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Noninvasive Ventilation Intolerance: Characteristics, Predictors, and Outcomes

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BACKGROUND: Noninvasive ventilation (NIV) intolerance is one reason for NIV failure. However, the characteristics, predictors, and outcomes of NIV intolerance are unclear. METHODS: A prospective observational study was performed in the respiratory intensive care unit of a teaching hospital. Subjects with acute respiratory failure who used NIV were enrolled. Initially, continuous use of NIV was encouraged. However, if the subject could not tolerate NIV, it was used intermittently. NIV intolerance was defined as termination of NIV due to subject refusal to receive it because of discomfort, even after intermittent use was attempted. RESULTS: A total of 961 subjects were enrolled in the study. Of these, 50 subjects (5.2%) experienced NIV intolerance after a median 2.4 h of NIV support. Age (OR = 0.98/y, 95% CI 0.963–0.996/y) and heart rate (OR = 1.02/beat/min, 95% CI 1.006–1.030/beat/min) measured before NIV were 2 independent risk factors of NIV intolerance. After 1–2 h of NIV, independent risk factors of NIV intolerance were heart rate (OR = 1.03/beat/min, 95% CI 1.016–1.044/beat/min) and breathing frequency (OR = 1.06/breath/min, 95% CI 1.027–1.099/breath/min). Intolerant subjects had no improvement in mean arterial pressure, heart rate, or breathing frequency after the NIV intervention. Moreover, intolerant subjects had a higher intubation rate (44.0% vs 25.8%, *P* = .008) and higher mortality (34.0% vs 22.4%, *P* = .08). The three most common complaints were that NIV worsened subjects' distress (46%), that NIV resulted in dyspnea (26%), and that the flow or pressure of NIV was too strong to bear (16%). CONCLUSIONS: NIV intolerance worsened subjects' outcomes. Younger subjects with a high heart rate and breathing frequency may be more likely to experience NIV intolerance. *Key words: noninvasive ventilation; intolerance; predictor; intubation.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) reduces intubation rates, decreases the incidence of ventilator-associated pneumonia, and shortens ICU stays in patients with acute respiratory failure.[1-4] However, some patients fail to see an improvement in their acute respiratory failure because of NIV failure, and are intubated. Previous studies have reported that NIV intolerance is one of the causes for intubation,[5-11] and one of the studies[8] has shown that poor NIV tolerance is associated with higher intubation rates. According to Antonelli et al,[7] NIV intolerance accounted for 25% of all intubations in subjects with ARDS. In another study, also reported by Antonelli et al,[12] it accounted for 9% of intubations in subjects with acute hypoxemic respiratory failure. However, these studies only reported the rate of NIV intolerance. The clinical characteristics, outcomes, and association with intubation of NIV intolerance are unclear. Thus, the aim of this study was to report the characteristics, predictors, and outcomes of NIV intolerance in subjects with acute respiratory failure.

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Methods

From May 2011 to September 2014, we performed a prospective observational study in the respiratory ICU of a teaching hospital. The investigational review board of the First Affiliated Hospital of Chongqing Medical University approved the study. The initiation of NIV in subjects with acute respiratory failure was in line with the following indictors but ultimately was at the discretion of attending physicians. At least one of the following indicators was required for NIV to be initiated: (1) breathing frequency >25 breaths/min, (2) pH <7.35, (3) P_{aCO_2} >45 mm Hg, (4) P_{aO_2}/F_{IO_2} <200 mm Hg, or (5) vigorous activity of accessory respiratory muscles.[13] Exclusion criteria for NIV were as follows: recent facial or cranial trauma or surgery, facial abnormalities, active upper gastrointestinal bleeding, high risk of aspiration, inability to clear sputum, and agitation. We enrolled all subjects who underwent NIV because of acute respiratory failure. However, patients younger than 18 y old and those with a do-not-intubate order were excluded from the study. Before or during the study, written informed consent was obtained from subjects. If subjects were unable to sign the written informed consent because of functional limitations, the informed consent was signed by their next of kin.

