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Transcutaneous CO_2 monitoring as indication for inpatient non-invasive ventilation initiation in patients with amyotrophic lateral sclerosis

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Abstract

Introduction/Aims: Amyotrophic lateral sclerosis (ALS) is characterized by profound muscle weakness, including diaphragmatic weakness resulting in hypercapnic respiratory failure. While non-invasive ventilation (NIV) is usually initiated in the home, patients presenting with hypercapnic respiratory failure may be at high risk of adverse outcomes with delays in treatment. We aim to describe the clinical utility of transcutaneous CO_2 (TCO_2) to assess the need for inpatient initiation of NIV.

Methods: Eight patients from the University of Michigan Pranger ALS clinic were directly admitted to the hospital for urgent initiation of NIV between May 2020–May 2021. A retrospective review of electronic medical records, including pre-hospital pulmonary function assessments, hospitalization blood gases, and NIV use metrics was performed.

Results: All eight patients had symptoms of respiratory insufficiency at time of admission, although not all patients had forced vital capacity (FVC) measurements that would identify need for NIV. All patients had measured TCO_2 > 45 mmHg. Seven of eight patients had worsening hypercapnia after admission, indicating advanced respiratory failure. All patients were titrated to tolerance of continuous nocturnal NIV while in the hospital, with an average length of stay of 6.5 days (range, 3–8). All patients demonstrated compliance with NIV, >4 h, at post-hospital follow-up.

Discussion: Many current ambulatory measurements underestimate, or incompletely evaluate, respiratory dysfunction, and arterial blood gases are not typically readily available. Outpatient TCO_2 measurements can serve as a useful screening tool to identify ALS patients who would benefit from inpatient initiation and titration of NIV.

KEYWORDS
amyotrophic lateral sclerosis, hypercarbia, non-invasive ventilation, respiratory failure, transcutaneous CO_2

1 | INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is characterized by profound muscle weakness, including diaphragmatic weakness resulting in hypercapnic respiratory failure.[1] Forced vital capacity (FVC) and maximum inspiratory pressure (MIP) are commonly used as surrogates for respiratory function, with an FVC <50% of predicted values typically indicative of significant respiratory muscle involvement.[2] Additionally, these tests generally

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FVC, forced vital capacity; MIP, maximum inspiratory pressure; MPV, mouthpiece ventilation; NIV, non-invasive ventilation; SpO_2, oxygen saturation by pulse oximetry; TCO_2, transcutaneous CO_2.

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underestimate respiratory dysfunction, are not designed to approximate alveolar hypoventilation leading to hypercapnic respiratory failure and become unreliable with increasing neuromuscular incoordination and worsening bulbar weakness. The ALS Functional Rating Scale Revised (ALSFRS-R) contains questions addressing respiratory function,[3] but alone may not accurately predict impending respiratory failure.

The mainstay of respiratory support in patients with ALS is non-invasive ventilation (NIV).[4] While most patients can safely initiate NIV at home, there are no clear or reliable criteria that would identify those patients at high risk of imminent respiratory collapse in need of inpatient admission. Transcutaneous CO_2 (TCO_2) monitoring is a non-invasive, reliable means of measuring $PaCO_2$ in an ambulatory setting.[5,6] It is a well-validated proxy for $PaCO_2$, typically underestimating measurements by 5–8 mmHg.[5] We aim to describe how TCO_2 monitoring can be a more useful surrogate for hypercapnia to identify patients with ALS who may benefit from hospital admission for immediate initiation and titration of NIV.

2 | METHODS

We identified eight patients that presented to the University of Michigan Pranger ALS clinic from May 2020 to May 2021 who were directly admitted for initiation or titration of NIV based on elevated TCO_2 levels. Decisions to admit patients were made based on elevated TCO_2 (TCO_2 > 45 mmHg), declining FVC measurements, and clinical symptoms concerning for impending respiratory failure in the judgement of the Pulmonology/Critical Care attending evaluating the patient in clinic. Data were collected via retrospective review of the medical records. All baseline clinic measurements were obtained either on day of admission or within 5 days prior. Pulmonary function measurements were obtained in clinic by a trained pulmonary function technician. All patients underwent three reproducible spirometry tests, with appropriateness of the patient effort indicated by the technician. The best of the three tests was chosen for interpretation by a pulmonary physician. Percent predicted values were based on sex, age, height, and race.[7] Clinic TCO_2 was obtained using a Digital Monitoring System (SenTec AG, Switzerland) (Supporting Information Figure S1, which is available online). ALSFRS-R questionnaires were administered by trained providers as part of routine ALS multidisciplinary care. Inpatient NIV settings were titrated to patient tolerance for continuous nocturnal ventilation with additional adjustments for daytime support as needed with nasal or mouthpiece interface. Readiness for discharge was determined by tolerance of NIV plus stable or improving $PaCO_2$ prior to discharge. Discharge blood gases were obtained in-hospital within 24 h of discharge. Post-hospitalization TCO_2 was obtained at the next in-person visit, typically within 30 days. NIV usage was determined based on data downloads using remote monitoring systems. Average daily use was recorded from these downloads. This study was approved by the Institutional Review Board.

