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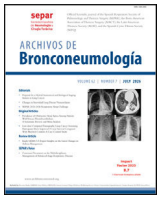

Scientific Letter

Hypercapnic Burden Derived From Nocturnal Transcutaneous CO_2 Measurement: A Preliminary Study in Patients With Slowly Progressive Neuromuscular Diseases

Respiratory impairment is a major complication of neuromuscular diseases (NMDs), primarily resulting from progressive respiratory muscle weakness and dysfunction, altered chest wall mechanics, impaired central respiratory drive, or peripheral nerve dysfunction [1–3]. Alongside cardiac involvement, respiratory failure is one of the principal determinants of morbidity and mortality in this population [4–6]. Clinically, respiratory dysfunction typically develops insidiously and is often first manifested by nocturnal alveolar hypoventilation, reflecting early ventilatory insufficiency during sleep before daytime hypercapnia becomes apparent [7–9].

Early diagnosis and management of respiratory failure in patients with NMDs are essential to prevent serious respiratory complications and improve prognosis [8,10]. Nevertheless, robust and reproducible prognostic indicators capable of guiding therapeutic decisions and their timing are currently lacking.

Nocturnal hypercapnia, even in the absence of daytime hypercapnia, appears to be the most informative prognostic marker of alveolar hypoventilation in individuals with NMDs [5,8]. However, there is no consensus regarding the thresholds that define nocturnal alveolar hypoventilation [10]. Moreover, the clinical heterogeneity among different NMDs means that diagnosis and prognosis may vary substantially according to the threshold selected in individual studies [11].

Novel physiological markers are therefore needed to better characterize the severity of nocturnal respiratory abnormalities in patients with NMDs. In this study, we investigated hypercapnic burden ($tcCO_2$bur), defined as the cumulative area of transcutaneous carbon dioxide tension ($tcCO_2$) above a predefined threshold, as a candidate metric for quantifying nocturnal hypercapnia.

The primary endpoint of this pilot study was to develop a computer algorithm for measuring $tcCO_2$bur in a population of patients with NMDs. The secondary objectives were to provide preliminary descriptive data regarding the value of this measurement by examining the relationship between $tcCO_2$bur and functional and blood gas parameters and by describing patient outcomes according to $tcCO_2$bur level.

We conducted an ancillary analysis of a single-center, cross-sectional, retrospective medical-record study involving patients with NMDs followed at the sleep disorders unit of a tertiary referral center specializing in slowly progressive neuromuscular diseases [12]. The ethical procedures specified under the MR-004 reference methodology were followed.

Data were collected retrospectively between October 2023 and March 2024. Demographic and clinical data, information on non-invasive ventilation (NIV), and details regarding the underlying neuromuscular disorder were extracted from electronic medical records (Supplementary Table 1).

To identify major cardiorespiratory events or death (MaCRED) in the study population, we used the Cohort360 platform, the health data warehouse of *Assistance Publique–Hôpitaux de Paris*. The platform provides coded information on reasons for consultation, symptoms, and diagnoses. International Classification of Diseases, 10th Revision codes were used to define MaCRED (Supplementary Table 2).

The eligibility of all patients included in the main study was assessed. Exclusion criteria for the ancillary study were opposition to the use of data from the institution's health data warehouse and insufficient data from the $tcCO_2$ recording.

All patients included in the original study had undergone nocturnal $tcCO_2$ monitoring using a Sentec® device, respiratory polygraphy, pulmonary function testing (PFT), and blood gas analysis between October 2018 and November 2023.

Hypercapnic burden was measured by calculating the area under the $tcCO_2$ curve above a threshold of 45 mm Hg over the entire recording period and was expressed in mm Hg s. This biomarker was calculated using a computer algorithm developed and implemented in MATLAB (Supplementary Fig. 1 and Supplementary Methods).

Based on the $tcCO_2$bur values obtained, the study population was divided into 3 groups. Patients with a hypercapnic burden of 0 were assigned to group 1 (no $tcCO_2$bur; $n = 50$). Among patients with a positive hypercapnic burden, the median $tcCO_2$bur was calculated and used to divide the remaining cohort into group 2 (low $tcCO_2$bur, $<8.3 \times 10^4$ mm Hg s; $n = 47$) and group 3 (high $tcCO_2$bur, $\geq 8.3 \times 10^4$ mm Hg s; $n = 48$).