NIV was managed by attending physicians, respiratory therapists, and nurses. An oronasal mask (ZS-MZ-A face mask, Shanghai Zhongshan Medical Technology, Shanghai, China) was used for all subjects. An appropriately sized mask was chosen based on the subject's facial type. A heated humidifier with a thermometer was used for all subjects. A temperature of <41°C was set based on the subject's comfort, tolerance, and adherence.[14] If humidification was not adequate, intermittent drinks were given. To balance skin breakdown and excessive air leaks, we kept air leaks at <30 L/min, and straps were made as tight as comfortably possible. If there were no contraindications, all subjects were positioned at 30–45° to avoid aspiration.

The initial modes were CPAP or spontaneous/time mode (BiPAP Vision or V60, Philips Respironics, Murrysville, Pennsylvania). For subjects with hypoxemia or heart failure only, the initial mode was set as CPAP. For subjects with hypercapnia or vigorous activity of accessory respiratory muscles, spontaneous/time mode was used. In subjects with hypoxemia or heart failure, expiratory positive airway pressure or CPAP was initially set at 4 cm H_2O and increased by 1–2 cm H_2O to the subject's maximum tolerance, but this was usually limited to <15 cm H_2O. F_{IO_2} was set to maintain S_{pO_2} at about 95%. In subjects with hypercapnia, expiratory positive airway pressure was initially set at 4 cm H_2O and titrated according to the flow curve to ensure that the expiratory flow reached zero before inspiration or to diminish ineffective efforts. Inspiratory positive airway pressure was adjusted by increments of 1–2 cm H_2O to obtain a tidal volume of >6 mL/kg every 5–6 min or to the maximum level tolerated by each subject.[13]

Before beginning NIV, we recorded the age, sex, diagnosis, heart rate, breathing frequency, blood pressure, arterial blood gas results, and APACHE II (Acute Physiology and Chronic Health Evaluation II) score of the subject. After 1–2 h of NIV, vital signs and ventilator parameters were recorded, and arterial blood gas tests were performed. However, for intolerant subjects who received NIV for <1 h, these variables were measured and tests were performed at the termination of NIV.

Initially, continuous use of NIV was encouraged.[14,15] Once respiratory failure was relieved, NIV was used intermittently, and subjects were eventually totally weaned from it. If subjects felt any discomfort during NIV, physicians, respiratory therapists, or nurses checked the parameters, circuit, humidification, air leak, straps, etc to ensure maximum comfort. If subjects still felt uncomfortable, NIV was used intermittently. NIV intolerance was

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) intolerance frequently occurs and is one cause for NIV failure. However, the clinical characteristics, predictors, and outcomes of NIV intolerance are unclear.

What this paper contributes to our knowledge

Reasons for NIV intolerance varied. Younger subjects with a high heart rate and breathing frequency were more likely to experience NIV intolerance. NIV-intolerant subjects showed no improvement in mean arterial pressure, heart rate, or breathing frequency after 1–2 h of NIV. Moreover, they were more likely to experience intubation and to experience it earlier.

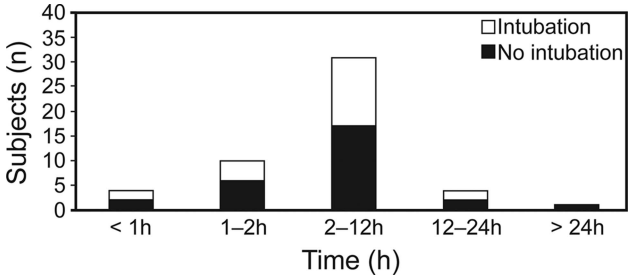

Fig. 1. Time from initiation of noninvasive ventilation to termination in intolerant subjects (median 2.4 h, interquartile range 1.8–4.8 h).

