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Relative hyperventilation in non-ventilated patients with spinal muscular atrophy.

Esther S. Veldhoen¹, Camiel A. Wijngaarde², Laura P. Verweij-van den Oudenrijn¹, Fay-Lynn Asselman², Roelie M. Wösten-van Asperen³, Erik H.J. Hulzebos⁴, Kors van der Ent⁵, Inge Cuppen², Michael A. Gaytant⁶, Ruben P.A. van Eijk²,⁷, W. Ludo van der Pol²

¹ Paediatric Intensive Care Unit and Centre of Home Mechanical Ventilation, Wilhelmina Children’s Hospital, University Medical Centre Utrecht, Utrecht University, The Netherlands

² Department of Neurology, Brain Centre Rudolf Magnus, University Medical Centre Utrecht, Utrecht University, The Netherlands

³ Paediatric Intensive Care Unit, Wilhelmina Children’s Hospital, University Medical Centre Utrecht.

⁴ Child Development and Exercise Centre, Wilhelmina Children’s Hospital, University Medical Centre Utrecht University, The Netherlands

⁵ Department of Paediatric Pulmonology, Wilhelmina Children’s Hospital, University Medical Centre Utrecht University, The Netherlands

⁶ Centre of Home Mechanical Ventilation, Department of Pulmonology, University Medical Centre Utrecht, Utrecht University, The Netherlands

⁷ Biostatistics & Research Support, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, The Netherlands

Corresponding Author: E.S. Veldhoen

Wilhelmina Children’s Hospital, University Medical Centre Utrecht,
PO box 85090,
3508 AB Utrecht
The Netherlands
Tel +31 887554702

E.S.Veldhoen@umcutrecht.nl
Take home message (for social media):

Lower range 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.

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 4 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), or 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 early ages on [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 case of symptoms of nocturnal hypoventilation and a carbon dioxide (pCO₂) level ≥45 mmHg, or when pCO₂ increases ≥52.5 mmHg without symptoms. Measurements of capillary pCO₂ during routine follow-up visits are therefore used to screen for hypoventilation. In case of symptoms of nocturnal hypoventilation or increased daytime pCO₂, overnight measurements are obtained to confirm or exclude nocturnal hypoventilation.

In daily practice we noticed that pCO₂ 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 pCO₂ 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 pCO₂ 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 pCO₂ 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.

We analysed 708 capillary blood samples from 69 patients with genetically confirmed SMA. The median number of samples per patients was 9 (IQR 4-14) with 9 years median follow up (IQR 3-13). Median age at sample collection was 16.2 years (IQR 10.6-28.4). The majority of patients had SMA type 2 ($n=52$, 75%), the remainder type 3 ($n=14$, 20%) or type 1 ($n=3$, 4%). Mean pCO$_2$ was 35.5 mmHg (95% CI 34.7-36.2; reference range of 35 - 45 mmHg), (Fig 1a). Lowered pCO$_2$ 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 (95% CI 23.3 - 24.1; reference range of 22.0 - 29.0 mmol/L).

At the time of writing, 48 patients (70%) did not require (non-)invasive ventilation, whereas in the other 21 patients (non-)invasive ventilation was initiated. Eight patients (38%) 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 age at initiation of ventilation for these 21 patients was 18.5 years (IQR 11.4 - 37.0).

As all samples were taken prior to initiating (non-)invasive ventilation, we compared blood pCO$_2$ levels over time between the two groups. Levels of pCO$_2$ were lowered or within the lower range of normal in blood samples of the 48 patients in whom mechanical ventilation has not been initiated (mean pCO$_2$ 35.4 mmHg, 95% CI 34.5-36.3, 192 samples). Similar results were found for the 21 patients that ultimately required ventilation, in their samples obtained more than one year prior to start of (non-)invasive mechanical ventilation. However, a significant increase in pCO$_2$ levels was observed in the year prior to initiation of mechanical ventilation (Figure 1b): five years prior to initiation of ventilation mean daytime capillary pCO$_2$ was 34.2 mmHg (95% CI 32.9 - 35.3, $n=21$), increasing to 36.7 mmHg (95% CI 35.2 - 38.1) one year prior to start of mechanical ventilation ($p<0.001$) and further to 37.8 mmHg (95% CI 36.2 - 39.5) at the start of mechanical ventilation.

Together, these data show that most non-ventilated patients with SMA have daytime pCO$_2$ 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 pCO$_2$ levels in non-ventilated patients show similar results. Mean overnight arterial pCO$_2$ (187 measurements, 34 patients) was
36.1 mmHg (95% CI 35.0 - 37.2). 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; P=0.013), whereas it remained stable in patients not requiring ventilation (n = 18).

Levels of pCO₂ in SMA have previously been studied by Khirani. They reported pCO₂ 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 pCO₂ levels ≤35 mmHg in at least 15 out of 35 measurements, similar to our observations [11]. 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 minimize breathing effort and to reduce diaphragmatic fatigue and would explain an increased pCO₂ washout [11]. However, in general rapid shallow breathing is associated with increased dead space ventilation, which primarily results in increased pCO₂ levels. We observed lowered pCO₂ 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 alpha-motor neurons are involved in the SMA disease process, including vasculature [6,12,13]. Relative hyperventilation may therefore be caused by altered CO₂ 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 can not exclude that higher pCO₂ 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 depended 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 pCO₂ levels in non-ventilated SMA patients. Increases of pCO₂ levels to normal may be a sign of pending respiratory insufficiency in some patients with SMA.

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Figure 1: Capillary carbon dioxide levels in all patients at different ages (A) and in patients who ultimately required ventilation, at time before initiation of ventilation (B).

Legend: horizontal lines represent normal range of carbon dioxide levels (35 - 45 mmHg).

Regression line in Figure 1B: pCO$_2$ = 38.0 + (1.272 x Time) + (0.126 x Time$^2$) + (0.004 x Time$^3$)