3 | RESULTS

Key demographic information and clinical measurements are presented in Table 1. Pre-hospitalization, inpatient and post-discharge respiratory measurements are presented in Table 2.

All eight patients presented to clinic with symptoms or signs of respiratory insufficiency, such as dyspnea on exertion or apparent accessory muscle use. Seven patients were in clinic for their first multidisciplinary clinic visit after receiving the diagnosis of ALS. Patient 5 had previously been diagnosed with sleep apnea and had been started on nocturnal continuous positive airway pressure (CPAP) with 2L continuous nasal canula bleed through. Patient 7 was an established patient and had been using NIV for an average of 8–10 h/night for at least 3 mo prior to admission from clinic. All other patients were naïve to supplementary respiratory support. All patients had some bulbar dysfunction as captured by the ALSFRS-R. Only two patients had bulbar subscores <9. One patient had documented cognitive impairment.

All patients were directly admitted to a moderate care pulmonary service at University of Michigan Health, comprised of pulmonary/

TABLE 1 Demographics and baseline clinical features of patients directly admitted for inpatient initiation of NIV

	Demographics			ALSFRS-R scores				
Patient	Age (y)	Gender (male/female)	BMI (kg/m^2)	Total score (0–48)	Bulbar sub-score (0–12)	Dyspnea (0–4)	Orthopnea (0–4)	Respiratory insufficiency (0–4)
1	73	F	25.5	29	9	2	1	4
2	54	M	28.9	35	11	2	3	4
3	65	M	21.7	38	8	3	4	4
4	62	F	39.2	NA	NA	NA	NA	NA
5	75	F	18.8	37	9	2	4	4[a]
6	56	M	19.1	29	10	3	0	3
7	70	F	21.6	35	10	4	4	4
8	69	F	26.17	23	5	1	2	4

Note: Obtaining outpatient clinical measurements were sometimes limited due to the COVID-19 pandemic.
Abbreviations: BMI, body mass index; NA, Not assessed.
[a]Patient 5 had previously been using nocturnal CPAP machine at home.

TABLE 2 Respiratory measurements of patients directly admitted for inpatient initiation of NIV

	Pre-admission clinic measurements				Inpatient serum blood gas measurements				Post-hospitalization clinic measurements	
Patient	TCO_2 (mmHg)	MIP (cmH20)	FVC (% predicted)	SpO2 (%)	Admission pH	Admission pCO_2 (mmHg)	Discharge pH	Discharge pCO_2 (mmHg)	TCO_2 (mmHg)	NIV use (hours)
1	62	−25	NA	91	7.35	84	7.4	75	45	>20
2	64	−45	66	88	7.38	66	NA	NA	43	>20
3	56	−18	46	96	7.33	72	7.41	59	47	>20
4	58	−29	39	87	7.38	66	7.4	58	46	>20
5	48	−28	61	93[a]	7.47[b]	51	7.42	55	48	14
6	52	NA	NA	96	7.41[b]	56	7.41	51	53	24
7	56	−19	44	94	7.44	54	7.5[b]	37	43	13
8	59	−14	47	94	7.38[b]	62[b]	7.39[b]	56	50	7-10

Abbreviation: NA, not assessed.
[a]Obtained while on baseline 2L nasal cannula oxygen support.
[b]Value obtained from venous blood gas, rather than arterial.

critical care physicians and respiratory therapists trained in NIV management. Average length of hospital stay was 6.5 days (range 3–8). Seven patients had worsening hypercapnia early in their admission, signifying advanced respiratory failure. All patients were titrated to tolerance of continuous nocturnal NIV while in the hospital. Seven patients required additional daytime ventilatory support via mouthpiece ventilation (MPV). At follow-up, all patients were using NIV an average of >4 h/day. Five patients reported at least 20 h of NIV use per day. All patients, other than Patient 5, who had concomitant chronic obstructive pulmonary disease (COPD), had an improvement in measured pCO_2 prior to discharge or at follow-up visits. Patient 6 had a stable TCO_2 at follow-up 30 days after hospitalization, but at return visit 3 months later had a measured TCO_2 of 38 mmHg.