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Table 1. Comparison of Data for Subjects With and Without Noninvasive Ventilation Intolerance

Characteristics	NIV Intolerance (n = 50 [5.2%])	NIV Tolerance (n = 911 [94.8%])	P
Age, mean ± SD y	63.2 ± 19.1	69.1 ± 13.8	.005
Male/female, n	37/13	659/252	.87
Diagnosis, n (%)			
COPD exacerbation	26 (52)	522 (57.3)	.47
Pneumonia	17 (34)	251 (27.6)	.33
ARDS	3 (6)	43 (4.7)	.73
Asthma	0 (0)	23 (2.5)	.63
Pulmonary cancer	2 (4)	21 (2.3)	.34
Pulmonary embolism	1 (2)	14 (1.5)	.55
Others	1 (2)	37 (4.1)	.72
Data collected at NIV initiation			
APACHE II score, mean ± SD	18.9 ± 6.0	17.9 ± 5.3	.15
Mean arterial pressure, mean ± SD mm Hg	99 ± 21	99 ± 17	.94
Heart rate, mean ± SD beats/min	125 ± 29	113 ± 24	.001
Breathing frequency, mean ± SD breaths/min	33 ± 7	30 ± 8	.02
pH, mean ± SD	7.36 ± 0.16	7.37 ± 0.11	.29
P_{aCO_2}, mean ± SD mm Hg	49 ± 23	56 ± 25	.049
P_{aO_2}/F_{IO_2}, mean ± SD mm Hg	173 ± 74	176 ± 86	.76
GCS, mean ± SD	14.8 ± 0.9	14.6 ± 1.3	.50
GCS = 15, n (%)	45 (90)	781 (86)	.53
GCS = 14, n (%)	2 (4)	73 (8)	.42
GCS ≤ 13, n (%)	3 (6)	57 (6)	>.99
Data collected at 1–2 h after initiation of NIV*			
S/T mode, n (%)	47 (94)	897 (98.5)	.054
CPAP mode, n (%)	3 (6)	14 (1.5)	.054
IPAP, mean ± SD cm H_2O	10 ± 4	15 ± 4	<.001
EPAP, mean ± SD cm H_2O	4 ± 1	5 ± 2	<.001
Mean arterial pressure, mean ± SD mm Hg	100 ± 20	91 ± 14	<.001
Heart rate, mean ± SD beats/min	127 ± 29	104 ± 22	<.001
Breathing frequency, mean ± SD breaths/min	34 ± 11	26 ± 7	<.001
pH, mean ± SD	7.39 ± 0.12	7.39 ± 0.09	.92
P_{aCO_2}, mean ± SD mm Hg	47 ± 20	54 ± 22	.045*
P_{aO_2}/F_{IO_2}, mean ± SD mm Hg	204 ± 101	206 ± 85	.92
Difference between beginning and 1–2 h after initiation of NIV, median (IQR)*			
Mean arterial pressure, mm Hg	−2 (−10 to 7)	6 (−1 to 16)	<.001
Heart rate, beats/min	−1 (−11 to 7)	8 (0–17)	<.001
Breathing frequency, breaths/min	0 (−5 to 4)	4 (0–8)	<.001
pH	−0.01 (−0.06 to 0.02)	−0.01 (−0.06 to 0.03)	.93
P_{aCO_2}, mm Hg	1 (−4 to 8)	1 (−4 to 8)	.77
P_{aO_2}/F_{IO_2}, mm Hg	−30 (−85 to 23)	−24 (−78 to 23)	.96

Normally distributed data are reported as mean ± SD, and non-normally distributed data are reported as median (interquartile range).
* In the intolerant group, these data were collected at termination of NIV in 4 subjects who received <1 h of NIV.
NIV = noninvasive ventilation
APACHE II = Acute Physiology and Chronic Health Evaluation II
GCS = Glasgow coma score
S/T = spontaneous/time
IPAP = inspiratory positive airway pressure
EPAP = expiratory positive airway pressure
IQR = interquartile range

defined as termination of NIV due to the subject's refusal to receive it because of discomfort, even after intermittent use was attempted.[16,17] We asked subjects why they refused to receive NIV and recorded their answers. After NIV was terminated, intubation was performed on subjects who met the criteria for intubation. Subjects who did not meet the criteria for intubation received oxygen therapy.

