Hypercapnia is not excluded by normoxia in neuromuscular disease patients: implications for oximetry

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Research Article

Hypercapnia is not excluded by normoxia in neuromuscular disease patients: implications for oximetry.

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\textbf{Short Title:} Hypercapnia and normoxia

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Statements

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved by Sydney Local Health District (RPAH-zone) Human Research Ethics Committee (Protocol no.X19-0243). Adult participant consent was waived by Sydney Local Health District (RPAH-zone) Human Research Ethics Committee.

Conflict of Interest Statement

Dr Amanda Piper has received honoraria from ResMed and Philips. The other authors have no conflicts of interest to declare.

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Dr Emma Gray received an NHMRC Postgraduate Scholarship.

Author Contributions

E Gray: Conception and design of study, acquisition of data, analysis and interpretation of data, drafting of manuscript, approval of manuscript to be published.

C Menadue: Conception and design of study, acquisition of data, revising and critical appraisal of manuscript, approval of manuscript to be published.

A Piper: Conception and design of study, revising and critical appraisal of manuscript, approval of manuscript to be published.

K Wong: Analysis and interpretation of data, revising and critical appraisal of manuscript, approval of manuscript to be published.

M Kiernan: Conception and design of study, revising and critical appraisal of manuscript, approval of manuscript to be published.

B Yee: Conception and design of study, revising and critical appraisal of manuscript, approval of manuscript to be published.
Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.
Abstract

Background:

Pulse oximetry is widely used in the assessment of chronic respiratory failure (CHRF) in neuromuscular disease (NMD) patients. CHRF is the major cause of morbidity and mortality, necessitating early diagnosis and intervention. Guidelines suggest an arterial blood gas (ABG) is indicated if oxygen saturations ($\text{SpO}_2$) $\leq$ 94% in the absence of lung disease. However, hypercapnia with normoxia ($\text{SpO}_2$ $\geq$ 95%) has been observed on ABGs of patients with NMD, in particular those with motor neurone disease (MND).

Methods:

A single-centre retrospective audit of room-air ABGs in stable hypercapnic chronic respiratory failure (CHRF) patients from 1990–2020 was performed. Patients with parenchymal lung disease were excluded. Patients were grouped into three main categories: non-NMD, other-NMD and MND.

Findings:

Two-hundred and ninety-seven ABGs with hypercapnia from 180 patients with extrinsic restrictive lung disease were analysed. No patients with non-NMD, 54% of other-NMD and 36% of MND patients demonstrated hypercapnia with normoxia ($\chi^2$ 61.33; $p<0.001$). The potential mechanism is proposed to be a difference in calculated respiratory quotient (RQ). If the A-a gradient is assumed to be normal, the calculated RQ was significantly higher in MND patients and other-NMD patients compared with non-NMD patients (estimated-marginal-mean 0.99 [95%CI 0.94–1.03]; 0.86 [95%CI 0.76–0.96]; 0.73 [95%CI 0.63—0.83] respectively; $p<0.001$) by mixed-model analysis.

Interpretation:

Hypercapnia is not excluded with normal oximetry in NMD patients and may be due to an elevated RQ. This has implications in the diagnosis and monitoring of respiratory insufficiency in NMD patients with oximetry alone.

Funding:
Dr Emma Gray received an NHMRC Postgraduate Scholarship.

**Keywords:** hypercapnia; neuromuscular disorders; respiratory failure; oxygen saturation; respiratory quotient.
Research in context

