Relative hyperventilation in non-ventilated patients with spinal muscular atrophy

To the Editor:

Spinal muscular atrophy (SMA) is a relatively common autosomal recessive neuromuscular disorder, characterised by progressive degeneration of spinal cord and bulbar motor neurons. It is caused by survival motor neuron (SMN) protein deficiency, due to homozygous loss of function of the *SMN1* gene. Due to the effects of genetic modifiers, SMA displays a broad range in severity. The current clinical classification system distinguishes four types, based on age at onset and acquired motor milestones, *i.e.* infantile onset without achieving the ability to sit (type 1), childhood onset with the ability to sit but not to walk (type 2), childhood onset with the ability to walk for at least a short period of time (type 3) and adult onset with mild symptoms (type 4) [1, 2]. Disease course is progressive, irrespective of type [3] and patients with SMA type 1, 2 and 3 are at high or moderate risk of developing respiratory insufficiency, which may necessitate initiating mechanical ventilation [4, 5].

Reduced lung function in SMA is probably the most important cause of morbidity and mortality in patients with SMA [1, 6, 7] and is caused by a rather unique pattern of weakness that predominates in the intercostal muscles and relatively spares the diaphragm [8]. Both inefficient secretion clearance, leading to recurrent respiratory tract infections and lung damage, as well as hypoventilation, can occur from an early age [6, 9].

There is consensus that patients with SMA type 2 and 3 with symptomatic nocturnal hypoventilation or daytime hypercarbia should start home mechanical ventilation [6] to correct hypoventilation and associated symptoms [10]. In accordance with national guidelines, mechanical ventilation is initiated in our centre in cases of symptoms of nocturnal hypoventilation and a carbon dioxide tension (P_{CO_2}) $\geq$45 mmHg, or when P_{CO_2} increases to $\geq$52.5 mmHg without symptoms. Therefore, measurements of capillary P_{CO_2} during routine follow-up visits are used to screen for hypoventilation. In case of symptoms of nocturnal hypoventilation or increased daytime P_{CO_2}, overnight measurements are obtained to confirm or exclude nocturnal hypoventilation.

In daily practice we noticed that P_{CO_2} levels are regularly lowered or within the lower range of normal, rather than increased, in patients with SMA without ventilatory support. Therefore, we retrospectively analysed capillary P_{CO_2} levels. We only used samples from patients who were not mechanically ventilated at the time of sample collection. Blood samples were obtained during visits to our outpatient clinic. Measurements obtained during hospital admissions or emergency department visits were excluded.

We assessed longitudinal changes of P_{CO_2} levels in non-ventilated patients with a linear mixed-effects model, which included a random intercept and random slope for time per individual. We accounted for the non-linear increase in P_{CO_2} by modelling the fixed effect of time as a cubic function. Confidence intervals were estimated using bootstrapping (n=1000) and significance tests were based on the likelihood ratio test. This study was approved by the local medical ethics committee. Informed consent was obtained from all participants and/or their parents in case of minors.

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Lower ranges of carbon dioxide levels are normal in non-ventilated SMA patients. Physicians should be aware of pending respiratory insufficiency if carbon dioxide levels increase to normal levels in patients with pre-existing low carbon dioxide levels https://bit.ly/2Ag7jQ5

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We analysed 708 capillary blood samples from 69 patients with genetically confirmed SMA. The median (interquartile range (IQR)) number of samples per patients was nine (4–14) with a median (IQR) 9 (3–13) years follow-up. Median (IQR) age at sample collection was 16.2 (10.6–28.4) years. The majority of patients had SMA type 2 (n=52, 75%), and the remainder had type 3 (n=14, 20%) or type 1 (n=3, 4%). Mean P_{CO_2} was 35.5 mmHg (95% CI 34.7–36.2 mmHg; reference range of 35–45 mmHg) (figure 1a). Lowered P_{CO_2} levels were not the result of concomitant metabolic acidosis, as mean pH was 7.44 (95% CI 7.43–7.44) and mean bicarbonate level was 23.6 mmol·L^{-1} (95% CI 23.3–24.1 mmol·L^{-1}; reference range 22.0–29.0 mmol·L^{-1}).

At the time of writing, 48 (70%) patients did not require (non-)invasive ventilation, whereas in the other 21 patients (non-)invasive ventilation was initiated. Eight (38%) patients could not be weaned off mechanical ventilation after an episode of acute respiratory failure due to infection (n=7) or surgery (n=1); the other 13 (62%) developed nocturnal hypoventilation. Median (IQR) age at initiation of ventilation for these 21 patients was 18.5 (11.4–37.0) years.

As all samples were taken prior to initiating (non-)invasive ventilation, we compared blood P_{CO_2} levels over time between the two groups. Levels of P_{CO_2} were lowered or within the lower range of normal in blood samples of the 48 patients in whom mechanical ventilation had not been initiated (mean P_{CO_2} 35.4 mmHg, 95% CI 34.5–36.3 mmHg; n=192). Similar results were found for the 21 patients who ultimately required ventilation, in their samples obtained >1 year prior to start of (non-)invasive mechanical ventilation. However, a significant increase in P_{CO_2} levels was observed in the year prior to initiation of mechanical ventilation (figure 1b): 5 years prior to initiation of ventilation mean daytime capillary P_{CO_2} was 34.2 mmHg (95% CI 32.9–35.3 mmHg; n=21), increasing to 36.7 mmHg (95% CI 35.2–38.1 mmHg) 1 year prior to start of mechanical ventilation (p<0.001) and further to 37.8 mmHg (95% CI 36.2–39.5 mmHg) at the start of mechanical ventilation.

