Incidence, Predictors, and Outcomes of Failure of Noninvasive Ventilation in Acute Heart Failure Hospitalization

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BACKGROUND: Some patients with acute heart failure (AHF) who are treated initially with noninvasive ventilation (NIV) will require endotracheal intubation, which indicates NIV failure. The incidence and prognosis of NIV failure in patients with AHF are not well characterized. METHODS: Using the National In-Patient Sample (NIS), we conducted a retrospective cohort study of subjects hospitalized with AHF between 2008 and 2014 who were treated with NIV within 24 h of hospital admission. We determined predictors of NIV failure and determined the association between NIV failure and in-hospital mortality using Cox proportional hazard models. RESULTS: Of 279,534 subjects hospitalized with AHF and treated with NIV, 4,257 (1.52%) failed NIV and required intubation. Cardiogenic shock (odds ratio 8.79, 95% CI 6.89–11.2) and in-hospital arrest (odds ratio 24.9, 95% CI 18.71–33.14) were associated with NIV failure. In-hospital mortality was 26.5% for NIV failure compared to 5.6% for those without NIV (*P* < .001). After adjustment for demographics, comorbidities, cardiogenic shock, and in-hospital arrest, NIV failure was associated with nearly a 2-fold risk of in-hospital mortality (odds ratio 1.95, 95% CI 1.59–2.40). CONCLUSIONS: Intubation after initial NIV treatment was required in 1.5% of subjects hospitalized with AHF and treated with NIV, and was associated with high in-hospital mortality. These findings can guide future prospective interventional trials and quality improvement ventures. *Key words: acute heart failure; respiratory failure; noninvasive ventilation; intubation.* [Respir Care 2020;65(10):1527–1533. © 2020 Daedalus Enterprises]

Introduction

Hospitalization for acute heart failure (AHF) is associated with respiratory failure and the need for respiratory support in a substantial and increasing number of cases.[1] Some patients with AHF who are initially supported with NIV will have progressive respiratory failure and will require endotracheal intubation. This clinical scenario describes a lack of response to NIV or a failure of NIV. Failure of NIV has been associated with excess mortality for patients with AHF,[2] yet further data are needed to clarify the magnitude of effect, which is important for prognostication and to guide intervention studies. The incidence of NIV failure in patients with AHF has been variable in prior studies,[3-11] and the lack of a comprehensive understanding of the incidence of NIV failure in patients with AHF represents a knowledge gap that is important for ICU triage and ICU and cardiac ICU staffing.[12-15] Finally, understanding the risk factors for NIV failure in patients with AHF is important to guide clinicians' choice of respiratory support modality.[9,16-22] To address these knowledge gaps, we conducted a nationwide cohort study of patients with AHF supported with NIV to determine the incidence and

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predictors of NIV failure and to characterize the magnitude of the association of NIV failure with mortality. We hypothesized that NIV failure would be associated with cardiogenic shock and noncardiac comorbidities and with excess mortality.

Methods

Study Population

The National In-Patient Sample (NIS) is a large database incorporating hospital data from in-patient facilities in the United States. All diagnoses and procedures in the NIS are identified with codes from the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). We assembled a cohort of all hospitalizations with a principal diagnosis of AHF based on ICD-9 codes 428.x, 402.x1, 404.x1, and 404.x3, which identify heart failure admissions with high sensitivity and specificity ($n = 6,534,675$ hospitalizations).[23] We adhered to the methodological checklist for research involving the NIS proposed by Khera and colleagues.[24] Our study population included all AHF hospitalizations with NIV use within the first 24 h between January 1, 2008, and December 31, 2014; we restricted NIV use to the first 24 h to ensure that the NIV use was related to the AHF episode rather than used for a subsequent cause of respiratory failure acquired during the hospitalization, such as aspiration or hospital-acquired pneumonia. For this analysis, we chose to focus on a pure heart failure population rather than those with primary acute coronary syndromes requiring respiratory support.[25] NIV was identified using code 93.90 based on previously published methodology.[26] Given that the NIS is a publicly available database containing no protected health information, the Johns Hopkins University Institutional Review Board deemed research with the NIS exempt from review.