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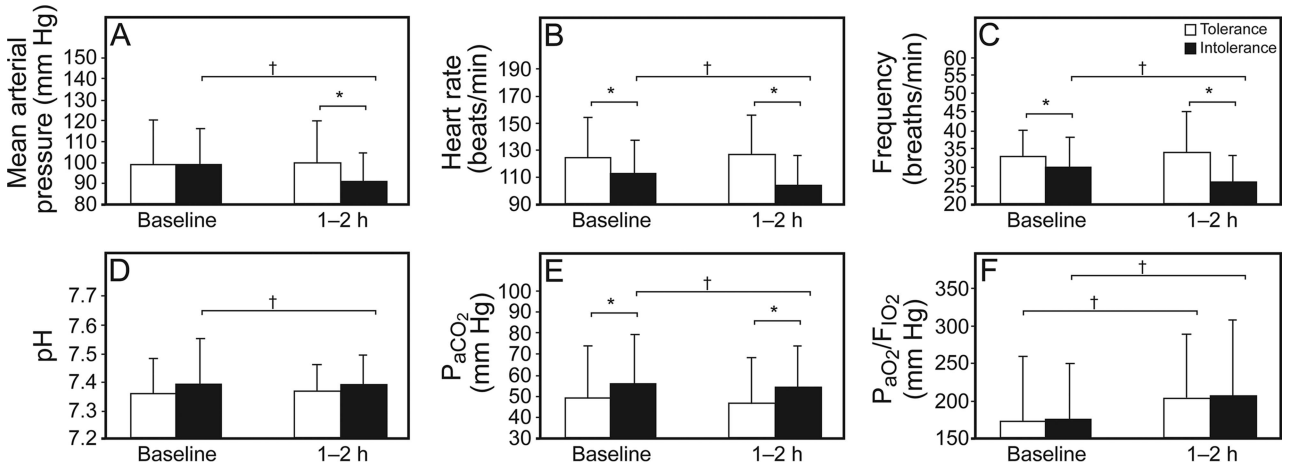

Fig. 2. Comparison of data between and among subjects with and without noninvasive ventilation intolerance. † $P < .05$, baseline versus 1–2 h of noninvasive ventilation. * $P < .05$, noninvasive ventilation intolerance versus tolerance.

Intubation was performed based on the following indicators (1 major criterion or at least 2 minor criteria after NIV intervention).[13] Major criteria were (1) respiratory arrest, (2) loss of consciousness, (3) hemodynamic instability, (4) inability to correct dyspnea, and (5) P_{aO_2}/F_{IO_2} <100 mm Hg. Minor criteria were (1) breathing frequency >35 breaths/min, (2) blood pH <7.30, (3) persistent tachypnea, (4) persistent activation of accessory respiratory muscles, and (5) P_{aO_2}/F_{IO_2} <200 mm Hg.

Outcomes, including duration of NIV, duration of ICU stay, and duration of hospital stay, were collected when subjects were discharged or died. For subjects who underwent intubation, the duration of invasive mechanical ventilation was also recorded.

Data were analyzed using SPSS 17.0 (SPSS, Chicago, Illinois). Normally distributed continuous variables were analyzed with the unpaired Student *t* test. Abnormally distributed continuous variables were analyzed with the Mann-Whitney *U* test. Categorical variables were analyzed with the chi-square test or Fisher exact test when appropriate. Variables with a *P* value of <.2 in univariate analysis and other variables clinically considered to be associated with NIV intolerance were entered into a multivariate logistic regression analysis.[18] However, the pressure of the ventilator was not included in the multivariate logistic regression analysis; because we believed NIV intolerance would result in low pressures that subjects could tolerate. At the start of NIV, age, sex, diagnosis, APACHE II score, heart rate, breathing frequency, pH, P_{aCO_2}, and P_{aO_2}/F_{IO_2} were analyzed with stepwise multiple logistic regression analysis. Data collected after 1–2 h of NIV, including ventilator mode, mean arterial pressure, heart rate, breathing frequency, pH, P_{aCO_2}, and P_{aO_2}/F_{IO_2}, were also analyzed with stepwise multiple logistic regression analysis. $P < .05$ was considered significant.