4 | DISCUSSION

Most patients with ALS are initiated on NIV in the outpatient setting, prior to developing hypercapnia, but those who present with signs and symptoms of advanced respiratory failure may require inpatient admission for more rapid titration. There are no clear objective criteria based on pulmonary function test values or physical examination that would identify patients who need to be admitted. Importantly, in our currently described cohort of patients, ambulatory measurements such as FVC, oxygen saturation by pulse oximetry (SpO_2), and the respiratory symptom portion of the ALSFRS-R did not seem to provide consistent and persuasive evidence of impending respiratory failure, with two patients admitted with FVC > 50% predicted. This implies that effort-dependent measurements and subjective symptom reports alone are not sufficient to capture the complexities or provide sensitive markers of alveolar hypoventilation leading to hypercapnic respiratory failure.

Based on our experience with these eight patients, TCO_2 measurement is a reliable, noninvasive means by which to identify patients with significant hypoventilation. Based on in-hospital $PaCO_2$ measurements, the patients identified in our case series could have progressed to fulminant respiratory failure requiring intubation and possibly death with any delay in starting NIV therapy. TCO_2 measurements in clinic provided important information that led to a decision to admit the patient for monitored titration of NIV, as the presence of hypercapnia indicated the patient's inability to maintain adequate minute ventilation without mechanical respiratory support. By admitting these patients, we were able to not only expeditiously initiate NIV, but also increase the probability of NIV tolerance and adherence in the immediate period after being seen in clinic, which has been shown to improve survival in ALS.[8] European evaluations have shown improved survival with rapid titration of NIV settings, particularly in patients without severe bulbar involvement.[9] When comparing planned outpatient versus inpatient titration, waiting time for initiation and adverse events (death and admission for respiratory failure) were higher in the outpatient group and survival was extended for those admitted; however, this was a very small group of patients ($n = 12$).[10]

There are several limitations to this case series. Foremost is the small sample size and retrospective nature of a case series. Additionally, all patients were seen in an ALS Center of Excellence with the presence of a pulmonary critical care physician trained in the management of neuromuscular disease. These patients were admitted to a pulmonary moderate care unit that frequently initiates NIV in patients with various conditions. These resources may not be available in smaller centers. Because outpatient initiation of NIV for ALS patients is primarily based on pulmonary function testing as opposed to $PaCO_2$, it is unclear what the natural course of home NIV initiation for hypercapnic patients would be. While prospective controlled studies comparing home versus inpatient initiation of NIV for hypercapnic ALS patients would be ideal, the feasibility of these studies would be challenging given the rapidly progressive nature of ALS. Future studies looking at the incidence of hypercapnia at the first visit to an ALS Center would be useful.

In summary, although NIV is usually initiated in the home, patients presenting with hypercapnic respiratory failure may be at high risk of adverse outcomes with delays in treatment. Outpatient TCO_2 measurements can serve as a useful adjunctive measurement to

identify ALS patients who would benefit from inpatient initiation and titration of NIV and avoid unwanted morbidity with prolonged outpatient titration, or more acute decompensation resulting in unwanted intubation or death. Further studies assessing the survival benefit of ambulatory TCO_2 monitoring and rapid initiation of NIV to tolerance with correction of CO_2 are also warranted.

CONFLICT OF INTEREST

Kellen Quigg: none. Matthew Wilson: none. Philip Choi: none.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Clinical course and outcome of an outpatient clinic population with myasthenia gravis and COVID-19

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Abstract

Introduction/Aims: Coronavirus disease-2019 (COVID-19) may have a more severe course in patients with myasthenia gravis (MG). We aimed to assess severity of the infection and factors contributing to its severity in a group of MG patients, most of whom were not hospitalized.

Abbreviations: AChR, acetylcholine receptor; MuSK, muscle-specific kinase; COVID-19, coronavirus disease-2019; CS, corticosteroids; HCQ, hydroxychloroquine; IS, immunosuppressive; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America clinical classification; NM, neuromuscular; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome–coronavirus-2.