Neurally-Adjusted Ventilatory Assist Versus Noninvasive Pressure Support Ventilation in COPD Exacerbation: The NAVA-NICE Trial

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BACKGROUND: This study was conducted to compare the effectiveness of noninvasive ventilation (NIV) with pressure support (NIV-PSV) to noninvasive neurally-adjusted ventilatory assist (NIV-NAVA) during COPD exacerbation. METHODS: In this study, 40 subjects with COPD and acute hypercapnic respiratory failure were randomized to receive either NIV-NAVA ($n = 20$) or NIV-PSV ($n = 20$) via a critical care ventilator. Subjects' vital parameters, arterial blood gas values, patient-ventilator asynchrony events, and asynchrony index were noted at specific time intervals in both groups. The duration of NIV, rate of NIV failure, and length hospital stay were also recorded for these 2 modes of NIV. RESULTS: NIV-NAVA significantly reduced the total number (median [interquartile range]) of asynchrony events compared to NIV-PSV: 22 (15–32.5) versus 65 (50.75–104.25), respectively, $P = .002$. Severe asynchrony defined as asynchrony index > 10% was also significantly lower in NIV-NAVA than in NIV-PSV ($P < .001$). There was no significant difference between the 2 groups regarding improvement in gas exchange and vital parameters. Rate of failure of NIV ($P = .73$), duration of the requirement of ventilatory support ($P = .40$), and hospital length of stay ($P = .46$) were also comparable between the 2 modes of ventilation. CONCLUSIONS: Compared to NIV-PSV, NIV-NAVA was associated with better patient-ventilator synchrony and a reduction in the number of asynchrony events in subjects with an exacerbation of COPD, with similar effects on improvement in gas exchange, duration of NIV, hospital lenght of stay, and rate of NIV failure. (Clinicaltrials.gov registration NCT02912689.) *Key words: NIV; neurally adjusted ventilatory assist; NAVA; patient–ventilator asynchrony* [Respir Care 2020;65(1):53–61. © 2020 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) is the standard of care for patients with COPD and acute hypercapnic respiratory failure. NIV has been shown to improve outcomes, including reduced mortality and reduced need for endotracheal intubation.[1-3] However, NIV fails to improve respiratory failure in a significant number of patients, endotracheal intubation and invasive mechanical ventilation are often required in these individuals.[4,5] NIV failure has been reported in 7–50% of COPD exacerbation cases.[4-7] Patient-ventilator asynchrony has been reported to be an important cause of NIV failure, and as many as 46% of patients exhibit severe patient-ventilator asynchrony during use of NIV.[8,9] Data also suggest that patients with COPD are at high risk of patient-ventilator asynchrony during NIV.[9,10] Reduction in patient-ventilator asynchrony should improve the rate of NIV success.

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Neurally-adjusted ventilatory assist (NAVA) is an assist mode of ventilation that uses electrical activity of diaphragm (EA_{di}), sensed by a special nasogastric catheter (EA_{di} catheter), to trigger and terminate the respiratory cycle. NAVA therefore provides assistance that is proportional to the patient's effort and hence improves patient-ventilator interaction and minimizes patient-ventilator asynchrony.[11-13] Physiological studies in subjects with respiratory failure have reported that NAVA was associated with improved patient-ventilator interaction and a reduction in the severity of patient-ventilator asynchrony compared to pressure-support ventilation (PSV).[11,14] However, these studies have evaluated the effect of NAVA use only for a short period of time, ranging from 10 min to 30 min.[11,13] In a case report, we showed that NIV provided with NAVA (NIV-NAVA) can be used as the initial mode of ventilation for COPD exacerbation, and this therapy may be continued during hospitalization until respiratory failure resolves.[15] NIV-NAVA has the potential to reduce patient-ventilator asynchrony and NIV failure during COPD exacerbation; however, data regarding its utility as the initial mode are lacking.

In this study we aimed to use NIV-NAVA as the initial mode of ventilation in subjects with an exacerbation of COPD, and to compare the use of NIV-NAVA to that of NIV-PSV. We hypothesized that use of NIV-NAVA in subjects with an exacerbation of COPD would be associated with better patient-ventilator interaction and improved clinical outcomes compared to NIV-PSV.