Evidence before this study

Chronic respiratory failure (CHRF) in neuromuscular disease (NMD) populations confers a worse prognosis, with early detection important to ensure timely delivery of non-invasive ventilation (NIV). We searched Medline for articles from inception to November 2023, using a combination of the following search terms, including their derivatives: “motor neurone disease”, “neuromuscular disease”, “hypercapnia”, “respiratory failure”, “respiratory quotient”, “indirect calorimetry”. In addition reference lists of relevant articles were reviewed. One study of 448 arterial blood gases (ABG) of patients with motor neurone disease (MND) showed a significant increased risk of death when the arterial partial pressure of carbon dioxide (PaCO₂) was greater than 42mmHg(1). In addition, isolated elevated bicarbonate levels were found in 25% of patients with normal PaCO₂ but conferred a worse survival outcome(1). A further study compared the differences in ABGs of patients with acute neuromuscular respiratory failure (NMRF), n=69, and non-NMRF, n=218, in the intensive care unit. The NMRF group showed lower frequency of hypoxia yet higher isolated bicarbonate levels(2). In addition, a study by Nardi et al assessed nocturnal gas exchange in 58 patients with neuromuscular disease on home ventilatory support, and found approximately one-third of patients with residual alveolar hypoventilation, manifesting as high transcutaneous carbon dioxide (TcCO₂) values, did not have substantial oxygen desaturations(3). However, the prevalence of hypercapnia with normoxia in ABGs in stable NMD patients has not been assessed.

Added value of this study To our knowledge, this is the first study to assess stable arterial blood gases and identify this paradox of co-existant hypercapnia and normoxia in substantial proportions of patients with neuromuscular disorders.
Implications of all the available evidence To date chronic hypercapnic respiratory failure has been thought to exclusively occur in the presence of hypoxia. Most guidelines for the investigation of respiratory failure suggest nocturnal oximetry as a screening test and only one mentions ABGs should be considered if oxygen saturations are ≤94%. Considering the improvement to quality of life and survival in patients upon commencing NIV in NMD populations, recognising the existence of this paradox has significant implications for the management of these patients.
**Introduction**

Neuromuscular diseases (NMD) are a heterogenous group of diseases affecting various components of the motor unit, leading to muscle atrophy and weakness. It is thought when the diaphragm and respiratory muscles become involved, chronic respiratory failure (CHRF) ensues. Non-invasive ventilation (NIV) is indicated and recommended in NMD patients if nocturnal hypoventilation with or without daytime CHRF is detected (4, 5) Motor neurone disease (MND, or amyotrophic lateral sclerosis (ALS)) is a rapidly progressive NMD and the degree of respiratory involvement is a major adverse prognostic factor and common cause of death.(6) NIV in MND has been shown to both prolong and improve quality of life.(7)

Pulse oximetry is widely available and used as part of the respiratory assessment of NMD patients. Both the European Federation of Neurological Societies (EFNS) guideline and American Academy of Neurology (AAN) practice paper recommends transcutaneous nocturnal oximetry as a screening test for hypoventilation, as well as other measures of lung function.(8, 9) Neither recommend an arterial blood gas (ABG), and the EFNS states that ABG abnormalities are generally a late finding.(8) The NICE guidelines for MND recommend an ABG if oxygen saturations ($SpO_2$) ≤94% in the absence of lung disease.(4) The basis of this guideline is that normoxia ($SpO_2$ ≥95%), usually results in an arterial partial pressure of carbon dioxide ($PaCO_2$) ≤45mmHg, when using the alveolar gas equation (AGE) below and the assumption that the respiratory quotient (RQ) is 0.8.

$$PAO_2 = (P_{atm} – P_{H2O})FiO_2 – PaCO_2/RQ$$

$P_{atm}$ = atmospheric pressure (sea level, 760mmHg)

$PH_{H2O}$ = partial pressure of water (45mmHg)
FiO₂ = fraction of inspired O₂ (0.21 on RA)

However in our clinical experience, hypercapnia with normoxia whilst breathing room air (RA) has been observed in stable patients with NMD, with more marked elevations in carbon dioxide seen in those with MND. If the PAO₂ is calculated via the AGE with the assumption that RQ=0.8, the resultant Alveolar-arterial (A-a) gradient is negative. This is not physiologically plausible.

The only variable to explain this paradox is the RQ, which is defined as the rate of carbon dioxide (CO₂) production (VCO₂) over the rate of oxygen (O₂) consumption (VO₂). It is generally accepted that RQ is 0.8, where fats (RQ=0.7), carbohydrates (RQ=1.0) and protein (RQ=0.8) are metabolised as part of a balanced diet. The RQ has been found to be within the range 0.67 – 1.3 in physiologic states.(10) It is a crude measurement of overall substrate utilisation and muscles are the major metabolic organ. Dysregulation of energy metabolism, involving lipids and carbohydrates, has been shown in many NMDs, (11-14) and in MND may contribute to disease progression.(15) Thus it is biologically plausible that altered metabolism in NMD patients could result in an altered RQ, and hence hypercapnia with normoxia.