Statistical analyses were performed using JASP software (Jeffreys's Amazing Statistics Program, version 0.96.0; JASP Team, 2020). Conventional analysis of variance was used to compare the 3 patient groups with respect to demographic data, $tcCO_2$ measurements, PFT results, and blood gas parameters. Pearson correlation coefficients (r) were calculated to assess linear associations between $tcCO_2$bur and the different PFT and blood gas parameters. A detailed description of the methods is provided in the online Supplementary Material.

Data from 145 of the 149 patients screened in the original study were analyzed in this pilot study (Supplementary Fig. 2). The most common NMD was myotonic dystrophy type 1, also known as Steinert disease ($n = 46$) (Supplementary Table 1). The study population comprised predominantly middle-aged patients, with a mean age of 45.4 years (SD, 18 years); 60% were men. The mean body mass index was 24.2 kg/m^2 (SD, 6.2 kg/m^2) (Supplementary Table 3).

The $tcCO_2$bur measurement algorithm was successfully applied to all $tcCO_2$ recordings, and a numerical $tcCO_2$bur value was obtained for every patient. Of the 145 patients, 50 had no hypercapnic burden and were assigned to group 1. The remaining 95 had a positive hypercapnic burden and were assigned to groups 2 and 3. Mean $tcCO_2$bur was 2.5×10^4 mm Hg s in group 2 and 3.7×10^5 mm Hg s in group 3.

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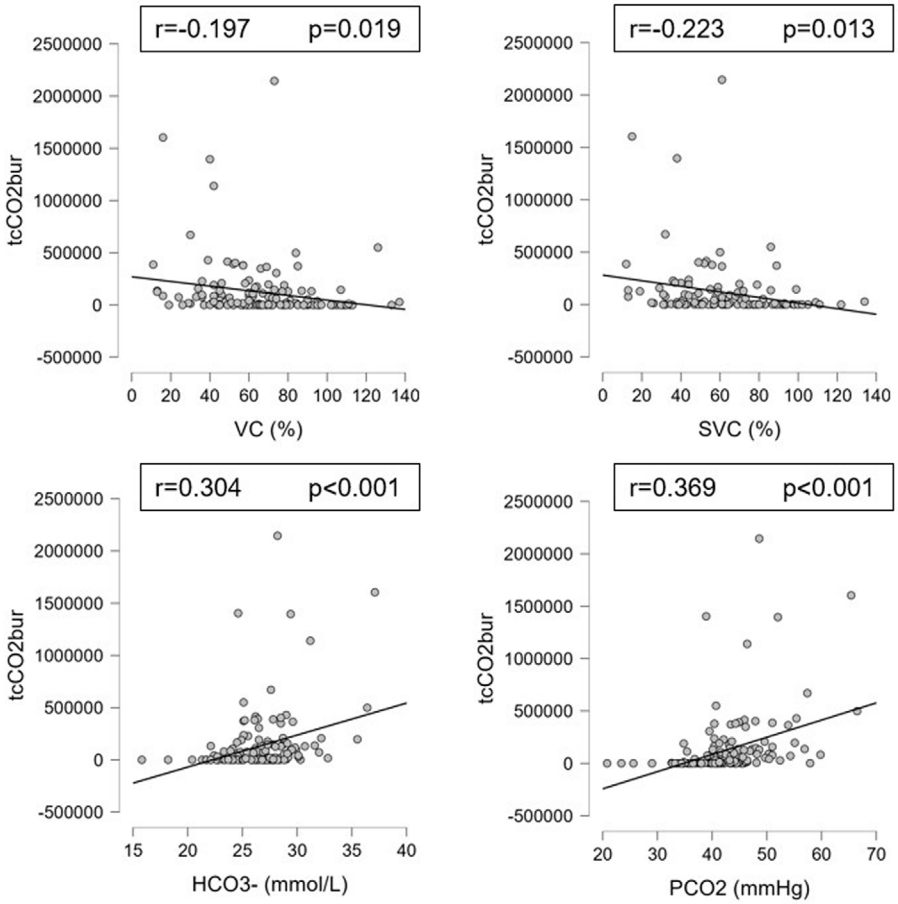

Figure 1. Correlation of hypercapnic burden with pulmonary function test results and blood gas parameters.

