2016 Year in Review: Noninvasive Ventilation

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Noninvasive ventilation (NIV) is an important modality in clinical practice and is extensively studied. The growth of literature related to NIV over the past 20 years has made it difficult for clinicians to stay up to date with current best practice. This article will summarize some of the important NIV literature published in 2016 and describe any impact it may have related to the clinical use of NIV. *Key words: noninvasive ventilation; respiratory failure; high flow nasal cannula; extubation failure; immunocompromised.* [Respir Care 2017;62(5):623–628. © 2017 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) is a common and extensively studied therapy option for the management of respiratory failure. The current landscape of NIV literature has an increased focus on predicting failure to prevent delaying intubation, treating specific subgroups of patients, and comparing different interface options for treating respiratory failure. This article will group some of the important NIV literature published in 2016 into treatment categories, summarize the findings, and provide insight into how it may impact current practice.

NIV Compared With High-Flow Nasal Cannula

Immunocompromised Patients

The use of high-flow nasal cannula (HFNC) in the management of acute hypoxemic respiratory failure gained a significant amount of popularity after the FLORALI study was published in 2015.[1] In the FLORALI trial, the use of HFNC in the treatment of acute hypoxemic respiratory

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failure resulted in a lower 90-d mortality compared with standard oxygen therapy and NIV (HFNC 12% vs standard oxygen therapy 23% vs NIV 28%). A post hoc analysis of the FLORALI study published in 2016 by Frat et al[2] looked at only the subjects enrolled in the study who were immunocompromised. There were 82 subjects classified as immunocompromised: 26 treated with HFNC, 26 treated with NIV, and 30 treated with standard oxygen therapy. After a multivariate logistic regression, age and the use of NIV as a first-line therapy were independently associated with higher rates of endotracheal intubation and mortality.

A retrospective study by Coudroy et al[3] compared HFNC with NIV as first-line therapy in 115 immunocompromised subjects. The primary outcome was mortality at 28 d, and the secondary outcomes were intubation rate, duration of mechanical ventilation and ICU stay, ICU mortality, and variables associated with intubation and mortality at day 28. There was significantly lower 28-d mortality (20% vs 40%), intubation rates (35% vs 55%), and ICU mortality (15% vs 36%) for subjects treated with HFNC as first-line therapy. In a multivariate analysis of variables associated with outcomes, NIV as first-line therapy was one of the variables independently associated with intubation and 28-d mortality. Furthermore, the authors compared propensity score-matched subjects, balanced for all other variables except NIV as first-line therapy and found that there was a greater difference in 28-d mortality (15% vs 42%), intubation rates (30% vs 54%), and mortality of subjects who were intubated (40% vs 77%). This study had several limitations, including its retrospective design and the fact that baseline characteristics were not matched evenly (subjects treated with NIV had higher CO_2 levels overall). However, severity of illness at baseline was not different between groups.

These studies comparing NIV with HFNC in immunocompromised patients are limited by design, and have only a limited number of subjects. However, they highlight the possibility that perhaps the least invasive therapy option for immunocompromised patients results in better outcomes, and avoiding intubation is an important goal of therapy when possible.

Postextubation in Patients at Risk of Extubation Failure

In a large randomized trial of 604 subjects, Hernández et al[4] randomized subjects at risk of extubation failure to receive HFNC or NIV for 24 h after extubation. The study was a non-inferiority study with a non-inferiority margin of 10%. A non-inferiority study is often used when the experiment is being compared with an intervention already supported by the literature, and in this example, postextubation NIV for patients at high risk of extubation failure is supported.[5] The primary outcome was re-intubation and postextubation failure within 72 h, and secondary outcomes included respiratory infection, sepsis, multi-organ failure, length of stay, mortality, adverse events, and time to re-intubation. The all-cause re-intubation for NIV versus HFNC was 19.1% versus 22.8% for a difference of −3.7% which did not exceed the non-inferiority margin. Postextubation respiratory failure for NIV versus HFNC was 39.8% versus 26.9% for a difference of 12.9%, which is $>$ 10% but is in favor of HFNC. Adverse events were higher in the NIV group, and ICU and hospital length of stay were shorter in the HFNC. The limitations of this study include the lack of a prospectively validated model that accurately predicts extubation failure. Therefore, the inclusion criteria for the study were quite extensive. Also, the number of subjects with an admission diagnosis of COPD exacerbation were not balanced at baseline. Fewer subjects with COPD exacerbation were treated with HFNC than with NIV postextubation (5.2% vs 10.5%).