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) using pressure support (PSV) is standard of care for the management of hypercapnic exacerbation of COPD. A significant number of patients require intubation due to NIV failure. Patient-ventilator asynchrony is an important factor associated with NIV failure.

What this paper contributes to our knowledge

NIV-NAVA as the initial mode was feasible in the management of subjects with exacerbation of COPD with hypercapnic respiratory failure. Compared to NIV-PSV, NIV-NAVA resulted in a significant reduction in the number and severity of patient-ventilator asynchronies, with no significant difference in clinical outcomes such as rate of NIV success, hospital or ICU length of stay, and rate of correction of blood gas abnormalities.

Methods

Study Design, Population and Setting

This was a single-center randomized controlled trial conducted at a tertiary care teaching hospital between August 2016 and December 2017. All patients with COPD and age $\geq$ 40 y who were admitted with an exacerbation of COPD and hypercapnic respiratory failure ($7.25 \geq$ pH ≤ 7.35 with $P_{aCO_2} \geq 45$ mm Hg) in the respiratory ward or ICU were eligible for this trial. Patients with any contraindication for use of NIV or placement of nasogastric tube, any known neuromuscular disorder affecting the diaphragm, NIV use for $>$ 6 h prior to randomization, requiring invasive ventilation, or unwilling to participate were excluded from the study.

Subjects who fulfilled the study inclusion criteria were randomized to receive either NIV-PSV or NIV-NAVA. The randomization was done with a computer-generated random-number sequence. The allocation codes were kept in an opaque envelope that was opened just prior to allocation of NIV.

Outcome Measures

The primary aim of the study was to compare various types of patient-ventilator asynchrony and the severity of asynchrony between NIV provided with PSV or NAVA during management of a COPD exacerbation. Various secondary outcome comparisons included clinical, ventilator, and arterial blood gas parameters; rate of NIV failure; and subjects' discomfort related to the ventilator or presence of EA_{di} catheter.

Initiation of NIV

In both groups, NIV was provided via a Servo-i critical care ventilator (Maquet, Solna, Sweden) using a non-vented oronasal mask that was fitted snugly enough to avoid leaks. An EA_{di} catheter (size 16 F, 125 cm) was placed in all subjects. The distal end of EA_{di} catheter was positioned at the level of diaphragm using the nose, ear, and xiphoid formula.[16] The correct placement was ensured by observing the characteristic tracing on the ventilator screen (see the supplementary materials at http://www.rcjournal.com). The position of the EA_{di} catheter was checked at least every 6 h, or whenever required. To reduce the leak around the mask, silicon padding was used.

Pressure support during NIV-PSV and NAVA level during NIV-NAVA were set to achieve a tidal volume of 6–8 mL/kg of ideal body weight. For NIV-PSV, the inspiratory flow trigger was set to avoid automatic and ineffective triggering, while the expiratory trigger threshold was set at 40–45% of peak expiratory flow. For NIV-

NAVA, the NAVA level was set using the manufacturer's software to obtain the same peak airway pressure as during pressure support (see the supplementary materials at http://www.rcjournal.com). For NIV-NAVA, trigger sensitivity and cycle values were fixed at 0.5 μV and 70% of peak EA_{di}, respectively. PEEP and F_{IO_2} were adjusted to achieve an oxygen saturation of at least 92%. Airway pressure limit was set at 25 cm H_2O. Back-up PSV was set to provide ventilation during loss of EA_{di} signals. NIV was used continuously during the first the 24 h and was discontinued only for feeding and secretion clearance. Treating physicians were allowed to adjust ventilator settings (eg, pressure support, NAVA levels, trigger sensitivity) to minimize patient-ventilator asynchrony.

Data Acquisition

On admission, demographic and clinical data such as age, gender, duration and severity of COPD, previous history of exacerbation, past use of mechanical ventilation, presence of any comorbid illness, severity of presenting illness, and time to randomization after admission were recorded. After initial stabilization for a period of 30 min, subjects in each group were observed for a prespecified period of 10 min. During this period, different types of patient-ventilator asynchrony, and various clinical, ventilator, and blood gas parameters were recorded. These observations were repeated at 6, 12, and 24 h on day 1, and subsequently every 6 h daily until NIV was discontinued.