Exposures and Outcomes

Our primary variable of interest was NIV failure, which we defined as a patient treated with NIV who required endotracheal intubation within 24 h after the initial application of NIV. We chose a priori to consider only intubation within this 24-h window after initial NIV was trialed, which was in turn within the first 24 h of admission. This decision was made to avoid confounding due to intubation for procedures or other complications that arose during the hospital stay. A total of 1,134 patients underwent intubation later in their hospital stay, and they were excluded. Endotracheal intubation was identified using ICD-9-CM code 96.7x for mechanical ventilation or 96.0 for endotracheal intubation, which are specific for receipt of mechanical ventilation (a list of ICD-9 codes used to identify other exposures is available in the supplementary table at http://www.rcjournal.com).[27,28]

> **QUICK LOOK**
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> **Current knowledge**
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> Hospitalization for acute heart failure (AHF) is associated with respiratory failure and the need for respiratory support in a substantial and increasing number of cases. In addition, some patients with AHF who are initially supported with NIV will have progressive respiratory failure and will require endotracheal intubation. The incidence of NIV failure in patients with AHF has been variable in prior studies, and the associated outcomes of NIV failure in AHF are not clear.
>
> **What this paper contributes to our knowledge**
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> We conducted a nationwide cohort study of patients with AHF who were treated with NIV. NIV failure occurred in 1.5% of all hospitalizations for AHF with NIV treatment, and the incidence is stable over time. Age and comorbidity are associated with lower risk of NIV failure, whereas cardiogenic shock and cardiac arrest are associated with dramatically higher odds of NIV failure. Patients with AHF who suffer NIV failure are at high risk of adverse outcome, and this did not decline over the study period.

Statistical Analysis

Subject characteristics and outcomes were compared between subjects with AHF who were treated with NIV and suffered NIV failure and subjects with AHF who were treated with NIV but did not experience NIV failure. The Pearson chi-square test was used for categorical variables, and linear regression (1-way analysis of variance) was used for continuous variables. Yearly rates of NIV failure were calculated per 1,000 hospitalizations for AHF. To assess the trend in in-hospital mortality over time among subjects with AHF who suffered NIV failure, clustered multivariable regression models adjusting for age and sex were constructed. To identify clinical factors associated with NIV failure, we constructed clustered survey-weighted logistic regression models with NIV failure as the dependent variable.

We determined the association of NIV failure with in-hospital mortality using Cox proportional hazard models censoring at hospital discharge or at 30-d of hospital stay. We used Stata/MP 13.0 (StataCorp, College Station, Texas) for analysis. A 2-tailed P value $< .05$ was considered statistically significant.

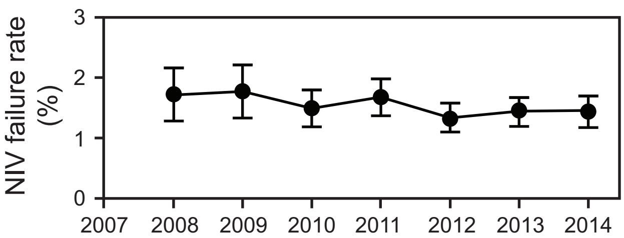

Fig. 1. Rate of NIV failure during the study period (P = .09 for trend). NIV = noninvasive mechanical ventilation.

Results

We included 279,534 hospitalizations for AHF that involved NIV use within the first 24 h. Of these, there were 4,257 instances of NIV failure within 24 hours of NIV use (1.5%). The rate of NIV failure was stable over the study period (Fig. 1, P = .09 for trend over time). The demographics of the study population are displayed in Table 1.

In-hospital outcomes for subjects with AHF treated with NIV are displayed in Table 2. In-hospital mortality for subjects with AHF and NIV failure was 26.5% compared to 5.6% for those successfully treated with NIV (P < .001).