Hypercapnic burden was significantly correlated with vital capacity (VC), supine VC, partial pressure of carbon dioxide (PCO_2), and bicarbonate concentration (HCO_3^-), with Pearson correlation coefficients ranging from 0.20 to 0.39, indicating weak correlations (Fig. 1). No significant correlation was observed between $tcCO_2$bur and maximum inspiratory pressure or maximum expiratory pressure.

Significant correlations were found between $tcCO_2$bur and mean $tcCO_2$, peak $tcCO_2$, and the percentage of recording time with $tcCO_2 > 50$ mm Hg, with Pearson correlation coefficients ranging from 0.60 to 0.79; $P < .001$. These findings indicated strong correlations.

A significant but weak correlation was also observed between hypercapnic burden and oximetry parameters, including mean oxygen saturation measured by pulse oximetry (SpO_2), percentage of recording time with $SpO_2 < 90\%$, and oxygen desaturation index, with Pearson correlation coefficients ranging from 0.20 to 0.39 (Supplementary Fig. 3).

Comparison of the 3 groups defined according to $tcCO_2$bur revealed significant between-group differences in $tcCO_2$ and blood gas parameters. Mean $tcCO_2$, peak $tcCO_2$, percentage of time with $tcCO_2 > 50$ mm Hg, PCO_2, and HCO_3^- increased with increasing $tcCO_2$bur (Table 1).

Significant differences were also found in several PFT parameters. Supine VC and VC were significantly lower in group 3; $P < .001$ for both comparisons. Sniff nasal inspiratory pressure was also significantly lower in group 3; $P = .041$ (Table 1). The percentage of time with $SpO_2 < 90\%$ and oxygen desaturation index were significantly higher in group 3. Patients in group 3 were significantly younger. No significant differences in body mass index were observed among the groups (Table 1).

Descriptive data on patient outcomes, including NIV and prognostic variables, according to $tcCO_2$bur level are provided in the online Supplementary data (Supplementary Results and Supplementary Figs. 4–6). These analyses are descriptive and should not be interpreted as demonstrating an independent association.

This study demonstrates that measurement of hypercapnic burden is feasible. During the course of the study, another research group formalized the concept of hypercapnic burden in 9 patients with obesity hypoventilation syndrome [13]. In that study, hypercapnic burden, calculated as the cumulative area of $tcCO_2$ above a predefined threshold during sleep, was technically feasible, reproducible, and potentially more informative than isolated mean or peak $tcCO_2$ measurements.

There is a lack of consensus regarding biomarkers for chronic respiratory failure. Nevertheless, nocturnal hypercapnia has emerged as a clinically meaningful prognostic indicator, particularly in neuromuscular disorders. In mechanically ventilated patients with NMDs, Ogna et al. [11] investigated the prognostic value of residual hypoventilation measured using nocturnal $tcCO_2$ monitoring. They found that residual hypoventilation assessed using $tcCO_2$ was significantly associated with adverse events, including death and admission to the intensive care unit for respiratory events, whereas oximetry was not. Our study identified strong correlations between $tcCO_2$bur and conventional $tcCO_2$ thresholds commonly used in clinical practice and the literature.

Our results showed weak correlations between $tcCO_2$bur and both PFT and blood gas parameters. However, a study involving

Table 1
Comparison of patients with neuromuscular diseases according to hypercapnic burden.

