Lowering P_{CO_2} With Noninvasive Ventilation Is Associated With Improved Survival in Chronic Hypercapnic Respiratory Failure

Jose Victor Jimenez, Jason Ackrivo, Jesse Y Hsu, Mathew W Wilson, Wassim W Labaki, John Hansen-Flaschen, Robert C Hyzy, and Philip J Choi

BACKGROUND: Chronic hypercapnic respiratory failure is associated with high mortality. Although previous work has demonstrated a mortality improvement with high-intensity noninvasive ventilation in COPD, it is unclear whether a P_{CO_2} reduction strategy is associated with improved outcomes in other populations of chronic hypercapnia. METHODS: The objective of this study was to investigate the association between P_{CO_2} reduction (by using transcutaneous P_{CO_2} as an estimate for P_{aCO_2} and survival in a broad population of individuals treated with noninvasive ventilation for chronic hypercapnia. We hypothesized that reductions in P_{CO_2} would be associated with improved survival. Therefore, we performed a cohort study of all the subjects evaluated from February 2012 to January 2021 for noninvasive ventilation initiation and/or optimization due to chronic hypercapnia at a home ventilation clinic in an academic center. We used multivariable Cox proportional hazard models with time-varying coefficients and P_{CO_2} as a time-varying covariate to test the association between P_{CO_2} and all-cause mortality and when adjusting for known cofounders. RESULTS: The mean ± SD age of 337 subjects was 57 ± 16 years, 37% women, and 85% white. In a univariate analysis, survival probability increased with reductions in P_{CO_2} to < 50 mm Hg after 90 d, and these remained significant after adjusting for age, sex, race, body mass index, diagnosis, Charlson comorbidity index, and baseline P_{CO_2}. In the multivariable analysis, the subjects who had a P_{aCO_2} < 50 mm Hg had a reduced mortality risk of 94% between 90 and 179 d (hazard ratio [HR] 0.06, 95% CI 0.01–0.50), 69% between 180 and 364 d (HR 0.31, 95% CI 0.12–0.79), and 73% for 365–730 d (HR 0.27, 95% CI 0.13–0.56). CONCLUSIONS: Reduction in P_{CO_2} from baseline for subjects with chronic hypercapnia treated with noninvasive ventilation was associated with improved survival. Management strategies should target the greatest attainable reductions in P_{CO_2}. *Key words: noninvasive ventilation; hypercapnia; respiratory insufficiency; mortality; amyotrophic lateral sclerosis; neuromuscular diseases; chronic obstructive pulmonary disease*. [Respir Care 2023;68(12):1613–1622. © 2023 Daedalus Enterprises]

Introduction

Elevated P_{CO_2} is associated with increased mortality and morbidity.[1,2] Although the causes are likely multifactorial, the association could be indirectly related to the severity of underlying disease (irrespective of the etiology) or directly through several pathophysiologic mechanisms. For example, elevated P_{CO_2} may hinder both skeletal muscle repair and host defenses against bacterial infections, which leads to increased mortality.[3,4] In addition, overloaded body tissue stores of CO_2 can result in a rapid, potentially intolerable further P_{CO_2} increments in response to an increase in CO_2 production or reduction in CO_2 removal.[5]

In the setting of chronic alveolar hypoventilation, noninvasive ventilation (NIV) can offload respiratory muscles while increasing alveolar ventilation to improve CO_2 clearance and reduce excess total body CO_2 stores.[5] NIV has been shown to improve survival in many conditions, including COPD,[6-8] obesity-hypoventilation syndrome,[9-11] and amyotrophic lateral sclerosis (ALS).[12] Although the importance of out-patient NIV therapy is becoming increasingly recognized,[13,14] there remain few data with regard to optimal treatment strategies and targets.

Transcutaneous carbon dioxide (P_{tcCO_2}) monitors are noninvasive devices that provide a real-time proxy for P_{CO_2} levels.[15] Their reliability and portability provide clinicians with a convenient, practical tool to follow P_{CO_2}. Aarrestad et al[16] reported that P_{tcCO_2} monitoring reflects P_{CO_2} in subjects who are stable and receiving NIV,[17] with limits of agreements within the proposed ranges.[18,19]

The purpose of this study was to determine whether reductions in P_{CO_2} (by using P_{tcCO_2} as an estimate for P_{aCO_2}) achieved through NIV are associated with improved survival in a sample of subjects with mixed etiologies of chronic hypercapnia. We hypothesized that reducing P_{CO_2} through NIV is associated with improved survival and that the survival benefit is dose-dependent based on the magnitude of P_{CO_2} decrease from baseline.

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QUICK LOOK

Current knowledge

Chronic compensated hypercapnia is associated with increased mortality and morbidity. In the setting of chronic alveolar hypoventilation, noninvasive ventilation can offload respiratory muscles while increasing alveolar ventilation and reducing excess total body P_{CO_2} stores.