The amount of literature regarding HFNC is growing rapidly, and more comparisons with HFNC are likely to be investigated. Clinicians must understand that currently there is established evidence for using NIV to prevent extubation failure in high-risk patients. However, for patients who do not tolerate NIV, it is valuable to know that this type of non-inferiority study has been done to support using HFNC as well.

Hypoxemic Respiratory Failure Following Abdominal Surgery

A randomized clinical trial by Jaber et al[6] included 293 subjects who developed hypoxemic respiratory failure within 7 d of undergoing abdominal surgery. The subjects were randomly assigned treatment by NIV or standard oxygen therapy to manage their symptoms. The primary outcome was re-intubation within 7 d of surgery, and secondary outcomes included re-intubation by day 30, health care-associated infections, and mortality. The primary outcome of re-intubation within 7 d was lower in the NIV group compared with the standard oxygen therapy group (33.1% vs 45.5%). Subjects treated with NIV also had lower health care-associated infections and significantly more ventilator-free days. As is common with other NIV clinical trials, the interventions cannot be blinded and therefore have the limitation of potential bias for re-intubation. To try to avoid bias, this study (and many others) create strict predetermined criteria for re-intubation, but this still does not eliminate the possibility of bias. There also appeared to be more subjects with COPD as a comorbidity randomized to the NIV group. However, hypercapnic failure was not a cause of respiratory failure in this study. Despite these limitations, the findings of this study

support the use of NIV to treat acute hypoxemic failure following abdominal surgery.

Predicting NIV Failure

Different Age Groups

Many NIV studies include patients admitted to specific areas of a hospital (eg, ICU, emergency department). This tends to underestimate the real-life outcomes of NIV therapy delivered outside of these areas. The study by Ozsancak Ugurlu et al[7] included 1,225 ventilator starts (invasive and noninvasive) in 8 different hospitals. The study included subjects receiving ventilation for acute respiratory failure (both hypoxemic and hypercapnic) in all areas of the hospital. The purpose of the study was to compare various age groups, their characteristics, and outcomes. The authors were correct in their hypothesis that NIV was most often used in older patients. In subjects 65 y of age and older, NIV made up nearly half of all ventilation starts. The most common reasons for NIV in this age group were acute-on-chronic lung disease and cardiogenic pulmonary edema. An interesting finding was that there was no significant difference in success rates or mortality between age groups. This was the same with or without the presence of a do not intubate order. There was a significantly longer hospital stay and duration of mechanical ventilation in the 18–44-y age group and a slightly longer duration of NIV for subjects in the 65–70-y age group. Although it was limited by its observational design, this study demonstrated a realistic snapshot of actual NIV use across a mix of academic and community hospitals.