Patient-ventilator asynchrony was quantified via offline analysis of recorded pressure-time, flow-time, and EA_{di} waveforms by one of the study authors, who is a trained clinician (S.T.). The following 5 patterns of patient-ventilator asynchrony were quantified by visual analysis as described previously: ineffective effort, auto-triggering, double triggering, premature cycling, and delayed cycling.[17] The total number of asynchronies was calculated by adding different asynchronies recorded over a10-min period. To measure the severity of asynchrony, the asynchrony index was calculated using the following formula: total number of asynchrony events divided by the number of EA_{di} signals $\times$ 100. Asynchrony index $>$ 10% was considered severe asynchrony.

Assessment of Discomfort

Visual analog scale was used to assess the intensity of respiratory discomfort caused by the mode of ventilation and or the EA_{di} catheter (0 = no discomfort and 10 = maximum discomfort).

Weaning From NIV

Weaning from each mode was considered when there was improvement in clinical parameters, absence of respiratory acidosis, and reduction in frequency to $<$ 25 breaths/min. Pressure support was reduced gradually by 2–4 cm H_2O every 4–6 h until pressure support $\leq$ 4–6 cm H_2O was attained, after which NIV was withdrawn.[18] The weaning protocol for NAVA was similar to one described previously by Garzando and colleagues.[19] Weaning from NAVA-NIV was considered when, at the same NAVA level, there was a decline in peak EA_{di} signal with minimal change in tidal volume and reduction in peak airway pressures. Once this stage was reached, NAVA levels were reduced by 0.1–0.2 cm of $H_2O/\mu V$. If there was no reduction in tidal volume and the EA_{di} signal increased, further reductions in NAVA levels were repeated after 4–6 h. This procedure was repeated until the EA_{di} waveform coincided with the pressure curve generated at a pressure support $\leq$ 4–6 cm H_2O, at which point NIV-NAVA was discontinued. If there was reduction in tidal volume with an increased EA_{di} signal (indicating persistent respiratory failure), settings were returned to previous levels and the subject was re-evaluated after another 4–6 h. NIV success was defined as the resolution of respiratory failure, without the need for intubation or death. All subjects were followed until discharge from the hospital or death. Data regarding total time spent on NIV and duration of stay in hospital and ICU were recorded.

Statistical Analysis

The sample size calculation was based on a previous study by Bertrand et al,[14] which reported severe patient-ventilator asynchrony during NIV-PSV and NIV-NAVA for 48% and 8% of subjects, respectively.[14] For 95% CI, an α level of 0.05, and 2-sided test, we required at least 20 subjects in each arm to achieve a power of 85% for the demonstration of a difference in patient-ventilator asynchrony between the 2 groups. Data were expressed as mean $\pm$ SD or median (range or interquartile range [IQR]). Qualitative data were presented as absolute numbers and percentages. Student *t* test, Mann-Whitney test, chi-square test, or Fisher exact test were used to observe differences between groups. A *P* value of $<$ .05 was considered significant. Statistical analysis was performed with Stata 12.0 (StataCorp, Lakeway, Texas).

The study was conducted following principles for biomedical research involving human subjects.[20,21] The study protocol was approved by our institutional ethics committee. Written consent was obtained from all participants or their legally authorized relative.

Results

A total of 230 patients with acute hypercapnic respiratory failure were screened for eligibility (Fig. 1); 40 subjects were included in the study and randomized to receive

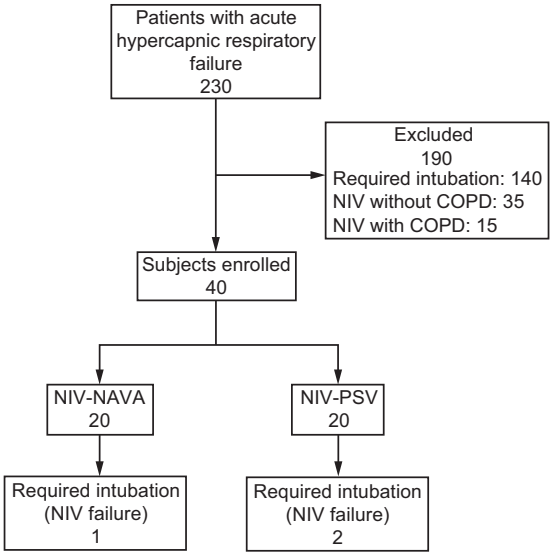

Fig. 1. Flow chart. NIV = noninvasive ventilation; NAVA = neurally adjusted ventilatory assist; PSV = pressure support ventilation.