What this paper contributes to our knowledge

The reduction in P_{CO_2} levels by using noninvasive ventilation is associated with improved survival in chronic hypercapnic respiratory failure. Larger reductions in P_{CO_2} had a stronger association with survival. Reductions of P_{CO_2} to levels < 50 mm Hg were achieved in most subjects.

Methods

We conducted a retrospective cohort study of adult subjects ($\geq$18 years) with chronic hypercapnic respiratory failure of any cause assessed for NIV initiation or optimization by the assisted ventilation clinic at a reference academic center. The institutional review board approved this study (HUM00162425) and waived the informed consent requirement for data collection. By using existing clinic patient databases, we identified all patients with a first-time encounter with the assisted ventilation clinic between February 2012 and January 2021. The first encounter was defined as either the first out-patient clinic visit or an in-patient encounter in which the assisted ventilation clinic team was consulted for the initiation of NIV.

We included subjects with chronic hypercapnia at the first encounter who were initiated or maintained on NIV. Chronic hypercapnia was defined as $P_{aCO_2} > 45$ mm Hg with a pH > 7.35 in the in-patient setting, or $P_{tcCO_2} > 45$ mm Hg by using P_{tcCO_2} monitoring in a stable state as an out-patient. We excluded patients who required invasive mechanical ventilation (patients who were tracheostomized) at the first visit, those who were not initiated on NIV, and patients lost to follow-up.

Follow-up P_{CO_2} measurements over a 2-year period were performed by using P_{tcCO_2} monitoring. We used electronic medical record chart review to identify demographic characteristics, comorbidities, and clinical data. All out-patient visits included a P_{tcCO_2} reading while the subject was at rest, breathing spontaneously without assistance unless the clinical status required continuous mechanical ventilation. P_{tcCO_2} measurements were performed by using a SenTec Digital Monitor (SenTec AG, Therwil, Switzerland). The P_{tcCO_2} sensor was applied to the subject's forehead at 42°C for at least 5–10 min, and the value at steady state was recorded.

At each clinic visit, assessments were made by a pulmonary clinician and respiratory clinician. Based on P_{tcCO_2} levels and device downloads, recommendations were made to continue current management strategies, adjust ventilator settings, or increase hours of use. For the subjects who had no change or had an increase in P_{tcCO_2} from baseline during the follow-up period, the clinical notes were reviewed to determine the reasons for the lack of P_{tcCO_2} improvement.

The primary outcome was all-cause mortality within 2 years of the initial encounter. We determined the vital status by reviewing the electronic medical record, funeral home web sites, and online obituaries. All the subjects were

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Supplementary material related to this paper is available at http://www.rcjournal.com.

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Table 1. Cohort Characteristics ($N = 337$)

Variable	Summary Statistics
Age at first visit, mean ± SD y	57 ± 16
Women, *n* (%)	125 (37)
Race, *n* (%)	
White	285 (85)
Black	39 (11)
Asian	6 (2)
Other	7 (2)
Body mass index class, *n* (%)	
<18.5 kg/m^2	30 (9)
18.5–24.9 kg/m^2	82 (24)
25–29.9 kg/m^2	69 (21)
≥30 kg/m^2	155 (46)
Primary diagnosis, *n* (%)	
Amyotrophic lateral sclerosis	56 (16)
Other NMD and/or RTD	138 (41)
COPD	40 (12)
Spinal cord injury	39 (12)
Obesity-hypoventilation syndrome	48 (14)
Other	16 (5)
Charlson comorbidity index score, median (interquartile range)	2 (1–4)
NIV start location, *n* (%)	
Out-patient	262 (78)
In-patient	75 (22)
Baseline NIV use, *n* (%)	
Naive	189 (56)
Previous use	148 (44)
Baseline P_{CO_2}, *n* (%)	
<50 mm Hg	87 (26)
50–59 mm Hg	134 (40)
60–69 mm Hg	83 (24)
≥70 mm Hg	33 (10)
Vital status at 2 y, *n* (%)	
Alive	260 (77)
Deceased	77 (23)

NMD = neuromuscular disease
RTD = restrictive thoracic disorder
NIV = noninvasive ventilation

followed up from the date of the first encounter to death, the last visit, or August 30, 2021, whichever came first, with a maximum follow-up time of 730 d. Subjects were considered lost to follow-up when their status within the past 6 months of the censoring date was unknown.