Table 2. Independent Risk Factors for Noninvasive Ventilation Intolerance Identified by Multivariate Logistic Regression Analysis

Risk Factors	OR (95% CI)	*P*
Data collected at NIV initiation		
Age, per y	0.979 (0.963–0.996)	.02
Heart rate, beats/min	1.018 (1.006–1.030)	.002
Data collected at 1–2 h initiation of NIV*		
Heart rate, beats/min	1.030 (1.016–1.044)	<.001
Breathing frequency, breaths/min	1.062 (1.027–1.099)	<.001

* In the intolerant group, these data were collected at termination of NIV in 4 subjects who received < 1 h of NIV.
OR = odds ratio
NIV = noninvasive ventilation

Results

A total of 961 subjects were enrolled in the study. Of these, 50 subjects (5.2%) experienced NIV intolerance. NIV intolerance occurred a median of 2.4 h after the initiation of NIV (Fig. 1). Of 257 subjects who required intubation, 22 (8.6%) subjects had experienced NIV intolerance. Table 1 and Figure 2 compare the data for subjects with and without NIV intolerance.

Independent risk factors of NIV intolerance were identified by multivariate logistic regression analysis (Table 2). At baseline, age was a protective factor for NIV intolerance; however, heart rate was a risk factor for NIV intolerance. After 1–2 h of NIV, independent risk factors for NIV intolerance were heart rate and breathing frequency.

Figure 3 shows the reasons intolerant subjects refused to receive NIV. Table 3 summarizes the outcomes for subjects with and without NIV intolerance. Intolerant subjects had a higher intubation rate (44.0% vs 25.8%, $P = .008$) and a trend toward higher mortality (34.0% vs 22.4%,

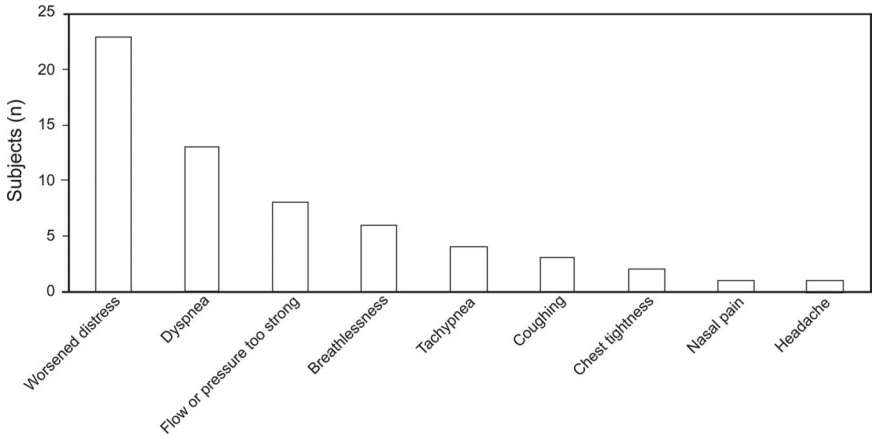

Fig. 3. Reasons given by subjects for refusing noninvasive ventilation, recorded at its termination.

Table 3. Outcomes for Subjects With and Without Noninvasive Ventilation Intolerance

Outcome	NIV Intolerance (n = 50 [5.2%])	NIV Tolerance (n = 911 [94.8%])	P
ICU stay, median (IQR) d	5.9 (2.6–10.1)	6.8 (3.9–11.9)	.24
Hospital stay, median (IQR) d	12.8 (6.8–18.0)	14.6 (8.5–24.0)	.10
Intubation, n (%)	22 (44.0)	235 (25.8)	.008
Mortality, n (%)	17 (34.0)	204 (22.4)	.08

NIV = noninvasive ventilation
IQR = interquartile range

P = .08). Subgroup analysis was performed on subjects who underwent intubation (Table 4). Time from initiation of NIV to intubation was much shorter in NIV-intolerant subjects than in tolerant subjects (2.4 h vs 60 h, $P < .001$).

Discussion

Here we report the rate of NIV intolerance in a relatively large sample of subjects. We found that age, heart rate, breathing frequency, and P_{aCO_2} collected before NIV began and mean arterial pressure, heart rate, breathing frequency, and P_{aCO_2} collected after 1–2 h of NIV were associated with NIV failure. Moreover, age and heart rate collected before NIV began and heart rate and breathing frequency collected after 1–2 h of NIV were independent risk factors for NIV intolerance. NIV intolerance in turn was associated with intubation and mortality. In addition, time from the initiation of NIV to intubation was much shorter in NIV-intolerant subjects than in tolerant subjects.