either NIV-PSV or NIV-NAVA (ie, 20 subjects in each group). There were no significant differences in baseline characteristics between the 2 groups (Table 1). See the supplementary materials at http://www.rcjournal.com for initial ventilatory settings and subject parameters.

Primary Outcome

The total number of asynchrony events during NIV-NAVA, presented as median (IQR) values, was 22.5 (15–32.5), which was significantly less than those for NIV-PSV, which totaled 65 (50.75–104.25) ($P = .002$). All 5 types of asynchrony events, presented as median (IQR), were significantly reduced with NIV-NAVA compared to NIV-PSV: ineffective triggering, 1 (0–3) versus 10 (8.5–18) ($P < .001$); auto-triggering, 0 (0–0) versus 5.5 (2.5–9.5) ($P < .001$); double-triggering, 11.5 (10–14) versus 19.5 (14–29) ($P = .004$); premature cycling, 0 (0–4.25) versus 15 (9–22.5) ($P < .001$); and delayed cycling 8 (3.5–9.25) versus 13 (8–17.25) ($P = .01$). Double-triggering was the most common asynchrony event in both groups; auto-triggering was not observed during NIV-NAVA (Table 2).

Asynchrony index was significantly lower in subjects receiving NIV-NAVA than in subjects receiving NIV-PSV at all time points of the assessment (Table 2). Further, the number (%) of subjects with severe asynchrony (asynchrony index > 10%) were significantly reduced in NIV-NAVA at 2 events (10%) versus 14 events (70%) with NIV-PSV ($P < .001$) (data not shown).

Secondary Outcomes

Secondary outcomes that were analyzed included rate of NIV failure, the effect on respiratory and blood gas parameters, various ventilatory parameters, and patient discomfort during both modes of ventilation.

The median duration of requirement of NIV was 4 d. The duration of NIV requirement was comparable between subjects managed with NAVA or with PSV. Overall, 37 of 40 subjects could be managed successfully with NIV using either PSV or NAVA. Three subjects failed NIV (1 in the NAVA group, 2 in the PSV group) and required endotracheal intubation and invasive mechanical ventilation. Median duration of hospital stay was 6 d and was comparable between both groups. However, in the 3 subjects (7.5%) who failed NIV and required invasive mechanical ventilation, hospital stay was longer (11 ± 1 d). There were 2 deaths in the study cohort. The comparison of various outcomes between the 2 groups is shown in Table 3.

Subjects' level of discomfort related to the mode of ventilation and the EA_{di} catheter was recorded using a visual analog score. There was no significant difference in the level of comfort with either mode of NIV. Similarly, the presence of the EA_{di} catheter was associated with similar levels of discomfort in both groups (Table 3).

Blood gas and respiratory parameters between both groups were compared at different time points from the initiation of NIV until day 4. No difference was observed in the rate of correction of arterial blood gas parameters and breathing frequency (Fig. 2).

Post Hoc Analysis

We compared the effect of asynchrony on various outcomes such as duration of NIV, length of hospital stay, and NIV success between subjects with severe asynchrony (asynchrony index > 10%) and without severe synchrony (asynchrony index < 10%), regardless of the mode of NIV received. There was no difference in the duration of NIV. Median (range) hospital stay was significantly higher in subjects with asynchrony index > 10%. There were trends that suggested that subjects with asynchrony index < 10% were more likely to have successful NIV (see the supplementary materials at http://www.rcjournal.com). The 3 subjects who failed NIV and required endotracheal intubation had an asynchrony index of > 10%.