We described baseline characteristics by using means ± SDs or medians (interquartile ranges) for continuous variables and as counts (percentage) for categorical variables. We used uni- and multivariable Cox proportional hazard models. To minimize immortal time bias,[20] we included time-varying P_{CO_2} levels in the Cox proportional hazards models. To determine P_{CO_2} associations at different time intervals, we used time-varying coefficients of P_{CO_2} in the Cox proportional hazards models.[21]

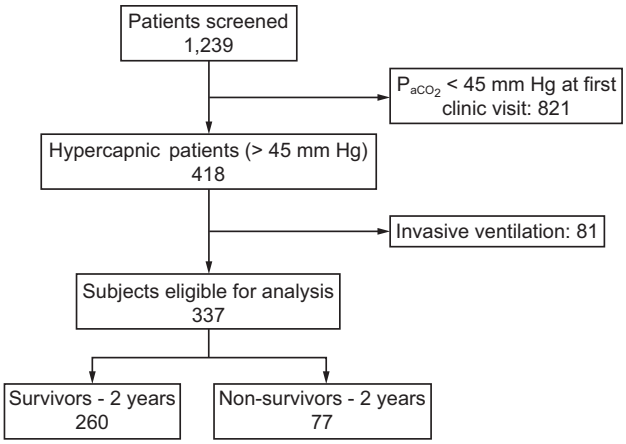

Fig. 1. Flow chart.

For the multivariable models, we adjusted for potential confounders that were associated with disease progression, a need for NIV, and overall survival in chronic respiratory failure, such as primary diagnosis for NIV indication, age, sex, race, body mass index, Charlson comorbidity index, and baseline P_{CO_2}. The primary diagnosis was considered the primary reason for chronic respiratory failure. We examined the proportional hazard assumption of P_{CO_2} within each time interval through Schoenfeld residual plots.[22,23]

We performed subgroup analyses by using the aforementioned approach to examine associations with mortality, including subjects with ALS versus subjects without ALS and those with both baseline P_{aCO_2} and P_{tcCO_2} versus baseline P_{tcCO_2} alone. Missing data were handled by using multiple imputation. We considered all P values of <.05 as statistically significant. We performed all analyses by using Stata version 15.0 (StataCorp, College Station, Texas).

Results

We identified 337 unique subjects who were evaluated at the assisted ventilation clinic for NIV initiation or optimization with baseline hypercapnia (Table 1). We excluded 81 patients who were receiving invasive mechanical ventilation at the time of the first visit (Fig. 1). The mean ± SD age was 57 ± 16 y, 125 (37%) were women, and 285 (85%) were white. The most common causes of chronic respiratory failure were neuromuscular diseases (NMD) other than ALS and restrictive thoracic disorders (41%), followed by ALS (16%), obesity-hypoventilation syndrome (14%), spinal cord injury (12%), and COPD (12%). Additional diagnoses (central congenital hypoventilation, pleural disease, cystic fibrosis, bronchiectasis) were categorized as other (5%). The mean ± SD baseline P_{CO_2} was 57 ± 10 mm Hg, with 40% ranging between 50 and 59 mm Hg. Most initial encounters occurred in the out-patient setting (78%), with 44% of the cohort already using NIV on

Table 2. P_{CO_2} Averages by Time and Group

Parameter	Subjects, *n* (%)	P_{CO_2}, mean ± SD mm Hg					
		Baseline	0–90 d	90–180 d	180–365 d	365–540 d	540–730 d
All subjects	337 (100)	57 ± 10	55 ± 9	50 ± 8	48 ± 7	47 ± 8	46 ± 8
Primary diagnosis							
ALS	56 (16)	51 ± 6	51 ± 6	47 ± 6	45 ± 6	44 ± 6	44 ± 6
Other NMD and/or RTD	138 (41)	55 ± 9	54 ± 9	50 ± 8	47 ± 6	46 ± 6	46 ± 7
COPD	40 (12)	66 ± 13	62 ± 11	55 ± 9	54 ± 10	53 ± 10	52 ± 10
Spinal cord injury	39 (12)	56 ± 7	54 ± 7	49 ± 7	46 ± 7	46 ± 6	46 ± 6
Obesity-hypoventilation syndrome	48 (14)	61 ± 11	60 ± 10	52 ± 8	49 ± 9	47 ± 10	46 ± 10
Other	16 (5)	59 ± 9	57 ± 8	51 ± 6	48 ± 6	47 ± 6	43 ± 4
NIV start location							
Out-patient	262 (78)	55 ± 9	54 ± 9	50 ± 7	48 ± 7	47 ± 7	46 ± 8
In-patient	75 (22)	63 ± 12	59 ± 11	50 ± 10	48 ± 9	47 ± 9	46 ± 8
NIV experience							
Previous NIV	189 (56)	58 ± 10	54 ± 9	50 ± 7	48 ± 7	47 ± 7	47 ± 8
NIV naive	148 (44)	56 ± 10	56 ± 10	50 ± 9	48 ± 8	47 ± 8	45 ± 8
Baseline P_{CO_2}							
<50 mm Hg	87 (26)	47 ± 2	47 ± 3	46 ± 4	45 ± 5	44 ± 5	43 ± 5
50–59 mm Hg	134 (40)	54 ± 3	53 ± 4	49 ± 6	47 ± 6	46 ± 6	46 ± 7
60–69 mm Hg	83 (24)	64 ± 3	61 ± 5	53 ± 9	50 ± 9	49 ± 10	48 ± 10
≥70 mm Hg	33 (10)	79 ± 9	74 ± 10	59 ± 10	55 ± 10	51 ± 10	50 ± 9