Table 1. Demographics and Clinical Characteristics of the Study Population

	All	Heart Failure Without NIV Failure	Heart Failure With NIV Failure	P
Characteristics				
Age, y	72.1 ± 0.1	72.2 ± 0.1	68.4 ± 0.5	< .001
Gender				< .001
Male	132,446 (47.4)	130,023 (47.2)	2,423 (56.9)	
Female	147,087 (52.6)	145,253 (52.8)	1,834 (43.1)	
Race/Ethnicity				.02
White	186,550 (66.7)	183,920 (66.8)	2,630 (61.8)	
Black	60,602 (21.7)	59,473 (21.6)	1,129 (26.5)	
Hispanic	24,152 (8.6)	23,766 (8.6)	386 (9.1)	
Asian/Pacific Islander	6,992 (2.5)	6,900 (2.5)	91 (2.1)	
Native American	1,238 (0.4)	1,217 (0.4)	21 (0.5)	
Comorbidities				
Aortic valve disease	21,919 (7.8)	21,575 (7.8)	344 (8.1)	.78
Chronic pulmonary disease	146,086 (52.3)	144,084 (52.3)	2,003 (47.0)	.002
Chronic renal failure	129,169 (46.2)	127,223 (46.2)	1,946 (45.7)	.77
Congestive heart failure				< .001
HFrEF	89,477 (32.0)	88,455 (32.1)	1,022 (24.0)	
HFpEF	75,851 (27.1)	74,499 (27.1)	1,352 (31.8)	
Unspecified	114,206 (4.9)	112,322 (40.8)	1,883 (44.2)	
Coronary artery disease	143,258 (51.2)	141,187 (51.3)	2,071 (48.6)	.14
Diabetes mellitus	143,596 (51.4)	141,438 (51.4)	2,158 (5.7)	.69
Dyslipidemia	124,933 (44.7)	123,245 (44.8)	1,688 (39.7)	.003
Hypertension	196,198 (70.2)	193,332 (70.2)	2,866 (67.3)	.065
Mitral valve disease	30,061 (10.8)	29,529 (1.7)	532 (12.5)	.09
Obesity	80,030 (28.6)	78,781 (28.6)	1,248 (29.3)	.66
Peripheral vascular disease	37,736 (13.5)	37,233 (13.5)	502 (11.8)	.17
Previous myocardial infarction	41,383 (14.8)	40,801 (14.8)	581 (13.7)	.34
Previous percutaneous coronary intervention	31,039 (11.1)	30,598 (11.1)	441 (1.4)	.49
Previous coronary artery bypass graft	35,119 (12.6)	34,665 (12.6)	454 (1.7)	.08
Smoking	85,276 (3.5)	83,937 (3.5)	1,339 (31.5)	.55
Charlson comorbidity index				< .001
1	28,917 (10.3)	28,299 (10.3)	618 (14.5)	
2	60,284 (21.6)	59,253 (21.5)	1,031 (24.2)	
≥ 3	190,333 (68.1)	187,724 (68.2)	2,609 (61.3)	

Data are presented as n (%) or mean ± standard error. Heart failure without NIV: n = 275,276; Heart failure with NIV: n = 4,257; N = 279,534.
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
NIV = noninvasive ventilation

Table 2. Select Outcomes of Subjects Hospitalized With Heart Failure and Treated With NIV

Outcomes	All	Heart Failure Without NIV Failure	Heart Failure With NIV Failure	P
Acute kidney injury	77,498 (27.7)	75,532 (27.4)	1,966 (46.2)	< .001
Cardiogenic shock	4,333 (1.6)	3,718 (1.4)	615 (14.5)	< .001
Coronary angiography	16,401 (5.9)	15,865 (5.8)	536 (12.6)	< .001
Delirium	8,459 (3.0)	8,193 (3.0)	266 (6.3)	< .001
Length of hospital stay, d	6.04 (0.03)	5.99 (0.03)	9.46 (0.38)	< .001
In-hospital arrest	1,806 (0.6)	1,254 (0.4)	551 (12.9)	< .001
In-hospital mortality	16,450 (5.9)	15,322 (5.6)	1,128 (26.5)	< .001
Renal replacement	25,485 (9.1)	24,917 (9.1)	568 (13.3)	< .001
Total hospital charges, $	52,863 ± 745	51,883 ± 731	116,021 ± 5,347	< .001
Total hospital costs, $	14,378 ± 137	14,113 ± 132	31,365 ± 1,302	< .001

Data are presented as n (%) or mean ± standard error. Heart failure without NIV: $n = 275,276$; Heart failure with NIV: $n = 4,257$; $N = 279,534$.
NIV = noninvasive ventilation

Mortality in subjects with AHF who suffered NIV failure remained high throughout the study period ($P = .9$ for trend over time; see the supplementary figure at http://www.rcjournal.com).

Factors associated with NIV failure are displayed in Table 3. Older age and female sex were associated with lower odds of NIV failure, and greater comorbidity index was associated with lower odds of NIV failure. In-hospital cardiac arrest and cardiogenic shock were associated with higher odds of NIV failure.

Survival curves are shown in Figure 2, dichotomized by NIV failure. In a univariable model, NIV failure was associated with 2.55 times the risk of death (95% CI 2.18–2.99, $P < .001$) and nearly twice the risk of death after adjusting for age, sex, race, comorbidity index, cardiogenic shock, and in-hospital arrest (odds ratio 1.95, 95% CI 1.59–2.40, $P < .001$).