ARDS: Predictors of Failure

Using NIV in patients with ARDS has been controversial and has been associated with high failure rates.[8] A prospective observational cohort study by Chawla et al[9] included all subjects diagnosed with ARDS according to the Berlin definition.[10] The aim of the study was to determine factors associated with NIV failure in this population so that NIV may be used appropriately and not delay intubation. The overall failure rate of NIV was 43.8%, and the factors associated with NIV failure were low baseline P_{aO_2}/F_{IO_2} ratio, presence of septic shock, and severity of ARDS. The Berlin definition defines ARDS severity using P_{aO_2}/F_{IO_2} as follows: mild (200–300) moderate (100–200), and severe (< 100).[10] There were significant differences in failure rates between ARDS severity groups (mild 18.9%, moderate 73%, severe 83.3%). The overall ICU mortality rate was 37.1%, and the factors associated with ICU mortality were high APACHE II (Acute Physiology and Chronic Health Evaluation II) score, low baseline P_{aO_2}/F_{IO_2}, presence of septic shock, and severity of ARDS. The mortality rates of moderate and severe ARDS were similar (46.5 and 45%), but the mortality rate for mild ARDS was significantly lower (20.3%). This study highlights the significant risk of NIV failure when used in patients with moderate and severe ARDS, whereas it supports the idea that in the absence of septic shock, patients with mild ARDS ($P_{aO_2}/F_{IO_2} >$ than 200) may be successfully managed with NIV.

The Role of Tidal Volume in De Novo Hypoxemic Respiratory Failure

A study by Carteaux et al[11] looked at predictors of NIV failure in subjects with de novo acute hypoxemic respiratory failure. The authors took a different approach by also assessing tidal volume and ventilation. Factors associated with NIV failure included immunosuppression, lower P_{aO_2}/F_{IO_2} before NIV initiation, Simplified Acute Physiology Score II at hospital admission, Sequential Organ Failure Assessment score at initiation of NIV, minute ventilation, and mean tidal volume during NIV. Failure of NIV was more accurately predicted by tidal volume in subjects with moderate and severe hypoxemia ($P_{aO_2}/F_{IO_2} < 200$), with the failure threshold being 9.5 mL/kg of predicted body weight. In subjects with $P_{aO_2}/F_{IO_2} < 200$, a mean tidal volume > 9.5 mL/kg of predicted body weight predicted NIV failure with a sensitivity of 82% and specificity of 87%. This was the first study to investigate the role of tidal volume in predicting NIV success or failure. Tidal volume monitoring has become an accepted standard for patients being invasively ventilated, and this study perhaps demonstrates the need for closer monitoring of tidal volume during NIV in our daily practice.

HACOR Score: Predicting NIV Failure in Hypoxemic Patients

The causes of acute hypoxemic respiratory failure are much more heterogeneous and can be significantly more complex than respiratory failure due to COPD exacerbation. This reality is most likely the underlying cause of the conflicting evidence present in the literature.[12] The key to successfully managing this patient population appears to lie in the early recognition of key variables associated with failure and acting on them in a timely fashion to avoid delaying intubation.[12,13] Many variables associated with NIV failure when treating acute hypoxemic respiratory failure patients are easily evaluated, but assessing risk of failure with only a few variables may not have predictive power.[14] The study by Duan et al[14] tested the hypothesis that combining several variables into a score could increase the predictive power. The goal of the study was to first use a test group to determine several easily obtained variables that were independently associated with NIV

Table 1. HACOR Score

Parameter Range	Score
Heart rate	
≤120	0
≥121	1
pH	
≥7.35	0
7.30–7.34	2
7.25–7.29	3
<7.25	4
GCS	
15	0
13–14	2
11–12	5
≤10	10
P_{aO_2}/F_{IO_2}	
≥201	0
176–200	2
151–175	3
126–150	4
101–125	5
≤100	6
Breathing frequency	
≤30	0
31–35	1
36–40	2
41–45	3
≥46	4

In patients receiving noninvasive ventilation for hypoxemic respiratory failure, a HACOR score >5 at 1 h of noninvasive ventilation predicted failure.