ALS = amyotrophic lateral sclerosis
NMD = neuromuscular disease
RTD = restrictive thoracic disorder
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referral to the assisted ventilation clinic. The median (interquartile range) follow-up time was 730 (600–730) d. With regard to missing data, we had one subject only in which the body mass index could not be calculated (height was missing throughout the chart).

Among the different diagnostic subgroups, the mean ± SD baseline P_{CO_2} were highest in the subjects with COPD (66 ± 13 mm Hg) and lowest in those with ALS (51 ± 6 mm Hg). Subjects initially encountered as in-patients had higher P_{CO_2} levels than those encountered as out-patients. Irrespective of the diagnosis, the mean P_{CO_2} was reduced for subjects in all the subgroups at 0–90 d, 90–180 d, 180–365 d, 365–540 d, and 540–730 d after the first encounter. The mean P_{CO_2} was < 50 mm Hg for surviving subjects in all primary diagnosis subgroups across both initial assessment locations at 1 and 2 years except for COPD (Table 2).

We found a 23% all-cause mortality within 2 years of the first evaluation at the assisted ventilation clinic. In the univariate analysis, we found significant associations between mortality and the diagnoses of ALS (hazard ratio [HR] 10.60, 95% CI 4.60–13.30) and COPD (HR 4.37, 95% CI 1.68–6.34). Female sex, higher age, body mass index ≥ 30 kg/m^2, and higher Charlson comorbidity index were associated with mortality.

Survival probabilities increased after 90 d based on the percent reduction in P_{CO_2} from baseline (Fig. 2). In the multivariate analysis, we found a 92% reduction in mortality between 180 and 364 d (HR 0.08, 95% CI 0.01–0.64) for the subjects with a reduction of >20% from the baseline P_{CO_2}. We did not find statistically significant differences in

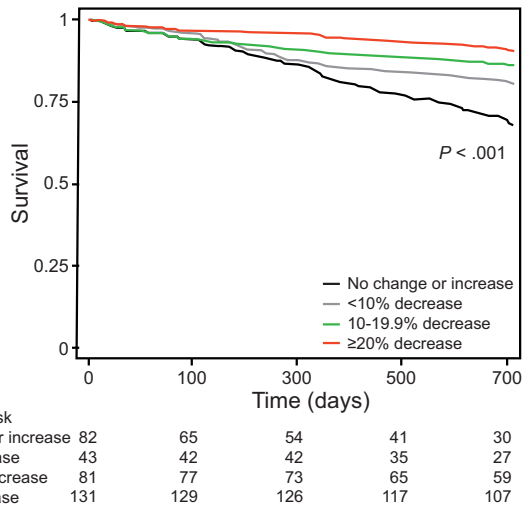


Fig. 2. Two-year survival by the percentage of P_{CO_2} change for the entire cohort of subjects who were hypercapnic. The model was adjusted for age, sex, body mass index, race, Charlson comorbidity index, primary diagnosis, and initial P_{CO_2}. Likelihood ratio test of equality, $P \leq .001$.

the other deciles of P_{CO_2} reduction or at < 180 d. However, after 365 d, we found a 77% reduction in mortality in subjects who had a reduction in P_{CO_2} between 10 and 19.9% (HR 0.23, 95% CI 0.08–0.65) and a 76% reduction in those who had a reduction in P_{CO_2} > 20% (HR 0.24, 95% CI 0.09 – 0.62) (Table 3).

Similarly, absolute values of P_{CO_2} < 50 mm Hg after 90 d were associated with improved survival (Fig. 3). After adjusting for age, sex, race, body mass index, primary diagnosis, Charlson comorbidity index, and baseline P_{CO_2}, there remained an increase in survival probability after 90 d for the subjects who attained P_{CO_2} < 50 mm Hg. In the multivariable analysis, we found a 94% reduction in mortality between 90 and 179 d (HR 0.06, 95% CI 0.01–0.50), a 69% reduction in mortality between 180 and 364 d (HR 0.31, 95% CI 0.12–0.79), and a 73% reduction in mortality between 365 and 730 d (HR 0.27, 95% CI 0.13 – 0.56) for the subjects who attained P_{CO_2} < 50 mm Hg (Table 4).

