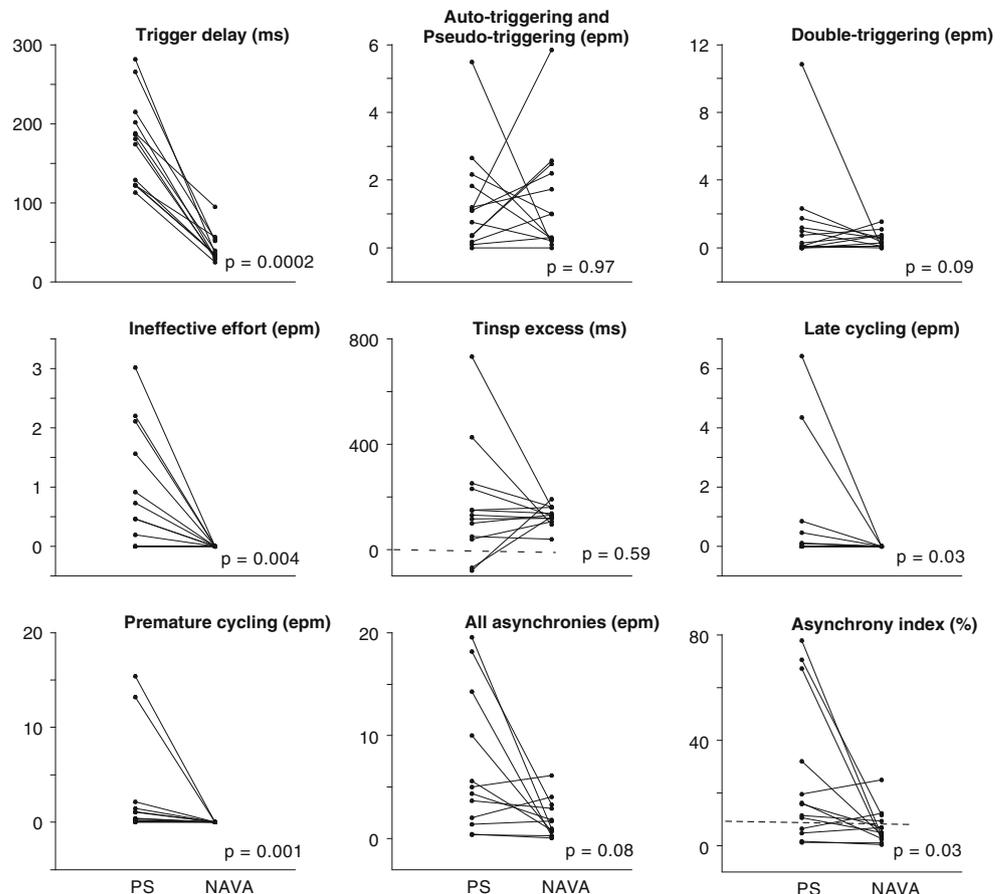


Table 2 Trigger delay, inspiratory time in excess and number of total and specific asynchronies per minute

	PS	NAVA	<i>p</i> value
T_d (ms)	181 (122–208)	35 (31–53)	0.0002
T_{iex} (ms)	131 (44–240)	129 (111–159)	0.59
Ineffective efforts (events/min)	0.5 (0–1.8)	0 (0–0)	0.004
Late cyclings (events/min)	0 (0–0.7)	0 (0–0)	0.03
Double triggerings (events/min)	0.3 (0–1.5)	0.4 (0.1–0.7)	0.59
Premature cyclings (events/min)	0.4 (0.1–1.8)	0 (0–0)	0.001
Autotriggerings in PS/pseudo triggerings in NAVA (events/min)	1.1 (0.3–2.0)	1 (0.2–2.3)	0.97
Total asynchronies (events/min)	4.4 (0.9–12.1)	1.0 (0.5–3.1)	0.08
AI (%)	15.8 (5.5–49.6)	4.9 (2.5–10.5)	0.03

Values are medians (IQR)

T_d trigger delay, T_{iex} inspiratory time in excess, AI asynchrony index

Table 3 Respiratory parameters and arterial blood gas

Parameter	PS	NAVA	<i>p</i>
Minute ventilation (l/min)	15.2 ± 3.9	15.6 ± 4.4	0.57
VT_i (ml/kg ideal body weight)	9.1 ± 1.5	10.0 ± 2.4	0.24
Leaks (l/min)	2.9 ± 3.0	2.7 ± 1.6	0.89
Ventilator respiratory rate (cycles/min)	27.4 ± 5.4	26.3 ± 6.2	0.39
Mean airway pressure (cmH ₂ O)	8.8 ± 1.3	8.8 ± 1.8	0.93
$E_{adi_{max}}$	33 ± 17	33 ± 15	0.97
PaO_2 (mmHg)	78 ± 19	77 ± 20	0.17
PaO_2/FIO_2	245 ± 76	240 ± 82	0.25
$PaCO_2$ (mmHg)	53 ± 15	54 ± 16	0.58
pH	7.37 ± 0.08	7.37 ± 0.08	0.88

Values are means ± SD

PS period of ventilation under pressure support, NAVA period of ventilation under neurally adjusted ventilatory assist, VT_i indexed tidal volume by ideal body weight in kilograms, $E_{adi_{max}}$ maximal value of the electrical diaphragmatic activity, PaO_2 arterial partial pressure of oxygen, FIO_2 inspired fraction of oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide

NAVA is questionable. Fifth, the tracings were analyzed by only one investigator, which could have led to systematic bias. However, the methodology and reading criteria were strictly defined before the analysis and were identical to those used in a previous study [13]. Sixth, under each mode patient ventilator synchrony was analyzed during 10 min randomly selected from the 20-min recordings. This could theoretically have influenced the results. However, as previously reported [27], patients adapt to a new ventilatory mode in less than ten respiratory cycles, so such an influence is very unlikely. Finally,

the number of included patients was small and as our group of patients included those admitted for acute respiratory failure and those at risk of developing respiratory failure after extubation, the group was heterogeneous. Nonetheless, despite this heterogeneity, all patients received NIV for well-validated indications [3, 17, 18]. It must also be pointed out that our study was a short-term evaluation and that the included patients were not in severe respiratory distress.