Discussion

Our results in subjects with COPD exacerbation indicate that the use of NIV-NAVA compared to the use of NIV-PSV improved patient-ventilator interaction and reduced the total number as well as the severity of asynchrony events. However, NAVA was equally effective as

Table 1. Baseline Characteristics of Study Population

Characteristics	All Subjects	NAVA	PSV
Age, y	61.36 ± 8.67	62.7 ± 7.8	60.1 ± 9.44
Male	31 (77.5)	14 (70)	17 (85)
Smoking status	32 (80)	17 (85)	15 (75)
Smoking index	250 (150–450)	240 (150–350)	305 (150–500)
COPD duration	6 (5–10)	7 (5–10)	6 (5–10)
Severity of COPD			
GOLD group B	15 (37.5)	6 (30)	9 (45)
GOLD group C	9 (22.5)	6 (30)	3 (15)
GOLD group D	16 (40)	8 (40)	8 (40)
Spirometry available	17 (42.5)	7 (35)	10 (50)
FEV_1, L	1.03 (0.75–1.28)	1.17 (0.84–1.51)	0.86 (0.72–1.17)
FVC, L	1.94 (1.58–2.33)	1.94 (1.71–2.43)	1.8 (1.53–2.21)
Use of long-term oxygen therapy	7 (17.5)	3 (15)	4 (20)
History of previous exacerbation	32 (80)	17 (85)	15 (75)
Exacerbations	2 (0–7)	2 (0–5)	2 (0–7)
History of NIV for exacerbation	7 (17.5)	4 (20)	3 (15)
History of intubation for exacerbation	5 (12.5)	2 (10)	3 (15)
Cause of current exacerbation			
Infective	27 (67.5)	11 (55)	16 (80)
Non-infective	13 (32.5)	9 (45)	4 (20)
Duration of NIV prior to randomization, h	3 (1–6)	3 (1–5)	3 (1–5)
Presence of comorbidities	23 (57.5)	13 (65)	10 (50)
Hypertension	22 (55)	13 (65)	9 (45)
Diabetes	5 (12.5)	4 (20)	1 (5)
Coronary artery disease	3 (7.5)	2 (10)	1 (5)
Duration of symptoms, d*	4 (2–10)	4 (2–10)	4 (2–7)
APACHE-II	12 (7–22)	12 (7–21)	12.5 (8–22)
SOFA	3 (2–10)	3 (2–7)	3 (2–10)
pH	7.28 ± 0.02	7.28 ± 0.23	7.27 ± 0.20
P_{CO_2}, mm Hg	74.69 ± 11.21	74.67 ± 13.34	74.72 ± 9.08
HCO_3, meq/L	33.24 ± 4.81	32.86 ± 5.06	33.60 ± 4.67
Frequency, breaths/min	27 (22–35)	26 (22–35)	28 (24–35)
Heart rate, beats/min	106 (82–148)	98 (88–130)	109 (82–148)
Systolic blood pressure, mm Hg	120 (90–168)	120 (90–168)	120 (90–160)

Data are presented as *n* (%), mean ± SD, or median (interquartile range). All subjects: $N = 40$; NAVA: $n = 20$ subjects; PSV: $n = 20$ subjects.
* Current acute exacerbations of COPD.
NAVA = neurally adjusted ventilatory assist
PSV = pressure support ventilation
GOLD = Global Initiative for Chronic Obstructive Lung Disease
NIV = noninvasive ventilation
APACHE = Acute Physiology and Chronic Health Evaluation
SOFA = Sequential Organ Failure Assessment scoring system

PSV in terms of rate of correction of respiratory failure and improvement in arterial blood gas parameters.

Patient-ventilator synchronization is critical for successful NIV. Studies have reported that patient-ventilator asynchrony results in increased work of breathing, patient discomfort, NIV failure, and endotracheal intubation.[9,22,23] Our study results indicated that NIV-NAVA, compared to NIV-PSV, was associated with better patient–ventilator interaction and synchrony. Similar results have been reported in other small studies.[11,14] Notably, severe patient-ventilator asynchrony (asynchrony index > 10%), which has been associated with adverse effects including failure of NIV,[13] were significantly reduced with the use of NAVA. These results are consistent with previous observations reported by Bertrand et al[14] and Wang et al;[24] however, both of these studies were limited by short duration (20–30 min) of NIV-NAVA use.[14,24] We used NIV-NAVA from the time of admission to full recovery of respiratory failure and established that use of NIV-NAVA is feasible in this setting.