To examine the potential effect modification of ALS, a disease with high short-term mortality, we performed a subgroup analysis that considered subjects with (Supplementary Figs. 1 and 2 and Supplementary Table 1) and without ALS (Supplementary Figs. 3 and 4) (see the supplementary materials at http://www.rcjournal.com). Due to the imperfect correlation between P_{tcCO_2} and P_{aCO_2}, we analyzed survival by considering those who had only P_{tcCO_2} measurements at baseline (Supplementary Fig. 5 [see the supplementary materials at http://www.rcjournal.com]). Similarly, we analyzed survival subjects who were NIV naive only (Supplementary Table 2 and Supplementary Fig. 6 [see the supplementary materials at http://www.rcjournal.com]). All subgroup analyses yielded similar results to our primary analysis. Forty-two subjects were unable to achieve any reduction in P_{CO_2} from baseline in 6–12 months. Of these 42 subjects, 12 (29%) were non-adherent with therapy, defined as consistently < 4 h of daily usage. The remaining 30 subjects (71%) were still unable to achieve a reduction in P_{CO_2}, despite > 4 h of consistent daily usage.

Discussion

In this single-center, retrospective study of subjects with chronic hypercapnic respiratory failure, we found a strong correlation between reduction in diurnal P_{CO_2} by means of NIV and 2-year mortality. A reduction in P_{CO_2} to <50 mm Hg by 3–6 months was associated with improved survival. In addition, increasing the percent reduction in P_{CO_2} from baseline was also associated with improved survival. Baseline hypercapnia can be a marker for more-severe cardiovascular-pulmonary or multi-organ system disease. Although the cause-effect relationship between P_{CO_2} reduction and 2-year mortality cannot be ascertained from this retrospective study, there are compelling reasons to suspect that improving diurnal P_{CO_2} in a dose-response manner could explain the prolonged survival.

Elevated P_{CO_2} directly impairs alveolar fluid reabsorption,[24] epithelial cell regeneration,[25] cytokine expression,[26] and phagocytosis,[27] independent of extracellular pH. In mice infected with *Pseudomonas aeruginosa* and Influenza A, hypercapnia was associated with increased mortality, independent from blood pH.[4,28] The researchers attributed these findings to the effects of hypercapnia on neutrophil and macrophage activity, which suggest that patients with chronic hypercapnia may be predisposed to developing life-threatening bacterial and viral infections. The concept of hypercapnia induced immune dysfunction is supported by observational studies of community-acquired pneumonia that demonstrated an association between hypercapnia and increased ICU admission, intubation, and mortality.[29,30]

In addition to its effects on host defenses, elevated P_{CO_2} has harmful effects on the respiratory pump. Hypercapnia, in both animal and human studies, has been shown to have direct effects on skeletal muscle function. Hypercapnia directly leads to catabolic muscle wasting while also impairing muscle regeneration in respiratory and non-respiratory skeletal muscles.[3,31] Patients with conditions that lead to alveolar hypoventilation may develop functional neuromuscular weakness. Adverse effects on brain function have been identified.[32-34] In addition, chronic hypercapnia increases total body tissue stores of P_{CO_2}, which renders patients vulnerable to acid/base and cardiorespiratory decompensation in the event of impairments in P_{CO_2} removal or modest acute increases in P_{CO_2} production as might occur during a febrile illness.[5]

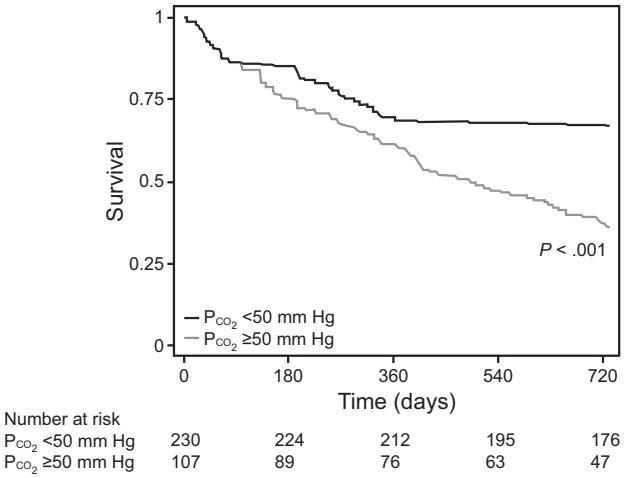
Our study showed that, although P_{CO_2} could be reduced within the first 3 months after the first visit, its impact on survival became evident with sustained P_{CO_2} reductions. This was seen in both the analyses of percent P_{CO_2} reduction as well as the P_{CO_2} reduction to < 50 mm Hg. These findings may simply be due to the infrequency of deaths within the first 3 months of evaluation. However, this greater survival benefit over time may also represent the time needed to affect host defenses and skeletal muscle function. Future studies that look at these factors in response to P_{CO_2} reduction in humans are warranted. Analysis of our findings suggests that future studies in hypercapnic respiratory failure should aim to explore the reduction in P_{CO_2} and maintain the P_{CO_2} reduction over time.