failure. With these variables, they would create a scoring system where numbers are given for various value ranges and then test this scoring system with a validation group of subjects. They included subjects with a $P_{aO_2}/F_{IO_2} < 300$, and patients with COPD were excluded. They enrolled 449 subjects in the test group, followed by 358 subjects in the validation group. After the test group, they determined the variables to include in the scoring system. The scoring system consisted of heart rate, acidosis (assessed by pH), consciousness (assessed by Glasgow coma scale), oxygenation (assessed by P_{aO_2}/F_{IO_2}), and breathing frequency (Table 1). After further analysis, they determined that a HACOR score > 5 at 1 h of NIV had a diagnostic accuracy for predicting NIV failure of 81.8% in the test group and 86.0% in the validation group. When combing all of the subjects, those with a HACOR score ≤ 5 at 1 h or NIV had a failure rate of 18.4% with a hospital mortality of 21.6%, and subjects with a HACOR score > 5 at 1 h of NIV had a failure rate of 87.1% with a hospital mortality of 65.2%. For subjects who had a HACOR score of > 5, early intubation resulted in significantly lower mortality than late intubation (within 12 h 66%; after 12 h 79%). Limitations of the study include the limited numbers of certain subgroups of patients, which limits the generalizability of the scoring system. Additionally, their early versus late intubation analysis was a secondary analysis. However, calculating the HACOR score is simple and convenient and clearly deserves further study to confirm its true potential. This could be a promising tool for the bedside clinician to help improve patient outcomes.

It is evident that choosing whether to deliver NIV in patients in acute hypoxemic respiratory failure is difficult. If the patient has been diagnosed as ARDS and has a $P_{aO_2}/F_{IO_2} < 200$, it seems clear that NIV is not the safest option. However, a low baseline P_{aO_2}/F_{IO_2} with acute hypoxemic respiratory failure is still a risk factor for NIV failure without the classification of ARDS. It is up to the bedside clinician to recognized and detect early risk factors of NIV failure to ensure that there is no delay in intubation.

NIV Interfaces

Helmet Versus Face Mask

The key difference between invasive ventilation and NIV is the use of an interface. The correct choice of interface needs to consider the advantages and disadvantages for delivering NIV.[15] Although there is growing evidence against using NIV for the treatment of ARDS, a study by Patel et al[16] was done to compare the traditional face mask approach with that of a helmet interface. A total of 83 subjects receiving NIV for a minimum of 8 h for the treatment of ARDS as defined by the Berlin criteria were randomized to continue the use of the face mask interface or be switched to a helmet interface. The primary outcome assessed was the need for endotracheal intubation. The secondary outcomes were 28-d invasive ventilator-free days, length of ICU and hospital stay, 90-d mortality, and adverse events. The study had initially intended to enroll 200 subjects but was stopped early for both efficacy and safety because of the significant difference in 90-d mortality between the 2 groups found at an interim analysis (56.4% vs 34.1%, in favor of the helmet interface). This significant benefit was probably due to the overwhelming difference in the primary outcome of treatment failure resulting in endotracheal intubation (61.5% vs 18.2%). Ventilator-free days and length of ICU stay were also significantly lower for subjects treated with the helmet interface. There were no significant differences in adverse events. The authors felt that the ability to deliver higher PEEP levels (mean level of 5.8 vs 8.0) with the helmet interface may have contributed to their results. Some of the limitations are that the study was a single-center study that was stopped early, it used a novel interface that is not available for use in North America, and due to the nature of the study, the interventions could not be blinded.