Together, these data show that most non-ventilated patients with SMA have daytime P_{CO_2} levels in the lower range of normal. These levels increase to or beyond the upper limit of normal in the year prior to initiation of (non-)invasive ventilation. Additionally, overnight P_{CO_2} levels in non-ventilated patients show similar results. Mean overnight arterial P_{CO_2} (187 measurements, 34 patients) was 36.1 mmHg (95% CI 35.0–37.2 mmHg). In patients who ultimately required (non-)invasive ventilation (n=16), there was a significant increase of 0.38 mmHg per year (95% CI 0.08–0.86 mmHg; p=0.013), whereas it remained stable in patients not requiring ventilation (n=18).

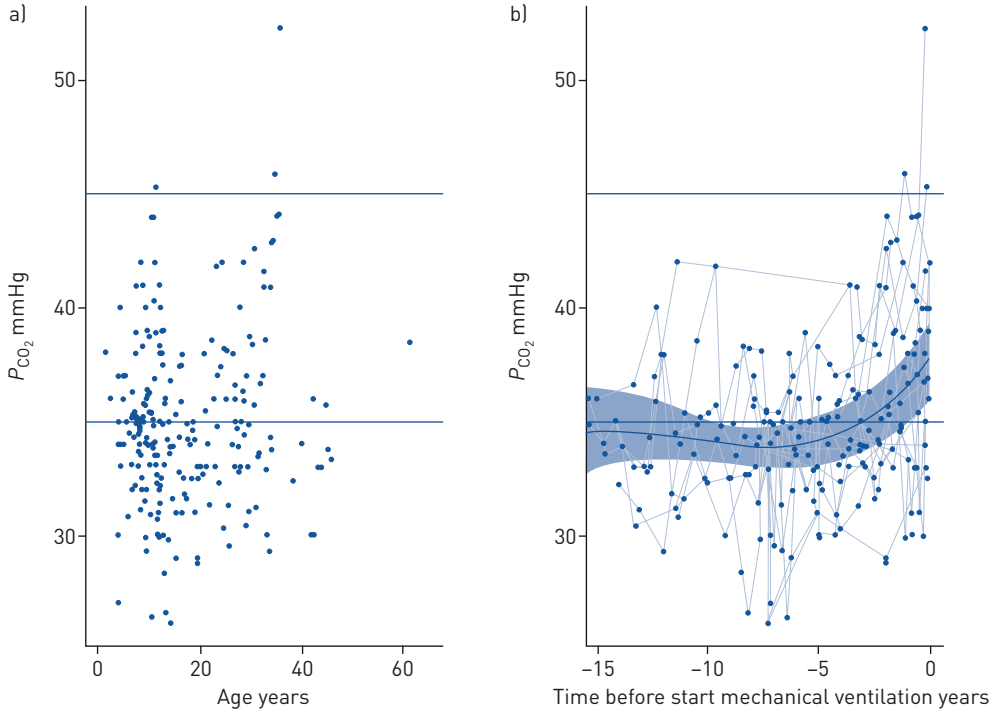

FIGURE 1 Capillary carbon dioxide tension (P_{CO_2}) in a) all patients at different ages and b) patients who ultimately required ventilation, at time before initiation of ventilation. Horizontal lines represent normal range of carbon dioxide levels (35–45 mmHg). Regression line: P_{CO_2}=38.0+(1.272×time)+(0.126×time^2)+(0.004×time^3).

Levels of P_{CO_2} in SMA have been studied previously by KHIRANI *et al.* [11]. They reported P_{CO_2} levels within normal range in 16 SMA patients and slight increase with age in patients with SMA type 2. Although mean values were not specified, their published longitudinal data suggest P_{CO_2} levels <35 mmHg in ⩾15 out of 35 measurements, similar to our observations. To the best of our knowledge, this phenomenon is not described in other neuromuscular diseases.

A possible explanation of this phenomenon is the changed mechanics of respiration due to respiratory muscle weakness in patients with SMA. Tidal volumes are known to decrease over time, leading to a compensatory increase in respiratory rate. The consequential rapid shallow breathing pattern is assumed to minimise breathing effort and to reduce diaphragmatic fatigue and would explain an increased P_{CO_2} washout [11]. However, in general, rapid shallow breathing is associated with increased dead space ventilation, which primarily results in increased P_{CO_2} levels. We observed lowered P_{CO_2} levels long before mechanical ventilation was initiated. Therefore, hyperventilation could also be a specific disease characteristic of SMA.

There is evidence that tissues other than α-motor neurons are involved in the SMA disease process, including vasculature [6, 12, 13]. Relative hyperventilation may therefore be caused by altered carbon dioxide sensing in brain(stem) or carotid bodies, adding a dimension to the complexity of respiratory care for patients with SMA. Limitations of this study are related to the retrospective nature. Only blood samples taken during routine follow-up were included for analysis, aiming to include clinically stable patients. However, we cannot exclude that higher P_{CO_2} levels may be explained by intercurrent problems, like respiratory tract infections. We included mainly patients with SMA type 2a (n=30) and 2b (n=22). Data are representative of the recently published longitudinal study on survival and respiratory failure. This study showed that 50% of patients with SMA type 2a (n=75) were dependent on at least nocturnal mechanical ventilation after 17.4 years compared to 14.3% of patients with type 2b (n=51) after 25 years [5].

This observational study highlights the low or low-normal range P_{CO_2} levels in non-ventilated SMA patients. Increases of P_{CO_2} to normal levels may be a sign of pending respiratory insufficiency in some patients with SMA.

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