Wilson et al[2] demonstrated that, in hospitalized patients with compensated hypercapnia, higher levels of P_{CO_2} were associated with increased mortality even when adjusted for severity of illness. In contrast to our study, Wilson et al[2] studied a population that mostly comprised subjects with obstructive sleep apnea, COPD, and heart failure, whereas only a minority had NMD. In our study, 57% of the population had a primary neuromuscular diagnosis as the cause for hypercapnic respiratory failure. Given the poor prognosis in specific neuromuscular disorders, for example, ALS, we performed sensitivity analyses excluding patients with

Table 3. Results of a 2-y Survival Analysis Adjusted for Percent Change in P_{CO_2} ($N = 337$)

Variable	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis, per decade	1.54	1.30–1.83	<.001	1.16	0.87–1.55	.31
Female sex	1.91	1.22–2.99	.004	1.51	0.91–2.52	.11
Race						
White	ND	ND	ND	ND	ND	ND
Black	0.42	0.15–1.15	.09	1.24	0.42–3.71	.70
Asian	2.69	0.85–8.54	.09	2.51	0.68–9.25	.17
Other	0.54	0.08–3.90	.54	1.07	0.14–8.43	.95
Body mass index class						
<18.5 kg/m^2	1.65	0.81–3.38	.17	2.90	1.28–6.56	.01
18.5–24.9 kg/m^2	ND	ND	ND	ND	ND	ND
25–29.9 kg/m^2	1.35	0.74–2.47	.34	1.81	0.90–3.63	.10
≥30 kg/m^2	0.51	0.28–0.94	.031	1.00	0.49–2.01	.99
Primary diagnosis						
Other NMD and/or RTD	ND	ND	ND	ND	ND	ND
ALS	10.60	4.60–13.30	<.001	10.90	5.21–22.78	<.001
COPD	4.37	1.68–6.34	<.001	2.51	1.09–5.78	.031
Spinal cord injury*	ND	ND	ND	ND	ND	ND
Obesity-hypoventilation syndrome	1.02	0.28–1.94	.53	1.17	0.38–3.61	.79
Other	2.59	1.25–5.37	.01	6.42	2.15–19.14	.001
Charlson comorbidity index, per 1-point increase	1.17	1.07–1.29	.001	1.08	0.89–1.32	.43
NIV experience						
NIV naive	ND	ND	ND	ND	ND	ND
Previous NIV	0.82	0.52–1.30	.41	ND	ND	ND
Location of NIV start						
Out-patient	ND	ND	ND	ND	ND	ND
In-patient	1.12	0.67–1.88	.68	ND	ND	ND
Baseline P_{CO_2}						
<50 mm Hg	ND	ND	ND	ND	ND	ND
50–59 mm Hg	0.96	0.57–1.63	.88	2.64	1.41–4.92	.002
60–69 mm Hg	0.57	0.29–1.13	.11	1.49	0.62–3.55	.37
≥70 mm Hg	0.81	0.35–1.89	.63	3.18	0.98–10.32	.053
Percent change in P_{CO_2}						
<180 d						
No change or increase	ND	ND	ND	ND	ND	ND
<10% decrease	0.74	0.09–5.94	.78	0.67	0.08–5.47	.71
10–19.9% decrease	1.47	0.40–5.39	.56	1.00	0.26–3.84	>.99
≥20% decrease	0.56	0.12–2.61	.46	0.55	0.11–2.76	.47
180–364 d						
No change or increase	ND	ND	ND	ND	ND	ND
<10% decrease	1.41	0.51–3.88	.51	1.08	0.37–3.12	.89
10–19.9% decrease	0.48	0.13–1.75	.27	0.39	0.10–1.46	.16
≥20% decrease	0.09	0.01–0.69	.02	0.08	0.01–0.65	.02
≥365 d						
No change or increase	ND	ND	ND	ND	ND	ND
<10% decrease	0.48	0.16–1.43	.19	0.33	0.10–1.07	.061
10–19.9% decrease	0.30	0.11–0.81	.02	0.23	0.08–0.65	.006
≥20% decrease	0.25	0.11–0.59	.001	0.24	0.09–0.62	.003

*HRs are not estimable because no subject with a spinal cord injury died during the follow-up.
HR = hazard ratio
ND = no data
NMD = neuromuscular disease
RTD = restrictive thoracic disorder
ALS = amyotrophic lateral sclerosis
NIV = noninvasive ventilation



Number at risk					
P_{CO_2} <50 mm Hg	230	224	212	195	176
P_{CO_2} ≥50 mm Hg	107	89	76	63	47

Fig. 3. Two-year survival by absolute P_{CO_2} higher on < 50 mm Hg for the entire cohort of subjects who were hypercapnic. The model was adjusted for age, sex, body mass index, race, Charlson comorbidity index, primary diagnosis, and initial P_{CO_2}. Likelihood ratio test of equality, $P \leq .001$.