This has implications for the diagnosis and management of respiratory insufficiency in NMDs, as pulse oximetry is used as a screening test, both in the clinic and nocturnally. Our primary aim was to systematically document the coexistence of hypercapnia and normoxia on ABGs in patients with CHRF. Our secondary aims were to determine whether there was a difference in prevalence between non-NMD, other-NMD and MND patients, and if there was a difference in the calculated RQ to potentially explain this observed phenomenon.
We hypothesise that hypercapnia is not excluded by the presence of normoxia in NMD patients, especially MND patients. The proposed mechanism is due to an elevated RQ.

**Materials and Methods**

1. **Study Design:**

This single-centre retrospective study was conducted at Royal Prince Alfred Hospital (RPAH), Sydney, Australia, following approval from the Sydney Local Health District (RPAH-zone) Human Research Ethics Committee (Protocol no. X19-0243). The need for informed consent for the retrospective collection of data from hospital medical records was waived.

2. **Participants:**

Patients were retrospectively identified from the institution’s home ventilation database over 30 years from 1990-2020. Patients were prospectively added to the database if they commenced and used home ventilation for nocturnal hypoventilation with or without daytime CHRF for at least one month. The ABGs analysed were included from any time, including prior to the institution of NIV. Physician diagnosed cause of CHRF, and other relevant respiratory history, including spirometry, was documented.

2.1 **Inclusion Criteria:**

Patients were grouped into three main categories based on the primary cause of CHRF:

1. Non-neuromuscular diseases (non-NMD)
   
   a. Obesity hypoventilation syndrome (including obesity and hemi-diaphragm paralysis)
b. Chest wall disorders

2. Other Neuromuscular diseases (other-NMD)
   a. Muscular Dystrophy (MD)
   b. Post-polio
   c. High-level spinal cord injury (C4/S)
   d. Other (e.g. myopathy)

3. Motor Neurone Disease (MND)

2.2 Exclusion Criteria:

Patients were excluded if they had either a background of physician-diagnosed parenchymal lung disease, or an obstructed spirometric ratio to ensure that the assumption of a normal A-a gradient for age was valid. In addition, patients were excluded if arterialised earlobe capillary blood gases (CBG) had been taken, due to the wide limits of agreement between CBG PO$_2$ and PaO$_2$, especially at higher PO$_2$ (16). Patients who were on supplemental oxygen, continuous ventilation or ventilated via a tracheostomy were excluded and patients who were on nocturnal ventilation only, had early morning ABGs excluded for analysis. This was to ensure PAO$_2$ was not falsely elevated.

3. Measurements:

Patient’s records were reviewed for demographic details, diagnosis and type of enteral nutrition (i.e. percutaneous gastrostomy (PEG) tube). ABGs were considered post-NIV if they were taken more than a month after prescription of NIV, regardless of compliance. Lung function was reviewed for each patient. Height and weight were documented for each patient.
Up to four ABGs were collected for each patient to reduce the bias in ABG selection, provided the following conditions were met:

1. $\text{PaCO}_2 \geq 46 \text{mmHg}$
2. Steady state ($\text{pH} 7.35-7.45$)
3. Documented on RA
4. Taken in an outpatient setting

The patient’s A-a gradient was assumed to be normal for their age and was calculated by:

$$\text{A-a gradient} = \text{PAO}_2 - \text{PaO}_2 = (\text{Age} + 10)/4 \quad (17)$$

The PAO$_2$ was calculated using the measured PaO$_2$ by:

$$\text{PAO}_2 = (\text{Age} + 10)/4 + \text{PaO}_2$$

The RQ was then calculated by rearranging the AGE:

$$\text{RQ} = \frac{\text{PaCO}_2}{[150.15- (\text{Age} + 10)/4 - \text{PaO}_2]}$$

4. Statistical Analysis:

The primary outcome was to assess for the coexistence of hypercapnia and normoxia. The secondary outcome was to determine whether there was a difference in prevalence between non-NMD, other-NMD and MND diagnostic groups and to see if there was a difference in the calculated RQ between the three groups which may explain this phenomenon.
Continuous variables were expressed as mean and standard deviation (SD), if normally distributed, or median and interquartile range or range if non-normally distributed. Chi-square test and Fisher’s exact test was used to assess proportions, and one-way ANOVA was used to assess continuous variables of demographic data across groups.

