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LETTER TO THE EDITOR

Improvement of daytime hypercapnia with nocturnal non-invasive ventilation in familial dysautonomia

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Dear Editors,

Chemoreceptor failure is a dramatic feature of familial dysautonomia (FD), a rare genetic disease caused by a founder mutation in the IκB kinase-associated protein gene (*IKBKAP*) [1–3]. As a consequence, ventilatory responses to hypercapnia are reduced, and those to hypoxia are almost absent. In response to hypoxia, patients can develop paradoxical hypoventilation, hypotension, bradycardia, and potentially death [4–7]. Chemoreflex failure can be devastating during sleep when conscious control of respiration withdraws. Virtually all patients with FD have some degree of sleep-disordered breathing [3, 7], which is a risk factor for sudden unexpected death during sleep [2].

Nocturnal non-invasive ventilation with bi-level positive pressure (BiPAP) reduces daytime hypercapnia in patients with neuromuscular disease, such as Duchenne muscular dystrophy [8, 9], suggesting that nocturnal non-invasive ventilation improves daytime respiratory drive by resetting peripheral and/or central chemoreceptor function [10]. We hypothesized that a similar chemoreceptor reflex resetting occurred in patients with FD after nocturnal non-invasive ventilation. To test this hypothesis, we obtained daytime arterial blood gases in 18 consecutive patients [10 women, 8 men, aged 28 ± 11.7 (mean ± standard deviation) years old] with genetically confirmed FD that were not being treated with non-invasive ventilation, despite having some degree of sleep-disordered breathing. Daytime arterial blood gases were measured at baseline before patients began treatment with nocturnal non-invasive ventilation [BiPAP in all cases except one using continuous positive airway pressure (CPAP)] and arterial blood gases were again obtained at variable follow-up times (ranging from 6 weeks to 6 months) after initiation of noctural non-invasive ventilation. Daytime blood gases after receiving non-invasive ventilation showed that their pCO_2 decreased from 45.9 ± 5.1 to 41.4 ± 4.7 mmHg (paired T test, $P < 0.0001$); and their pO_2 remained stable (from 84.2 ± 14.7 to 91 ± 16 mmHg; paired T test, $P = 0.1167$), as did their pH (7.4 ± 0.04 before and after non-invasive ventilation) (Fig. 1).

As nocturnal non-invasive ventilation virtually eliminated diurnal CO_2 retention in patients with FD, it is possible that the procedure, by normalizing pCO_2 during the night, resets the chemoreflexes to operate at lower CO_2 values, a mechanism postulated in patients with neuromuscular disorders. If confirmed in larger studies, our findings may have clinical implications, as diurnal hypercapnia has been associated with poor prognosis in patients with sleep-disordered breathing [11].

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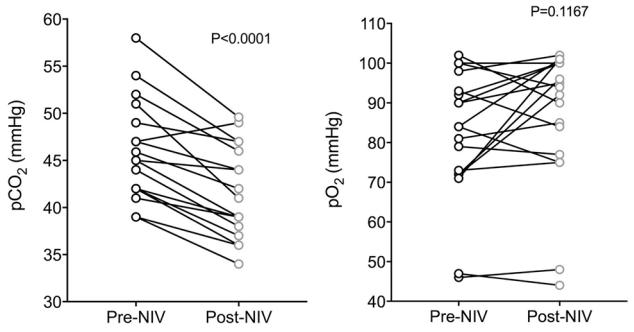

Fig. 1 Arterial blood gas concentrations during wakefulness (daytime) before (Pre-NIV) and after non-invasive ventilation (Post-NIV). Treatment with non-invasive ventilation in patients with familial dysautonomia resulted in significantly reduced arterial pCO_2 concentration during daytime ($P < 0.0001$, left panel), suggesting that nocturnal non-invasive ventilation could reset the chemoreceptor during daytime. Nocturnal non-invasive ventilation did not change arterial pO_2 levels ($P = 0.1167$, right panel)

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Compliance with ethical standards

Conflict of interest Dr. Kaufmann receives funding support from the Familial Dysautonomia Foundation and is Editor in Chief of *Clinical Autonomic Research*. Dr. Palma receives funding support from the Familial Dysautonomia Foundation and is Managing Editor of *Clinical Autonomic Research*. Dr. Norcliffe-Kaufmann receives funding support from the Familial Dysautonomia Foundation.

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