ALS in which we found a consistent signal for survival benefit in those who decreased P_{CO_2} to < 50 mm Hg. With regard to the subgroup analysis in the subjects with ALS, although there was a trend toward improved survival, we are heavily limited in our ability to detect statistically significant differences due to the small sample size of this subgroup.

Both in uni- and multivariable analyses, the baseline P_{CO_2} was not significantly associated with higher mortality. This could reflect that P_{CO_2} correction mitigates the mortality risk attributable to baseline hypercapnia. The fact that, during the follow-up period, we were able to achieve a mean P_{CO_2}, of 50 mm Hg, for all baseline P_{CO_2} categories, (including the most extreme cases of P_{CO_2} > 70 mm Hg) could account for the neutral effect of baseline hypercapnia in mortality and supports the notion that hypercapnia is a modifiable risk factor rather than just a marker of severity. In addition, a change of P_{CO_2} may be more indicative of the trajectory of the disease and reflects outcomes more strongly than a snapshot in time, such as a baseline P_{CO_2}.

Although there is increasing evidence of the benefits of NIV on quality of life and symptom burden,[35] little is known about how specific NIV management strategies impact survival. NIV for the management of chronic respiratory failure has focused primarily on hours of usage per day as opposed to specific physiologic variables. Adherence goals have been derived largely from insurance coverage criteria for the use of CPAP therapy for sleep apnea,[36] and studies have shown a mortality benefit in patients using NIV for > 4 h/d.[12,37] However, 4 h may grossly underestimate the hours of use needed to achieve normocapnia. Patients' ventilatory needs may vary from a few hours per days to 24 h/d depending on the severity of the disease and underlying pathophysiology. Therefore, although the hours of use may be sufficient for CPAP therapy secondary to obstructive sleep apnea, our study bolsters the argument for a shift in the way we manage NIV in chronic respiratory failure toward prioritizing P_{CO_2} over hourly usage alone.

It is unknown whether targeting an absolute P_{CO_2} threshold (eg, <50 mm Hg) or a P_{CO_2} percent reduction has superior outcomes. Given the equipoise, we feel this creates a clinical research question that is ripe for a future randomized control trial that compares CO_2 reduction strategies in patients with chronic hypercapnia. Until further evidence is available, the ideal strategy may depend on the degree of baseline P_{CO_2} elevation, comorbidities, patient comfort with NIV settings, and aligning treatment strategy with patient goals of care.

Arterial blood gas testing remains the standard assessment for P_{CO_2}. However, there are many barriers to its regular use in the out-patient setting, including access to a blood gas analyzer and patient discomfort. P_{tcCO_2} monitors provide an alternative, noninvasive method for longitudinal monitoring of alveolar ventilation. P_{tcCO_2} has been shown to correlate with P_{CO_2}, with limits of agreement of –6 to 6 mm Hg when using modern sensors placed on the earlobe at a temperature of 42°C.[38] This technique is practical for trending P_{CO_2} during titration of NIV. In addition, P_{tcCO_2} has been used to diagnose respiratory failure in NMDs and to aid in the decision making of in-patient NIV initiation in a small case series.[39] The high cost likely hinders the dissemination of P_{tcCO_2} monitors. End-tidal pressure of expired CO_2 also provides noninvasive continuous monitoring of P_{CO_2} levels amenable to an out-patient setting. End-tidal pressure of expired CO_2 is less costly than P_{tcCO_2}, which makes it a potentially attractive noninvasive option.

However, the accuracy of end-tidal pressure of expired CO_2 is limited by inherent differences in P_{aCO_2} and end-tidal pressure of expired CO_2 due to dead space, the effect of increasing age and ventilation/perfusion mismatch, and of decreasing with large tidal volume.[40] Therefore, end-tidal pressure of expired CO_2 may be error prone in patients who are spontaneously breathing for 2 reasons: (1) patients with chronic respiratory failure have frequent ventilation/perfusion mismatches, and (2) patients who require continuous NIV will experience mask leakage with measurements.[41] Finally, serum bicarbonate has been used as a surrogate for blood P_{CO_2} levels and may give a general sense of responses to NIV. However, primary metabolic alkalosis, including the use of diuretics, may limit its practical use for the monitoring of alveolar ventilation.