As up to four ABGs were recorded for each patient, mixed-model analysis was used to assess the difference in ABG parameters as well as the calculated RQ, using a patient level random intercept. Potential predictors of RQ were assessed by univariate analyses with continuous variables BMI, time, vital capacity and age, and factor variables diagnostic group, sex, NIV status and method of nutrition. Using a forward stepwise process, multivariate models were evaluated including candidate variables found significant on univariate analysis with p<0.10. IBM SPSS Statistics for Windows, version 27.0.1.0 (SPSS Inc., Chicago, Ill. USA) was used for analysis and statistical significance was considered p<0.05.

**Results**

A total of 807 CHRF patients were treated with long-term NIV from 1990 until 2020. One-hundred and eighty patients had extrinsic restrictive lung diseases and met the inclusion criteria for hypercapnia demonstrated by ABGs (Fig. 1). Up to four ABGs for each patient were included, totalling 297 ABGs. The demographics of the three groups differed considerably due to the inherent differences of the disease profiles (Table 1).

**Figure 1.**

**Table 1.**
Table 2 shows that despite similar pH, PaCO$_2$ and bicarbonate levels on ABGs across all groups, the PaO$_2$ and arterial oxygen saturation (SaO$_2$) are considerably higher in both neuromuscular groups compared to the non-NMD group.

Table 2.

A plot of arterial SaO$_2$ and PaCO$_2$ (Fig. 2) shows a clear group of patients with NMDs that have co-existent hypercapnia and normoxia. Thirty-seven of 69 (54%) other-NMD and 8 of 22 (36%) MND patients demonstrated normoxia with hypercapnia on at least one ABG, whilst no non-NMD patients displayed this phenomenon (difference in proportions, X$^2$ 61.33; p<0.001).

Figure 2.

A plot of the calculated A-a gradient against age, using the assumption RQ=0.8, shows several NMD patients with a negative A-a gradient, which is physiologically impossible (Fig. 3).

Figure 3.

From the AGE there were 33 ABGs (11%) with a calculated RQ below the physiologic range and one ABG (0.3%) with a calculated RQ above the physiologic range (0.67-1.3).

On univariate analysis diagnostic group (F$_{(2,189.7)}$=58.96; p<0.001), BMI (F$_{(1,193)}$=56.44; p<0.001), age (F$_{(1,215.8)}$=7.07; p=0.008) and sex (F$_{(1,176.8)}$=3.82; p=0.05) were significant predictors of the RQ. By
multivariate mixed-model analysis only diagnostic group \((F_{(2,189)} = 16.2; p<0.001)\) and BMI \\
\((F_{(1,189)} = 19.05; p<0.001)\) were independent predictors of RQ with an interaction effect between them \\
\((F_{(2,189)} = 6.48; p=0.002)\).

The calculated RQ was significantly higher in MND patients and other-NMD patients compared with non-NMD patients (estimated-marginal-mean 0.99 [95%CI 0.94-1.03]; 0.86 [95%CI 0.76-0.96]; 0.73 [95%CI 0.63-0.83] respectively; \(p<0.001\) for both comparisons) (Fig. 4).

**Figure 4.**

In both NMD groups, the RQ increases 0.01 for every 1kg/m\(^2\) decrease in BMI. The RQ was higher for the MND and other-NMD groups than the non-NMD at lower BMIs (Fig. 5). BMI had little effect in the non-NMD group and the intercept of 0.79, is very close to clinically used 0.8.