Variable	Group 1 ($n=49$)	Group 2 ($n=49$)	Group 3 ($n=47$)	P value
Age, y	52.4 ± 18.8	45.0 ± 16.7	38.5 ± 15.8	**<.001**
Male sex, No. (%)	23 (46)	32 (68)	32 (67)	**.028**
BMI, kg/m²	24.9 ± 4.8	24.6 ± 5.9	23.2 ± 7.5	**.368**
Nocturnal capnography				
Mean $tcCO_2$, mm Hg	39.5 ± 4.2	44.3 ± 1.9	52.2 ± 7.0	**<.001**
Peak $tcCO_2$, mm Hg	43.3 ± 4.2	49.5 ± 2.6	60.0 ± 11.7	**<.001**
Time with $tcCO_2$ > 50 mm Hg, %	1.5 ± 10.6	2.0 ± 4.9	53.4 ± 31.5	**<.001**
Mean SpO_2, %	95.1 ± 1.6	94.7 ± 2.5	94.0 ± 3.4	**.087**
Time with SpO_2 < 90%, min	9.3 ± 36.0	26.6 ± 69.4	57.1 ± 116.7	**.015**
ODI, events/h	8.2 ± 9.2	9.5 ± 11.0	16.0 ± 19.4	**.015**
Pulmonary function testing				
VC, L	2.7 ± 0.9	2.6 ± 0.9	2.4 ± 1.1	**.303**
VC, % predicted	75.7 ± 24.3	64.9 ± 23.6	57.1 ± 24.3	**<.001**
Supine VC, L	2.5 ± 0.9	2.5 ± 1.1	2.2 ± 1.1	**.285**
Supine VC, % predicted	72.1 ± 22.2	61.1 ± 25.0	51.8 ± 21.6	**<.001**
MEP, cm H_2O	59.0 ± 32.9	53.3 ± 27.0	46.9 ± 27.5	**.134**
MIP, cm H_2O	48.7 ± 26.9	44.8 ± 23.5	40.1 ± 22.6	**.233**
SNIP, cm H_2O	49.3 ± 21.1	47.4 ± 22.0	38.7 ± 18.7	**.041**
Blood gas parameters				
PCO_2, mm Hg	38.0 ± 5.4	43.8 ± 4.8	46.7 ± 6.9	**<.001**
HCO_3^-, mmol/L	24.9 ± 2.8	26.9 ± 2.4	27.9 ± 3.1	**<.001**
Hypercapnic burden, mm Hg s	0	$2.5 \times 10^4 \pm 2.5 \times 10^4$	$3.7 \times 10^5 \pm 4.4 \times 10^5$	**<.001**

Values are presented as mean ± SD unless otherwise indicated.
BMI, body mass index; HCO_3^-, bicarbonate; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; NMD, neuromuscular disease; ODI, oxygen desaturation index; PCO_2, daytime partial pressure of carbon dioxide measured by blood gas analysis; SNIP, sniff nasal inspiratory pressure; SpO_2, oxygen saturation measured by pulse oximetry; $tcCO_2$, transcutaneous carbon dioxide tension; $tcCO_2$bur, hypercapnic burden derived from $tcCO_2$ monitoring; VC, vital capacity.
Group 1 comprised patients with no hypercapnic burden. Among patients with a positive hypercapnic burden, the median $tcCO_2$bur was used to define group 2 (low $tcCO_2$bur, $<8.3 \times 10^4$ mm Hg s) and group 3 (high $tcCO_2$bur, $\geq 8.3 \times 10^4$ mm Hg s). Groups were compared using analysis of variance. Statistical significance was defined as $P < .05$.

128 patients with NMDs showed, after reviewing the different definitions of alveolar hypoventilation, that VC was a less informative prognostic marker than nocturnal hypercapnia [5].

Blood gas analysis is also less sensitive than $tcCO_2$ monitoring for identifying nocturnal hypoventilation. In a study by Georges et al. [14], nocturnal $tcCO_2$ monitoring detected nocturnal hypoventilation in patients with NMDs or restrictive thoracic disorders despite normal arterial blood gas and nocturnal oximetry results in 30% of cases. Accordingly, the limited correlations between $tcCO_2$bur and standard pulmonary function and blood gas measurements do not undermine the potential value of this novel biomarker.

This study has several limitations. First, because there is no universally accepted reference standard for diagnosing nocturnal alveolar hypoventilation, our analyses relied on conventional measurements of nocturnal and daytime hypercapnia. This precluded definitive conclusions regarding the diagnostic performance of hypercapnic burden.

Second, the retrospective design may have resulted in underestimation of MaCRED because the Cohort360 database captures only events managed within our institution. Missing data also limited the assessment of ventilatory management and adherence to treatment. Consequently, the lower MaCRED rate observed among patients with the highest $tcCO_2$bur in group 3 may partly reflect more appropriate ventilatory management.

Third, the heterogeneity of the neuromuscular disorders included in the study may limit the generalisability of the findings and preclude disease-specific conclusions. However, this heterogeneity also highlights the need for robust biomarkers that can be applied across different neuromuscular conditions.