We were unable to reduce P_{CO_2} at 6–12 months in 12% of our subjects who were hypercapnic. Some subjects did not use NIV regularly or for sufficient hours per day to reduce diurnal P_{CO_2}. Other subjects had such severe thoracic or lung disease that we were unable to achieve settings that effectively reversed hypercapnia. Such

Table 4. Results of 2-y Survival Analysis Adjusted for Absolute P_{CO_2} > 50 mm Hg or < 50 mm Hg ($N = 337$)

Variable	Univariate Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age at diagnosis, per decade	1.54	1.30–1.83	<.001	1.15	0.87–1.54	.33
Women	1.91	1.22–2.99	.004	1.60	0.96–2.64	.08
Race						
White	ND	ND	ND	ND	ND	ND
Black	0.42	0.15–1.15	.09	1.28	0.44–3.75	.65
Asian	2.69	0.85–8.54	.09	2.93	0.79–10.9	.11
Other	0.54	0.08–3.90	.54	1.13	0.15–8.68	.91
Body mass index class						
<18.5 kg/m^2	1.65	0.81–3.38	.17	2.39	1.03–5.53	.042
18.5–24.9 kg/m^2	ND	ND	ND	ND	ND	ND
25–29.9 kg/m^2	1.35	0.74–2.47	.34	1.94	0.99–3.80	.053
≥30 kg/m^2	0.51	0.28–0.94	.033	1.05	0.51–2.14	.90
Primary diagnosis						
Other NMD and/or RTD	ND	ND	ND	ND	ND	ND
ALS	10.60	4.60–13.30	<.001	11.26	5.38–23.60	<.001
COPD	4.37	1.68–6.34	<.001	2.49	1.09–5.67	.030
Spinal cord injury*	ND	ND	ND	ND	ND	ND
Obesity-hypoventilation syndrome	1.02	0.28–1.94	.53	0.99	0.32–3.03	.98
Other	2.59	1.25–5.37	.01	4.73	1.58–14.18	.006
Charlson comorbidity index, per 1-point increase	1.17	1.07–1.29	.001	1.11	0.91–1.34	.30
NIV experience						
NIV naive	ND	ND	ND	ND	ND	ND
Previous NIV	0.82	0.52–1.30	.41	ND	ND	ND
Location of NIV start						
Out-patient	ND	ND	ND	ND	ND	ND
In-patient	1.12	0.67–1.88	.68	ND	ND	ND
Baseline P_{CO_2}						
<50 mm Hg	ND	ND	ND	ND	ND	ND
50–59 mm Hg	0.96	0.57–1.63	.88	1.33	0.69–2.56	.40
60–69 mm Hg	0.57	0.29–1.13	.11	0.62	0.26–1.45	.27
≥70 mm Hg	0.81	0.35–1.89	.63	0.76	0.26–2.28	.63
Time-varying P_{CO_2}						
≥50 mm Hg per time interval	ND	ND	ND	ND	ND	ND
<50 mm Hg between 0 and 89 d	0.83	0.26–2.64	.75	0.43	0.11–1.75	.24
<50 mm Hg between 90 and 179 d	0.10	0.01–0.84	.033	0.06	0.01–0.50	.009
<50 mm Hg between 180 and 364 d	0.44	0.18–1.07	.07	0.31	0.12–0.79	.01
<50 mm Hg after 365–730 d	0.35	0.18–0.68	.002	0.27	0.13–0.56	<.001

*HRs are not estimable because no subject with a spinal cord injury died during the follow-up.
HR = hazard ratio
ND = no data
NMD = neuromuscular disease
RTD = restrictive thoracic disorder
ALS = amyotrophic lateral sclerosis
NIV = noninvasive ventilation

difficulties highlight the complexities involved in personalizing the management of chronic respiratory failure to each patient. P_{tcCO_2} should be used in conjunction with a full understanding of device downloads to optimize home mechanical ventilation strategies. An inability to reduce P_{CO_2} despite adjustments to ventilator settings and increasing hourly usage should prompt discussing advanced goals of care planning, including tracheostomy and/or palliative care for symptom management and end-of-life care planning.

We acknowledge several limitations of our study. Due to the study's retrospective design, we cannot attribute causality or exclude the role of unmeasured confounders in the outcome. The subjects in our single-center study were followed up in a specialized clinic with expertise in home mechanical ventilation and P_{tcCO_2} monitoring. Therefore, our

findings are prone to selection bias and may not be generalizable to settings with fewer resources. The majority of P_{CO_2} measurements were taken by using a P_{tcCO_2} monitor, which is prone to bias compared with the accepted standard arterial blood gases. In addition, the placement of the transcutaneous sensor on the forehead has not been widely studied[40] and could have introduced measurement bias.

Conclusions

P_{CO_2} reductions were associated with improved survival in chronic hypercapnic respiratory failure, a condition associated with high mortality. Given the strong association between improved P_{CO_2} and survival, our study sets the rationale for larger prospective studies that explore this association and its potential role in improving clinically meaningful outcomes. In addition, our study highlights the importance of a home mechanical ventilation program with integrated P_{tcCO_2} monitoring. Future work should focus on P_{tcCO_2} technology dissemination to a wider clinical audience to facilitate multi-center cohort studies on how P_{tcCO_2} reduction affects clinical outcomes, including hospitalizations and readmissions.

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