**Figure 5.**

Data on feeding was available for 133 (74%) patients, with 6 patients having PEG tubes in-situ (2 MND, 4 other-NMD). There was no effect of this on RQ \((F_{(2,98.5)} = 0.25; p=0.78)\). There were 93 (31%) ABGs taken prior to NIV commencement and 202 (68%) taken after at least one month of prescribed NIV therapy. There was no effect of NIV on RQ \((F_{(1,227.7)} = 0.62; p=0.43)\).
Discussion

We found hypercapnia can occur in the presence of normoxia in patients with NMDs. Around a third of MND and half of other-NMD patients had elevated PaCO₂ levels in the presence of normoxia on at least one ABG. Elevations in the calculated RQ were seen in NMD patients, more marked in the MND population. This may point to a potential mechanism. There is no literature to date overtly describing this phenomenon, however there is increasing literature to support monitoring CO₂ rather than oximetry alone in this group of patients.

The implications for this normoxia-hypercapnia paradox are far reaching. In MND, there is a median 12-month delay from onset of first symptom to diagnosis,(18, 19) which occurs at the midpoint of the disease pathway, delaying the only available disease modulating pharmacotherapy, Riluzole, and access to clinical trials.(18) From there the diagnosis of CHRF is made from a constellation of symptoms and investigations, of which oximetry plays a significant part, namely due to its ease of collection. Our physiological training, as upheld by current guidelines, has led us to be reassured by normal SpO₂ negating the presence of significant hypercapnia, itself a late sign of respiratory involvement and a poor prognostic sign. However, as this study has shown, relying on SpO₂ without a direct measure of CO₂ may further delay the diagnosis of respiratory involvement and institution of therapy proven to improve quality and length of life.(7)

The majority of guidelines acknowledge that symptoms of respiratory insufficiency occur insidiously and that the initiation of NIV confers a survival advantage, recommending close monitoring. In addition most guidelines include PaCO₂≥45mmHg, to be an indication to commence NIV, however direction surrounding when to do an ABG is variable. The UK NICE guidelines for MND suggest an ABG if SpO₂<94% in the absence of lung disease.(4) Neither the EFNS or AAN recommend CO₂
measurement.(8, 9) The section on ABGs in the 2002 ATS/ERS guideline on respiratory muscle testing,(20) suggest daytime hypercapnia is unlikely unless respiratory muscle strength testing is reduced to <40% or predicted VC <50%. This was updated in 2020 and did not include ABGs.(21) The 2019 MND position statement by the Canadian Thoracic Society recommended CO₂ measurement by ABG, CBG or TcCO₂ when hypercapnia was “suspected by symptoms”.(22)

A retrospective assessment of 624 patients from a French MND centre showed that guidelines for NIV initiation were followed in 91% of cases, comprising one symptom and one physiological parameter, yet at initiation the majority (58%) had evidence of daytime hypercapnia (median PaCO₂ 48mmHg).(23) In addition one in ten were started in the context of acute respiratory distress. They suggested that late initiation of NIV is more often due to poor surveillance of pulmonary function.

Previous research comparing the sensitivity of nocturnal TcCO₂ monitoring to SpO₂ in patients with NMD has emphasised the importance of CO₂ monitoring. A study by Nardi et al,(3) assessing nocturnal gas exchange in 58 patients with NMD, mostly DMD, on ventilatory support found approximately one-third of patients with elevated TcCO₂ values did not have substantial oxygen desaturations. Likewise, a study of 72 patients with either NMD (predominantly MND) or chest wall disorders, identified nocturnal hypoventilation using TcCO₂ criteria without associated hypoxemia in 33% of the cohort.(24) A recent retrospective analysis of ABGs from the intensive care unit of acute respiratory failure in the NMD and non-NMD populations showed that those with NMD had a lower frequency of hypoxia (33.8% vs 50.5%, p<0.05), yet higher isolated serum bicarbonate levels (24.8mmol/L vs 23.4mmol/L, p<0.01).(2) Furthermore a review of 448 ABGs of MND patients showed a significant increase in risk of death when PaCO₂ >42mmHg.(1) In addition bicarbonate elevation without significant PaCO₂ elevation occurred in about 25% of patients, with no difference in the frequency of respiratory symptoms compared to those with normal ABG parameters, but with a lower survival time (0.87 years vs 1.39
years, p<0.001).