Finally, we focused exclusively on hypercapnic burden without accounting for concomitant hypoxic burden. The cardiovascular consequences of hypoxic burden are well established and may have contributed to the higher MaCRED rate observed among patients with isolated obstructive sleep apnoea [15,16].

We developed a novel algorithm for quantifying hypercapnic burden from transcutaneous CO_2 recordings by integrating both the duration and severity of nocturnal hypercapnia into a single metric. In this exploratory study, hypercapnic burden was associated with established markers of respiratory impairment, supporting its potential utility as a complementary measure of nocturnal alveolar hypoventilation in patients with neuromuscular disorders.

However, given the retrospective design, the heterogeneous study population, and the absence of a validated reference standard for nocturnal alveolar hypoventilation, these findings should be considered hypothesis-generating.

Because physiological markers that better reflect the severity and heterogeneity of nocturnal respiratory abnormalities in patients with NMDs are needed, future prospective studies should determine whether hypercapnic burden represents a clinically relevant biomarker of disease severity, prognosis, and response to treatment. They should also investigate whether its integration into clinical practice could influence therapeutic decision-making and improve patient outcomes.

Future studies should validate hypercapnic burden against clinically meaningful outcomes, determine its incremental value beyond conventional measurements, investigate its relationship with hypoxic burden, and assess its applicability in homogeneous neuromuscular cohorts and other disorders associated with nocturnal alveolar hypoventilation.

Authors' contributions

Conceptualisation: S.B., A.L., I.B., G.B., and H.P. Data curation: S.B., P.D., and A.P. Formal analysis: S.B., P.D., M.A.M., P.T., M.P., H.P., and A.L. Funding acquisition: none. Methodology: S.B., A.L., and I.B. Supervision: M.P., G.B., H.P., and A.L. Validation: all authors. Writing—original draft: S.B., P.D., M.A.M., P.T., and A.L. Writing—review and editing: all authors.

Research involving human participants

All procedures involving human participants were performed in accordance with the ethical standards of the relevant institutional and national research committees and with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Informed consent

The study followed the ethical procedures applicable to research involving routine care data under the MR-004 reference methodology. Specific patient information was provided in accordance with national regulations. All patients were fully informed about the nature of the study and were given the opportunity to object to the use of their medical data. No patient objected to participation.

Declaration on the use of generative artificial intelligence and AI-assisted technologies

During preparation of this manuscript, the authors used ChatGPT to improve the English language and readability of the text under human supervision. The authors subsequently reviewed and edited the content as necessary and take full responsibility for the content of the published article.

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Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, including honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership or other equity interests, expert testimony, or patent-licensing arrangements, related to the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2026.07.010.

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Siham Benkerrou[a,b], Piotr Dolecki[a], Marie Anne Melone[c], Pierre Tankéré[d,e,f], Isabelle Bossard[b], Amélie Pillot[g], Maxime Patout[h], Guillaume Bao[g], Hélène Prigent[a,i], Antoine Leotard[a,i,*]

[a] *Service de Physiologie et d'Explorations Fonctionnelles, AP-HP, GHU Paris Saclay, Hôpital Raymond Poincaré, FHU UMANHYS, Garches, France*
[b] *Centre d'investigation clinique 1429, AP-HP, Hôpital Raymond Poincaré, Garches, France*
[c] *Service de Soins Intensifs Respiratoires, AP-HP, Hôpital Raymond-Poincaré, Garches, France*
[d] *Center for Sleep Medicine and Respiratory Disease, Hospices Civils de Lyon, Lyon, France*
[e] *University Grenoble Alpes, Inserm 1300, HP2, Grenoble, France*
[f] *CNRS UMR 5292, INSERM U 1028, Université Lyon 1, Lyon, France*
[g] *Clinical Neurophysiology and Neuromodulation Unit, Department of Physiology, Raymond Poincaré Hospital, Assistance Publique-Hôpitaux de Paris, Garches, France*
[h] *La Pitié-Salpétrière University Hospital, Pulmonology and Sleep Department, Sorbonne University, FHU UMANHYS, Paris, France*
[i] *Unité de recherche PHARMAColigo, UR 20261, Université Paris-Saclay, Université de Versailles Saint-Quentin-en-Yvelines, 78000 Versailles, France*

*Corresponding author.
E-mail address: antoine.leotard@aphp.fr (A. Leotard).