Previous studies have reported NIV intolerance rates of 11.4–15% in subjects who used an oronasal mask.[16,17] These studies have strictly defined NIV intolerance as the subject's refusal to continue NIV because of discomfort caused by the mask. However, the sample size was small in the 2 studies (35 and 59 subjects, respectively). This may have led to inaccuracy in the reported rates of NIV intolerance. In our study, we enrolled 961 subjects. Our rate of NIV intolerance may be more accurate than others. However, we administered NIV to some subjects with mild acute respiratory failure. The subjects in our study may have had less severe respiratory failure than those in previous studies. This may be a reason for the relatively low rate of NIV intolerance in the present study.

At the initiation of NIV, intolerant subjects had a higher heart rate and breathing frequency than tolerant subjects. This may indicate that the condition of the intolerant subjects was more serious than that of the tolerant subjects, although APACHE II scores were not significantly different in the 2 groups. After 1–2 h of NIV, the vital signs and arterial blood gas results of the tolerant subjects had significantly improved. However, these variables did not improve in the intolerant subjects, except for P_{aO_2}/F_{IO_2} (Fig. 2). In addition, the time from initiation of NIV to intubation was a median 2.4 h in the intolerant subjects, much shorter than in the tolerant subjects. NIV intolerance probably worsened the subjects' condition or at least did not improve it. Consequently, intubation was performed earlier in intolerant subjects.

NIV intolerance is common in patients with acute respiratory failure. However, few studies have reported why subjects cannot tolerate this device. In our study, we asked intolerant subjects why they refused NIV. The reasons varied, but 3 complaints were frequently heard: NIV worsened subjects' distress (46%), NIV resulted in dyspnea (26%), and the flow or pressure of NIV was too strong to bear (16%). These factors can be due to patient-ventilator asynchrony.[19] However, some factors, such as NIV giving subjects a continuous cough or headache, cannot be explained by patient-ventilator asynchrony. This may be an interesting issue for further exploration.

Previous studies have reported several methods for dealing with NIV intolerance. Antonelli et al[20] reported that

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Table 4. Comparison of Data for Subjects With and Without Noninvasive Ventilation Intolerance Who Underwent Intubation

Factors	NIV Intolerance (n = 22)	NIV Tolerance (n = 235)	P
Age, mean ± SD y	56.3 ± 23.5	69.6 ± 13.6	<.001
Male/female, *n*	14/8	178/57	.21
Diagnosis			
COPD exacerbation, *n* (%)	8 (36.4)	101 (43)	.65
Pneumonia, *n* (%)	11 (50)	78 (33.2)	.16
ARDS, *n* (%)	2 (9.1)	21 (8.9)	>.99
Asthma, *n* (%)	0 (0)	7 (3)	>.99
Pulmonary cancer, *n* (%)	1 (4.5)	9 (3.8)	.60
Pulmonary embolism, *n* (%)	0 (0)	3 (1.3)	>.99
Other, *n* (%)	0 (0)	16 (6.8)	.38
GCS, mean ± SD	14.5 ± 1.3	14.3 ± 1.8	.75
GCS = 15, *n* (%)	17 (77)	181 (77)	>.99
GCS = 14, *n* (%)	2 (9)	30 (13)	>.99
GCS ≤ 13, *n* (%)	3 (14)	24 (10)	.71
Data collected at NIV initiation			
APACHE II score, mean ± SD	20.5 ± 6.9	20.0 ± 5.7	.68
Mean arterial pressure, mean ± SD mm Hg	99 ± 23	98 ± 19	.87
Heart rate, mean ± SD beats/min	137 ± 29	121 ± 24	.004
Respiratory rate, mean ± SD breaths/min	35 ± 8	32 ± 7	.11
pH, mean ± SD	7.30 ± 0.20	7.37 ± 0.12	.02
P_{aCO_2}, mean ± SD mm Hg	46 ± 27	51 ± 25	.39
P_{aO_2}/F_{IO_2}, mean ± SD mm Hg	157 ± 82	153 ± 82	.80
Data collected at 1–2 h after initiation of NIV, mean ± SD*			
IPAP, cm H_2O	11 ± 4	15 ± 4	<.001
EPAP, cm H_2O	4 ± 1	5 ± 2	.001
Mean artery pressure, mm Hg	102 ± 23	93 ± 16	.01
Heart rate, beats/min	143 ± 24	113 ± 23	<.001
Breathing frequency, breaths/min	39 ± 13	29 ± 9	<.001
pH	7.34 ± 0.13	7.38 ± 0.12	.21
P_{aCO_2}, mm Hg	46 ± 25	52 ± 26	.36
P_{aO_2}/F_{IO_2}, mm Hg	180 ± 107	158 ± 83	.26
Time from NIV initiation to intubation, median (IQR) h	2.4 (1.9–3.0)	60 (17–144)	<.001
Duration of invasive mechanical ventilation, median (IQR) d	5.2 (0.7–10.1)	5.0 (2.4–7.7)	.76
ICU stay, median (IQR) d	8.9 (1.2–13.4)	9.0 (4.6–15.6)	.17
Hospital stay, median (IQR) d	10.1 (6.1–15.7)	14.7 (6.5–24.2)	.25
Mortality, *n* (%)	14 (63.6)	150 (63.8)	>.99