Discussion

We conducted a nationwide cohort study of subjects with AHF treated with NIV to investigate the incidence and prognostic connotation of NIV failure in hospitalizations for AHF. We report several major findings. First, NIV failure occurs in 1.5% of all AHF hospitalizations with NIV treatment, and the incidence is stable over time. Second, age and comorbidity are associated with a lower risk of NIV failure, whereas cardiogenic shock and cardiac arrest are associated with dramatically higher odds of NIV failure. Third, subjects with AHF who suffer NIV failure are at high risk of adverse outcomes, and this trend did not decline over the study period.

Incidence of NIV Failure in AHF

We report that 1.5% of hospitalizations for AHF nationwide treated initially with NIV subsequently required intubation. This rate is lower than other reports, which describe NIV failure rates of 25–30%, although few cardiac subjects were represented in those reports.[7,18,20,29] Pladeck et al[3] described a failure rate of 14% for subjects with cardiogenic pulmonary edema treated with NIV. These studies represent selected cohorts of ICU subjects. A prehospital study of subjects with cardiogenic pulmonary edema reported NIV failure rates of 0.7%, which is more in keeping with our results.[11] Therefore, NIV failure as a percentage of all heart failure hospitalizations is rare. Clinicians should therefore consider NIV failure as a rare event among all patients with AHF who are treated with NIV, which has implications for patient triage to cardiac ICU versus intermediate care as well as for staffing of respiratory programs within AHF programs. The low NIV failure rate in hospitalizations for AHF also suggests that exceedingly large numbers of patients would need to be included in an adequately powered study of therapies to reduce NIV failure.

Factors Associated With NIV Failure in AHF

We report that worsening cardiac disease, in the form of cardiogenic shock and cardiac arrest, are associated with NIV failure. Shock,[29] more severe heart failure,[7,9] multisystem organ failure defined by Sequential Organ Failure Assessment (SOFA) score,[22] frailty,[30] poor mental status,[8] weak cough,[31] and higher tidal volume on NIV[29] are factors that have been reported in the literature to be associated with NIV failure. Similar to our findings, Liu and colleagues[18] also reported that older age was associated with lower risk of NIV intolerance. We describe a somewhat counterintuitive finding that higher comorbidity index is associated with lower odds of NIV failure. These findings lead to a hypothesized conceptual model related to phenotypes of respiratory failure in the setting of AHF: one phenotype due to severe cardiac dysfunction and another due to milder cardiac dysfunction in the setting of advanced age

Table 3. Association Between Select Factors and Noninvasive Ventilation Failure for the Entire Study Period

Factor	Odds Ratio (95% CI)			
	Unadjusted	*P*	Adjusted	*P*
Heart failure type				
HFpEF	Reference		Reference	
HFrEF	1.57 (1.30–1.89)	< .001	1.20 (0.99–1.47)	.064
Unspecified	1.45 (1.22–1.73)	< .001	0.87 (0.82–0.92)	.031
Age*	0.84 (0.80–0.87)	<.001	< .001	< .001
Gender				
Male	Reference		Reference	
Female	0.68 (0.59–0.77)	< .001	0.83 (0.72–0.97)	.02
Race/Ethnicity				
White	Reference		Reference	
Black	1.32 (1.12–1.57)	.001	1.15 (0.94–1.39)	.17
Hispanic	1.14 (0.88–1.46)	.33	0.98 (0.74–1.29)	.88
Asian/Pacific Islander	0.92 (0.59–1.46)	.74	0.84 (0.51–1.36)	.47
Native American	1.21 (0.51–2.86)	.66	1.32 (0.54–3.21)	.54
Charlson comorbidity index				
1	Reference		Reference	
2	0.80 (0.64–1.0)	.051	0.85 (0.66–1.10)	.22
≥ 3	0.64 (0.52–0.78)	< .001	0.59 (0.44–0.80)	.001
Cardiogenic shock	12.34 (1.08–15.10)	< .001	8.79 (6.89–11.2)	< .001
Coronary artery disease	0.90 (0.78–1.03)	.14	0.93 (0.80–1.08)	.32
Aortic valve disease	1.03 (0.82–1.31)	.78	1.15 (0.89–1.49)	.29
Chronic pulmonary disease	0.81 (0.71–0.93)	.002	0.98 (0.84–1.15)	.64
Chronic renal failure	0.98 (0.85–1.12)	.64	1.20 (0.99–1.46)	.09
Hypertension	0.87 (0.76–1.01)	.07	1.09 (0.93–1.28)	.28
Mitral valve disease	1.15 (0.97–1.36)	.01	1.17 (0.95–1.44)	.15
Obesity	1.03 (0.89–1.20)	.66	0.91 (0.76–1.08)	.26
Smoking	1.05 (0.90–1.21)	.55	1.06 (0.90–1.24)	.50
Diabetes mellitus	0.97 (0.85–1.11)	.69	1.15 (0.97–1.36)	.10
In-hospital arrest	32.5 (25.68–41.12)	< .001	24.90 (18.71–33.14)	< .001