These studies lend support to the hypothesis that hypercapnia and normoxia can co-exist in NMD patients.

An elevated RQ, the proposed mechanism thorough which this hypercapnia-normoxia paradox can occur, found in patients with NMD in our study was further exaggerated in those with lower BMIs. An elevated RQ can occur when there is elevated CO₂ production through either the intake of excess calories where lipogenesis occurs, or a hypermetabolic state. Hypermetabolism, defined as a significant increase in measured resting energy expenditure (REE) relative to predicted REE, is known to occur in around 50% of MND patients. A recent retrospective study of 48 patients with MND calculated RQ from indirect calorimetry (IC), and found RQ increased as the percentage body-fat decreased. Furthermore, body-fat percentage was positively correlated with BMI. Proposed mechanisms for the presence of hypermetabolism in MND patients include excitotoxicity and uncontrolled fasciculations, subthalamic dysfunction, dysregulated autophagy and mitochondrial dysfunction. Hypermetabolism is also thought to occur in Duchenne muscular dystrophy (DMD) due to hypercatabolism of skeletal muscle and increasing basal metabolic rate with age.

Disturbances in energy metabolism, particularly surrounding glucose metabolism and intolerance have been shown to occur in many NMDs. Glycolysis and fatty acid metabolism alterations have been found in DMD, as well as hyperinsulinaemia, glucose resistance and mitochondrial dysfunction in MD type 1. There is also increasing evidence, particularly surrounding altered glucose metabolism, in people with MND which may contribute to disease progression. In addition, the majority of the pathogenic genes associated with MND have important roles in glucose uptake as well as lipid and carbohydrate metabolism. Overall, it appears that metabolic dysfunction is implicated in part, in the disease process of many NMDs, supporting the proposed mechanism of an increased RQ.
It is likely that the mild elevation of CO\textsubscript{2} production through the hypermetabolic state and metabolic disturbances seen in NMD is unable to be offset by an appropriate increase in V\textsubscript{A} due to respiratory muscle weakness, especially as the disease progresses. However, hypercapnia in the presence of normoxia cannot be explained solely through hypoventilation. Although the RQ is a blunt instrument in that it is the summary of whole body substrate oxidation, it does appear to be elevated in a subset of patients with NMD.

There are several key limitations in this study. The first is generalisability of results given the retrospective nature of this single-centre study. In addition, over the last decade our practice has been to use CBG analysis instead of ABGs in our NMD patients. This led to approximately 40\% of our NMD patients being excluded from this analysis. This study assumes a normal A-a gradient for age, which is subsequently used to calculate the RQ. In addition, some ABGs were taken prior to the initiation of NIV, whilst others after at least one month of prescribed therapy. Although there was no statistical relationship between the RQ relative to the initiation of NIV, it did not take into account compliance or hours of usage. However this study highlights that normal SpO\textsubscript{2} on therapy does not preclude hypercapnia, and hence the measurement of CO\textsubscript{2} is required to assess the effect of NIV on gas-exchange.

The gold standard for the measurement of RQ is by IC under stable conditions including a minimum of 5 hours fasting, no physical activity, and abstinence from nicotine, caffeine and other stimulants.(32) These conditions were not documented in this study. Additionally, a calculated value by rearranging the AGE assuming a normal A-a gradient is less rigorous. Nevertheless it would be assumed that the same issues bias the results of all groups of CHRF by a similar amount, indicating that the relative differences may hold the answers to how this observed phenomenon occurs. Additionally the non-NMD group had a linear relationship with BMI, with an imperceivable slope and an intercept of 0.79,
close to the current assumed RQ 0.8. There was also no information available regarding muscle mass, and BMI was used as a surrogate of body composition.