Normally distributed data are reported as mean ± SD, and non-normally distributed data are reported as median and interquartile range.
* In the intolerant group, these data were collected at termination of NIV in 2 subjects who received <1 h of NIV.
NIV = noninvasive ventilation
GCS = Glasgow coma score
APACHE II = Acute Physiology and Chronic Health Evaluation II
IPAP = inspiratory positive airway pressure
EPAP = expiratory positive airway pressure
IQR = interquartile range

subjects who used a facial mask had a higher proportion of NIV failure resulting from NIV intolerance than those who used a helmet. Roy et al[21] reported that vital signs and arterial blood gas tests improved in subjects who could not tolerate a nasal mask or oronasal mask and switched to a full face mask. This indicates that changing the interface may improve NIV tolerance in some subjects. In addition, Rocco et al[22] reported that analgesia and sedation improved tolerance in subjects who could not tolerate a helmet or total face mask. Although analgesia and sedation may improve NIV tolerance, they should only be used by trained ICU physicians and with selected patients.

Another interesting finding in our study is that not all NIV-intolerant subjects required intubation because we enrolled some subjects with mild respiratory failure. The therapeutic effect of NIV on managing respiratory failure was between those of oxygen therapy and invasive mechanical ventilation. There are large areas of overlap be-

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tween oxygen therapy and invasive mechanical ventilation. In subjects with mild respiratory failure, the intubation rate was very low. However, 2 previous studies reported that subjects with mild respiratory failure received benefits from NIV.[23,24] Thus, the use of NIV in patients with mild respiratory failure is reasonable but perhaps unnecessary.

Our study has several limitations. First, our hospital only used oronasal masks for NIV; thus, these results reflect NIV intolerance in subjects using an oronasal mask only. However, the oronasal mask is the most common interface for NIV. In Europe and India, nearly 70% of physicians use oronasal masks.[25,26] In the United States, 76% of emergency physicians reported using oronasal masks in >50% of cases, and in 17% of centers, only oronasal masks were used.[27] Thus, our study reflects most cases of NIV intolerance. Second, NIV was initiated in some subjects with mild acute respiratory failure. Perhaps some subjects did not really need NIV. Third, air leaks around the oronasal mask may play an important role in NIV intolerance. We did not record air leaks, although we kept them at <30 L/min. Fourth, organ dysfunction may influence NIV intolerance, but this information was lacking. The results may be skewed because of these limitations.

Conclusion

This study shows a rate of NIV intolerance of 5.2% in subjects using an oronasal mask. Younger subjects with a high heart rate and breathing frequency were more likely to experience NIV intolerance. They showed no improvement in mean arterial pressure, heart rate, or breathing frequency after 1–2 h of NIV. Moreover, they were more likely to experience intubation and to experience it earlier.

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