Table 2. Brief Summary of Article Take-Home Messages

Author	Subjects	Take-Home Message Summary
Frat et al[2]	NIV vs HFNC for immunocompromised subjects	HFNC was associated with better outcomes compared with NIV in immunocompromised subjects.
Coudroy et al[3]	NIV vs HFNC for immunocompromised subjects	HFNC was associated with better outcomes compared with NIV in immunocompromised subjects.
Hernandéz et al[4]	HFNC vs NIV high-risk extubation	Immediately post-extubation, HFNC was not inferior to NIV in preventing extubation failure in subjects at risk of extubation failure.
Jaber et al[6]	Hypoxemic failure after abdominal surgery	Treatment with NIV for hypoxemic respiratory failure after abdominal surgery had better outcomes than standard oxygen therapy.
Ozsancak Ugurlu et al[7]	NIV across different age groups	Success and mortality were similar between different age groups regardless of DNI status. NIV was used more often in subjects >65 y old for acute-on-chronic illness and cardiogenic pulmonary edema.
Chawla et al[9]	ARDS: predictors of NIV failure	Mild ARDS may be safely treated with NIV. Moderate and severe ARDS have very high NIV failure rates.
Carteaux et al[11]	De novo hypoxemic failure: role of tidal volume	In subjects with de novo hypoxemic respiratory failure and a $P_{aO_2}/F_{IO_2} \leq 200$, a mean expired tidal volume > 9.5 mL/kg was a predictor of NIV failure.
Duan et al[14]	HACOR score	In subjects receiving NIV for hypoxemic respiratory failure, a HACOR score >5 at 1 h of NIV predicted NIV failure. Early intubation may lower mortality.
Patel et al[16]	Helmet vs face mask for NIV treatment of ARDS	For the NIV treatment of ARDS, the helmet interface resulted in lower intubation and mortality rates and less time on the ventilator compared with face mask.
Liu et al[17]	Helmet interface meta-analysis	The helmet interface had lower intubation and mortality rates, without significant CO_2 clearance issues. However, CO_2 clearance data had high heterogeneity.
Korang et al[18]	NIV for acute asthma in children	Current evidence does not confirm or reject the effects of NIV for the treatment of acute asthma in children.

NIV = noninvasive ventilation
HFNC = high-flow nasal cannula
DNI = do not intubate

This was also a small study, which makes it difficult to consider these results as high-level evidence.

Concerns over P_{aCO_2} clearance using a helmet were addressed by ensuring that the inspiratory flows while using the helmet interface were > 100 L/min. This was achieved using modest levels of pressure support (5.6–10.0 cm H_2O). It is also worth noting that the helmet interface must be used with a dual limb circuit, which excludes many standalone NIV devices from being used.

Helmet Meta-Analysis

A systematic review and meta-analysis by Liu et al[17] compared the helmet interface with other mask devices. The analysis included 11 studies composed of both randomized and case-controlled trials. It looked at outcomes such as mortality, intubation rate, and whether the helmet interface causes an increase in P_{aCO_2} due to its design. The analysis favored the helmet interface with regard to mortality and intubation rates and claimed that the helmet interface did not cause an increase in P_{aCO_2}. However, the evidence assessing whether the helmet increased P_{aCO_2} had a significant amount of heterogeneity ($I^2 = 72\%$) and therefore should be cautiously interpreted. This study had several limitations, including the variety of control interfaces and the inconsistency of NIV settings between studies, but this article is still important to highlight the need for larger randomized trials.

The helmet interface is not a new interface, and research continues to evaluate its utility. The results of the study by Patel et al[16] highlight the need for further study to determine whether the risk of treating ARDS with NIV truly lies in the choice of interface.

Pediatric Asthma

A Cochrane review was published regarding NIV for acute asthma in children.[18] The authors describe the cur-

rent landscape of NIV used to treat asthma in children as increasing but without supportive evidence. Unfortunately, due to the low numbers of studies (2 very small randomized controlled trials for a total of only 40 subjects), a recommendation cannot be made. The studies were of low numbers and quality and with serious risk of bias. The current evidence does not confirm or reject the effects of NIV in treating acute asthma in children. Further study is clearly needed before its effects can be determined.

Summary

There is a rapidly growing literature base for NIV, and it is difficult for clinicians to stay up-to-date with current literature. The purpose of this article was to summarize some of the relevant literature to keep bedside clinicians informed (Table 2). The literature discussed in this review covers important aspects of NIV management, such as when HFNC may or may not be a better selection for patients, understanding predictors of NIV failure, preventing intubation in select patient populations, performance of different NIV interfaces, and highlighting an area where further research using NIV is needed to support or reject its use.

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