* Age is coded in decades.
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction

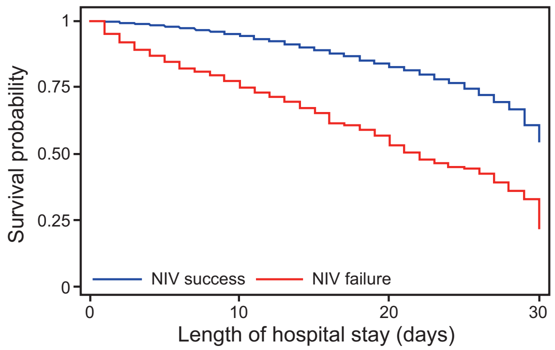

Fig. 2. Kaplan-Meier curves for 30-d in-hospital survival for subjects with acute heart failure receiving NIV with success or failure of this modality ($P < .001$ by log-rank). NIV = noninvasive mechanical ventilation.

and other comorbidities.[32,33] For example, a patient with advanced age, significant comorbidity, and less severe heart failure treated with NIV is more likely to succeed. On the other hand, patients with severe pump failure and pulmonary edema in that setting are less likely to respond to NIV. These factors associated with NIV failure can inform clinicians at the point of care as to the selection of therapy and increased vigilance and monitoring for early signs of NIV failure in subgroups of patients.

Prognosis of NIV Failure in AHF

The mortality rate was 26.5% in subjects with AHF who experienced NIV failure, which is comparable to our previous report of 27% mortality in AHF subjects treated with initial endotracheal intubation.[1] Mortality among patients who suffer NIV failure has not declined over time. Our findings reiterate the need for novel therapies in this high-risk patient population, which is an unmet need in critical care cardiology research.[17] Although this finding is intuitive, the magnitude of the effect is important to understand and should also serve as an impetus to improve these adverse outcomes. Clinicians could consider several potential means to improve this prognosis, such as improved patient selection for NIV, avoidance of inappropriate pharmacologic sedation for patients maintained on NIV,[34,35] intensivist and cardiac intensivist management,[36-39] and use of a dedicated respiratory therapy team to deliver NIV.[40] A compelling direction for future study is the use of high-flow nasal cannula therapy in these patients, which could reduce work of breathing and improve ventilation/perfusion matching, but this requires further research.[41-43] The specific research agenda should include exploration of the specific ventilation strategies that could forestall NIV failure. Multi-center prospective networks, such as the Cardiac Critical Care Trials Network, are well suited to conduct such studies.[44,45] It is plausible that patients at risk of NIV failure who move right to invaseive ventilation would have better prognosis; although our study did not suggest that finding, our results inform that future hypothesis, which should be investigated.

Limitations of our study include those inherent to the NIS, namely that the database consists of administrative and coding data that lack granular data regarding lab evaluation, specific echocardiography findings, indications, and cause-specific mortality. Furthermore, data from the specific ventilation modes or strategies and the specific reasons for NIV failure are not captured in this administrative database. Our inferences are limited by observational design, and thus we reported risk-factor associations rather than direct causes. In addition, the NIS entries are hospitalizations, not unique subjects, and we used survey weighting for national estimates. Although we adjusted for available clinically important covariates, such as comorbidity index and cardiogenic shock, unmeasured confounders could still be present.

Conclusions

In conclusion, 1.5% of subjects with AHF who were initially treated with NIV suffered NIV failure. Factors suggesting more severe cardiac disease such as cardiogenic shock and cardiac arrest were associated with NIV failure. NIV failure in patients with AHF is associated with substantially increased mortality compared to successful NIV treatment. Our findings can help guide clinicians in selecting patients with AHF who are more likely to have success with NIV treatment and can support the need for prospective interventional trials in this high-risk patient population.

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