Various asynchrony events can occur during NIV use, particularly in COPD patients, including ineffective trig-

Table 2. Comparison of Asynchrony Index and Types of Asynchrony

	NIV-NAVA	NIV-PSV	*P*
Asynchrony index			
30 min after initiation	6.02 ± 2.36	14.33 ± 8.63	< .001
Day 1	4.42 ± 2.03	12.06 ± 7.98	.002
Day 2	3.05 ± 2.29	8.43 ± 6.61	.001
Day 3	1.88 ± 2.09	5.07 ± 3.38	.001
Day 4	0.74 ± 0.89	3.88 ± 3.96	.007
Types of asynchrony			
Ineffective efforts	1 (0–3)	10 (8.5–18)	< .001
Auto triggering	0 (0–0)	5.5 (2.5–9.5)	< .001
Double triggering	11.5 (10–14)	19.5 (14–29)	.004
Premature cycling	0 (0–4.25)	15 (9–22.5)	< .001
Delayed cycling	8 (3.5–9.25)	13 (8–17.25)	.01
Total asynchrony	22.5 (15–32.5)	65 (50.75–104.25)	.002

Data are presented as mean ± SD or median (interquartile range). NIV-NAVA: $n = 20$ subjects; NIV-PSV: $n = 20$ subjects.
NIV = noninvasive ventilation
NAVA = neurally adjusted ventilatory assist
PSV = pressure support ventilation

Table 3. Comparison of Various Secondary Outcome Measures

Outcome Variable	NIV-NAVA	NIV-PSV	*P*
NIV success	19 (95)	17 (85)	.73
Need for intubation	1 (5)	2 (10)	
In-hospital mortality	0 (0)	2 (10)	.48
Visual analog scale (EA_{di} catheter)	5 (2–9)	5 (3–8)	.08
Visual analog scale (mode of NIV)	4 (3–6)	5 (4–7)	.07
Duration of NIV	4 (2–5)	4 (0.5–7)	.40
Length of hospital stay	6 (4–12)	6 (3–11)	.46

Data are presented as *n* (%) or median (interquartile range). NIV-NAVA: $n = 20$ subjects; NIV-PSV: $n = 20$ subjects.
NIV = noninvasive ventilation
NAVA = neurally adjusted ventilatory assist
PSV = pressure support ventilation
EAdi = electrical activity of the diaphragm

gering, auto-triggering, double-triggering, delayed cycling, and premature cycling.[9,10,25] Ineffective effort is the most common type of asynchrony observed among patients with COPD, and this is attributed to the presence of hyperinflation and auto-PEEP.[9,25] The improvement in patient–ventilator interaction is predominantly due to a reduction in the percentage of ineffective efforts and cycling asynchrony. Our results as well as those of previous studies by Bertrand et al[14] and Piquilloud et al[11] indicate that NAVA significantly reduced ineffective efforts. The presence of excessive levels of assistance and leaks are other important factors that may be responsible for ineffective efforts.[26] In our study, it is unlikely that over-assistance and leaks around the mask explain the reduction of ineffective efforts with NAVA because the percentage of air leak (40 ± 10.6% vs 40 ± 5.79%, $P = .98$) and tidal volume (408 ± 32.97 mL vs 431 ± 33.08 mL, $P = .02$) were not higher in the PSV group. The effect of NAVA on double-triggering is variable. In our study, double-triggering was the most common type of asynchrony observed in the NAVA group, but these events were significantly fewer compared to subjects on PSV. In our results, NAVA was not associated with a significant reduction in double-triggering compared to PSV during NIV as reported in other studies.[11,14] Interestingly, double-triggering was significantly more common during NAVA than during PSV in subjects receiving invasive ventilation.[27,28] However double-triggering during NAVA does not result in breath-stacking or increases in delivered tidal volume.