Despite these limitations in attempting to explain the co-existence of hypercapnia and normoxia, this study clearly shows that normoxia does not categorically rule out the presence of significant daytime hypercapnia in patients with NMD. This has clinical implications not only in the diagnosis of CHRF but also in the ongoing management once patients are commenced on therapy, especially as the presence of CHRF has implications for prognosis, and therapy with NIV can affect quality and quantity of life. Oximetry alone, without measuring CO₂ either directly with blood-gases or via TcCO₂ will miss significant proportions of NMD patients with hypercapnia.
Tables

**Table 1.** Demographic details of the three groups

<table>
<thead>
<tr>
<th></th>
<th>Non-NMD (n=89)</th>
<th>Other-NMD (n=69)</th>
<th>MND (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 14.0</td>
<td>44 ± 16.8</td>
<td>64 ± 12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female n, (%)</td>
<td>50 (56%)</td>
<td>15 (22%)</td>
<td>6 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.2 ± 16.97</td>
<td>25.7 ± 7.44</td>
<td>23.5 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vital Capacity (% predicted)</td>
<td>54 ± 19.5 (n=85)</td>
<td>32 ± 18.8 (n=64)</td>
<td>62 ± 19.7 (n=21)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Non-NMD = non-neuromuscular disease; Other-NMD = other-neuromuscular disease; MND = motor neurone disease; BMI = body mass index.

**Table 2:** Mean values of arterial blood gases for the three groups

<table>
<thead>
<tr>
<th></th>
<th>Non-NMD (n=89)</th>
<th>Other-NMD (n=68)</th>
<th>MND (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.39 ± 0.02</td>
<td>7.39 ±0.02</td>
<td>7.39 ± 0.02</td>
<td>=0.7</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>60.0 ±7.33</td>
<td>75.2 ±12.37</td>
<td>76.5 ± 9.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>52.7 ± 5.15</td>
<td>51.6 ± 4.69</td>
<td>54.0 ± 5.82</td>
<td>=0.1</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>90.0 ± 3.68</td>
<td>94.4 ± 2.55</td>
<td>94.6 ± 1.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>32 ± 5.8</td>
<td>30 ± 2.5</td>
<td>32 ± 3.7</td>
<td>=0.08</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td>5.5 ± 3.63</td>
<td>4.4 ± 2.00</td>
<td>5.9 ± 2.64</td>
<td>=0.04</td>
</tr>
</tbody>
</table>

Non-NMD = non-neuromuscular disease; Other-NMD = other-neuromuscular disease; MND = motor neurone disease; PaO₂ = arterial partial pressure of oxygen; PaCO₂ = arterial partial pressure of carbon dioxide; SaO₂ = arterial oxygen saturation; HCO₃⁻ = bicarbonate; BE = base excess
References


Figure 1: Flow diagram

ABG = arterial blood gas; RA = room air; OHS = obesity hypoventilation syndrome; MD = muscular dystrophy; SMA = spinal muscular atrophy; MG = myasthenia gravis
Figure 2. Arterial oxygen saturation and arterial partial pressure of carbon dioxide for patients with non-neuromuscular disorders (cross), other-neuromuscular diseases (triangles) and motor neurone disease (circle). Individual ABGs included. Lines at normoxia (SaO$_2$ ≥ 95%) and hypercapnia (PaCO$_2$ > 45mmHg). Non-NMD = non-neuromuscular disease; Other-NMD = other neuromuscular disease; MND = motor neurone disease; SaO$_2$ = arterial oxygen saturation; PaCO$_2$ = arterial partial pressure of carbon dioxide.
Figure 3. The predicted alveolar-arterial gradient for patients based off the arterial blood gases if the respiratory quotient (RQ) is assumed to be 0.8. The line is the estimated A-a gradient based on age.

Non-NMD = non-neuromuscular disease; Other-NMD = other-neuromuscular disease; MND = motor neurone disease
Figure 4. Mean calculated respiratory quotient (RQ) for each patient by mixed model analysis by diagnostic group (error bars are 95% confidence intervals). (*: p<0.001; ^: p=0.001). Dotted line (...) represents physiological range of RQ 0.67-1.3, dashed line (---) represents RQ 0.8. Non-NMD = non-neuromuscular disease; Other-NMD = other-neuromuscular disease; MND = motor neurone disease
**Figure 5.** Effect of body mass index (kg/m^2) on respiratory quotient for each of the diagnostic groups.

Non-neuromuscular diseases (--), other neuromuscular diseases (—) and motor neurone disease (- -).

Non-NMD = non-neuromuscular disease; Other-NMD = other-neuromuscular disease; MND = motor neurone disease