Interestingly, in contrast to recordings during invasive ventilation [13], no artifact required the exclusion of a recorded session during NIV. This was probably related to a higher EAdi amplitude during NIV. Furthermore, there was no automatic reversion to back-up PS during NAVA throughout the study.

Regarding triggering, our results show a major reduction in T_d with NAVA compared to PS, which is in line with previous reports in intubated patients [13, 14]. This was expected, as NAVA uses the EAdi to trigger the ventilator and as EAdi, which is the expression of the patient's inspiratory demand generated in the brainstem, occurs earlier than any flow or pressure variation used to trigger the ventilator during PS. This positive effect of NAVA on T_d could, however, potentially be reduced because of a built-in triggering system that can use either EAdi or a pneumatic signal to trigger the ventilator during NAVA on a first-come first-served basis. However, in our dataset, only 15 % of the breaths were triggered by a pneumatic signal, which means that T_d was reduced during NAVA in at least 85 % of all respiratory cycles. The reduction in T_d during NAVA to a value far below the conscious threshold of perception of about 150 ms [28] could potentially improve patient tolerance to NIV by reducing the discomfort due to the triggering process and the related feeling of dyspnea.

Of note, there were no ineffective efforts during NAVA-NIV, in contrast to PS-NIV. As ineffective efforts are related to increased work of breathing [29] and as increased work of breathing and insufficient unloading of respiratory muscles during NIV can lead to NIV failure, this point is of major clinical relevance. The ability of NAVA to reduce ineffective efforts is particularly interesting for patients with chronic obstructive pulmonary disease who exhibit a high number of ineffective efforts related to the inspiratory threshold load associated with intrinsic PEEP when flow or pressure triggering is used [30]. Despite NAVA improving the triggering process, we noted that it did not suppress double triggering. However, in contrast to the findings of our study on NAVA during invasive ventilation [13], we found no increase in double triggering under NAVA-NIV. This difference can probably be explained by the fact that EAdi amplitude during NIV was higher, thus reducing the vulnerability to artifacts in the EAdi signal and the consecutive generation of double triggering. An unsolved problem with NAVA related to the triggering process is the possible occurrence

of autotriggering events (called pseudotriggerings) due to the fact that during NAVA ventilator pressurization is initiated in response to each increase in EAdi including increases due to signal artifacts or to any kind of “subrespiratory” diaphragmatic activity. However, in our dataset there was no increase in autotriggering events in comparison to PS. Moreover, as pseudotriggerings during NAVA were related to lower airway pressure variations than autotriggerings during PS, their detrimental effect on the patients’ respiratory pattern could be limited. We cannot exclude, however, the possibility that pseudotriggerings during NAVA could be a source of patient discomfort.

Our results show that NAVA improved the expiratory cycling by suppressing both delayed and premature cycling, which was expected because of the EAdi-based termination of pressurization. Of note, as pressurization is interrupted when the EAdi signal decreases to 70 % of its maximal value, there is an expected delay between the time of the maximal EAdi value and the time of termination of pressurization, which was obvious in our results. Contrary to expectations, we found no reduction in median T_{iex} during NAVA-NIV, which could be explained by the fact that the ETS selected by the clinicians during PS-NIV was adapted to the patients according to published recommendations [25]. In particular, in patients with known obstructive pulmonary disease, the ETS was set to a value of 45 % (IQR 41–49 %). Figure 1 shows that during NAVA, T_{iex} decreased in all patients with normal or obstructive respiratory mechanics. In patients with restrictive respiratory mechanics, T_{iex} had a negative value during PS because of premature cycling. During NAVA, T_{iex} reached a positive value in these patients, indicating the absence of premature cycling. Thus, NAVA seems to normalize both premature and delayed expiratory cycling.

If we consider the total number of asynchrony events, our results show a trend in reducing patient–ventilator asynchronies during NAVA-NIV. In our small group of patients, this reduction was not statistically significant. However, the

AI, which reflects the severity of asynchrony, was significantly reduced during NAVA. Moreover, severe asynchrony (defined as an AI of more than 10 %) was present in 9 of 13 patients (69.2 %) during PS and in only 3 of 13 patients (23.1 %) during NAVA. As severe asynchrony has been associated with increased duration of mechanical ventilation [5, 31] and with a poor outcome when mechanical ventilation is prolonged [31] in intubated patients, the ability of NAVA to reduce patient–ventilator asynchrony could be clinically important.

Regarding other respiratory parameters and despite improved synchrony observed with NAVA, we found no differences in PaO₂, pH or PaCO₂ after 20 min under PS or NAVA. EAdi amplitude was also the same in NAVA-NIV and in PS-NIV, suggesting that NAVA-NIV did not globally increase respiratory muscle unloading in comparison to PS-NIV with clinicians’ ventilator settings. General limitations related to the use of NAVA during NIV are given in the Electronic Supplementary Material.

Conclusions

This study showed that NAVA can be used to deliver NIV in intensive care patients and could improve patient–ventilator synchrony by reducing T_d and severe asynchronies compared with PS. It also highlighted NAVA’s ability to eliminate ineffective efforts, and delayed and premature cyclings. However, whether these promising physiological effects could favorably impact patient outcome remains to be determined and should be explored in large-scale randomized studies.

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