Patients with COPD are at increased risk of patient-ventilator asynchrony.[9,23] Several studies have described use of NAVA in subjects with COPD exacerbation.[11,14,29-33] Among these, few studies have used NAVA while subjects were receiving either mechanical ventilation[29,30] or veno-venous extracorporeal membrane oxygenation,[31] and reported the effects of NAVA on patient-ventilator interactions. However, other studies have compared NIV-NAVA to NIV-PSV in various patient populations.[11,24,32,33] In a heterogeneous sample of 13 subjects with respiratory failure due to COPD exacerbation, asthma exacerbation, sepsis, and pneumonia, Piquilloud et al[11] reported that NAVA was associated with improved patient–ventilator interaction and severity of asynchrony compared to PSV. Similar observations were reported in other observational studies by Doorduin et al[32] and Wang et al.[24] Researchers who have used helmet interfaces instead of a face mask for delivery of NIV-NAVA have reported better patient–ventilator interaction and reduced patient-ventilator asynchrony.[33] From these studies it can be concluded that, among patients with exacerbation of COPD, use of NIV-NAVA results in significant reductions of asynchrony events and the asynchrony index compared to NIV-PSV.

Improvement in various clinical and blood gas parameters (eg, pH and P_{aCO_2}) remains one of the targets that decide the need for NIV. Therefore, rapid improvement in these parameters is desirable. Our results indicate that the values of blood gas parameters were comparable between both study groups at different time points (Fig. 2). Similar observations were reported in a short randomized cross-over trial of NAVA by Wang et al.[24] None of the previously published studies[11,24,32] were designed to assess the effects of NIV-NAVA on clinical outcomes. We observed that both groups had comparable total duration of NIV (median of 4 d in both groups) and length of hospital stay (median of 6 d for both groups). Our results also indicate that there was no significant difference in the rate of NIV failure and requirement of endotracheal

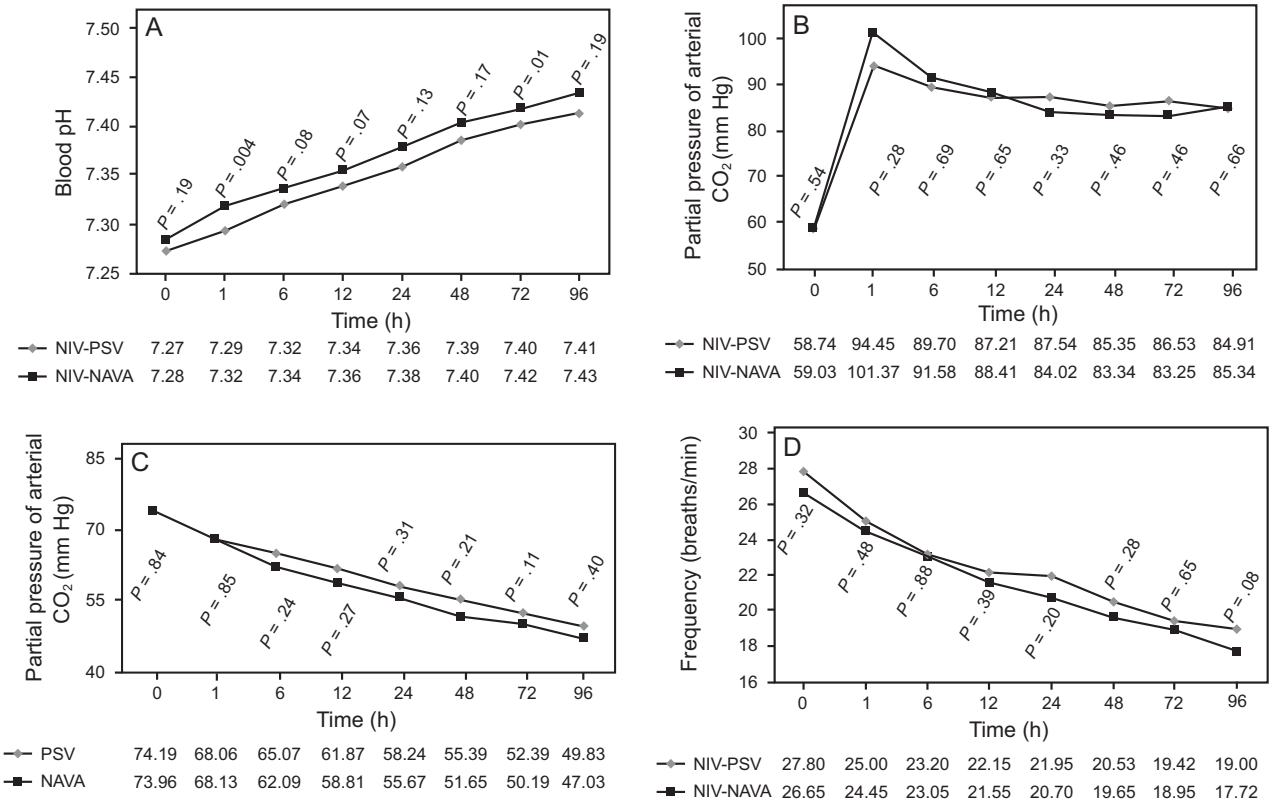

Fig. 2. Comparison of blood gases and breathing frequency at different time points. NIV = noninvasive ventilation; NAVA = neurally adjusted ventilatory assist; PSV = pressure support ventilation.

intubation between these 2 modes of ventilation. These results suggest that reduction in patient-ventilator asynchrony may not result directly in better outcomes in terms of reduced duration of NIV or hospital stay. It is also possible that this study is underpowered to detect the differences for these outcomes.

The presence of the EA_{di} catheter can potentially worsen the leak around the mask and act as a source of patient discomfort. In our study, discomfort due to the presence of the catheter did not result in discontinuation of NIV. In addition, the intensity of respiratory discomfort due to ventilation mode was similar between NAVA and PSV. So, despite the fact that NAVA improved patient–ventilator interactions, it was not associated with significant improvement in the subject's comfort level compared to PSV.

Strengths and Limitations

This is the first randomized controlled trial that used NIV-NAVA as the initial ventilation mode in subjects with COPD and acute hypercapnic respiratory failure. NIV-NAVA was used continuously until respiratory failure was resolved. To maximize the detection of asynchrony events, frequent observations at prespecified time were included in the study protocol. Unlike previous studies that observed and recorded various clinical, ventilator, and blood gas parameters for a short period of time (ie, 10–30 min at a single point of time), we recorded all such parameters until subjects were weaned from NIV. To our knowledge, this is the first study to assess clinical outcomes comparing NAVA with PSV in subjects with COPD, whereas previous studies[11,24,32] only looked for differences in asynchrony events and various physiological parameters. Finally, patients were randomized within 6 h of presentation to minimize the effect on various clinical and blood gas parameters by prior NIV use.

There are several limitations to our study. First, because the study cohort consisted of only subjects with COPD and acute hypercapnic respiratory failure, our results cannot be generalized to other causes of respiratory failure. Second, the sample size was calculated to look for the difference in patient-ventilator asynchrony between 2 NIV modes, therefore it may not be powered to detect differences in various clinical outcomes. Third, calculations of asynchronies were based on a visual analysis of various waveforms. The visual analysis of waveforms has high specificity but lacks adequate sensitivity, and therefore it may have underestimated asynchrony events.[34] Fourth, ventilator waveform analysis was done by a single investigator, which could

have led to bias. Fifth, it was difficult to differentiate whether the discomfort reported by subjects were related to the presence of the EA_{di} catheter, mode of NIV used, or both. Finally, a large number of patients were excluded at the time of screening due to endotracheal intubation and invasive ventilation without an NIV trial. This might have resulted in selection bias. Our hospital is a tertiary care center and we receive the highest acuity patients, with most likely too sick to qualify for a trial of NIV. In addition, due to the limited availability of beds, more stable patients are often referred to other hospitals and were not available for inclusion in the study.

Conclusions

This randomized trial demonstrated that NIV-NAVA may be used as the initial mode of NIV for management of acute hypercapnic respiratory failure in patients with COPD. The use of NIV-NAVA compared to NIV-PSV in subjects with an exacerbation of COPD was associated with better patient-ventilator interactions and a reduction in the severity of asynchrony. Larger studies using NIV-NAVA as the initial mode in subjects with COPD exacerbation are required to assess its effects on clinical outcomes such as rate of NIV failure, duration of NIV, length of ICU or hospital stay, and mortality.

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