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

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Shareable abstract (@ERSpublications)
Hypercapnia is not excluded with normal oximetry in NMD patients and may be due to an elevated respiratory quotient. This has implications in the diagnosis and monitoring of respiratory insufficiency in NMD patients with oximetry alone. https://bit.ly/4bFKUsu

Abstract

Background Pulse oximetry is widely used in the assessment of chronic respiratory failure in neuromuscular disease (NMD) patients. Chronic respiratory failure is the major cause of morbidity and mortality, necessitating early diagnosis and intervention. Guidelines suggest that an arterial blood gas (ABG) measurement is indicated if oxygen saturation (S_{pO_2}) is ⩽94% in the absence of lung disease. However, hypercapnia with normoxia (S_{pO_2} ⩾95%) has been observed on ABGs of patients with NMD, in particular those with motor neurone disease.

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

Findings 297 ABGs with hypercapnia from 180 patients with extrinsic restrictive lung disease were analysed. No patients with non-NMD, 54% of patients with other NMD and 36% of motor neurone disease patients demonstrated hypercapnia with normoxia (Chi-squared 61.33; p<0.001). The potential mechanism is proposed to be a difference in calculated respiratory quotient. If the alveolar–arterial gradient is assumed to be normal, the calculated respiratory quotient was significantly higher in motor neurone disease patients and other NMD patients compared with non-NMD patients (estimated marginal mean 0.99, 95% CI 0.94–1.03; 0.86 0.76–0.96; 0.73, 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 respiratory quotient. This has implications in the diagnosis and monitoring of respiratory insufficiency in NMD patients with oximetry alone.

Introduction

Neuromuscular diseases (NMDs) are a heterogeneous group of diseases affecting various components of the motor unit, leading to muscle atrophy and weakness. It is thought that when the diaphragm and respiratory muscles become involved, chronic respiratory failure (CHRF) ensues. Noninvasive ventilation (NIV) is indicated and recommended in NMD patients if nocturnal hypoventilation with or without daytime CHRF is detected [1, 2]. Motor neurone disease (or amyotrophic lateral sclerosis) is a rapidly progressive NMD and the degree of respiratory involvement is a major adverse prognostic factor and common cause of death [3]. NIV in motor neurone disease has been shown to both prolong and improve quality of life [4].

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 [5, 6]. Neither recommend an arterial blood gas (ABG), and the EFNS states that ABG abnormalities are generally a late finding [5]. The National Institute for Health and Care Excellence (NICE) guidelines for motor neurone disease recommend an ABG if oxygen saturations (S_{pO_2}) $\leqslant$94% in the absence of lung disease [1]. The basis of this guideline is that normoxia (S_{pO_2} $\geqslant$95%) usually results in an arterial partial pressure of carbon dioxide (P_{aCO_2}) $\leqslant$45 mmHg, when using the alveolar gas equation following and the assumption that the respiratory quotient (RQ) is 0.8.

$$P_{AO_2} = (P_{atm} - P_{H_2O})F_{IO_2} - P_{aCO_2}/RQ$$

where P_{AO_2}: alveolar oxygen tension; P_{atm}: atmospheric pressure (at sea level, 760 mmHg); P_{H_2O}: partial pressure of water (45 mmHg); F_{IO_2}: fraction of inspired oxygen (0.21 on room air); P_{aCO_2}: arterial carbon dioxide tension.

However, in our clinical experience, hypercapnia with normoxia while breathing room air has been observed in stable patients with NMD, with more marked elevations in carbon dioxide (CO_2) seen in those with motor neurone disease. If the P_{AO_2} is calculated *via* the alveolar gas equation 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 CO_2 production over the rate of oxygen consumption. 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 physiological states [7]. 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 [8–11], and in motor neurone disease may contribute to disease progression [12]. 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 motor neurone disease 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 motor neurone disease patients. The proposed mechanism is due to an elevated RQ.

Materials and methods
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 number X19-0243). The need for informed consent for the retrospective collection of data from hospital medical records was waived.

Participants
Patients were retrospectively identified from the institution's home ventilation database over 30 years from 1990 to 2020. Patients were prospectively added to the database if they commenced and used home ventilation for nocturnal hypoventilation with or without daytime CHRF for $\geqslant$1 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.

Inclusion criteria
Patients were grouped into three main categories based on the primary cause of CHRF: 1) non-NMDs: obesity hypoventilation syndrome (including obesity and hemi-diaphragm paralysis) and chest wall disorders; 2) other NMDs: muscular dystrophy, post-polio, high-level spinal cord injury (C4/5) and other (*e.g.* myopathy); and 3) motor neurone disease.

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 oxygen tension and arterial partial pressure of oxygen (P_{aO_2}), especially at higher oxygen tension [13]. 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 that P_{AO_2} was not falsely elevated.

Measurements

Patient 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) $P_{aCO_2} \geqslant 46$ mmHg; 2) steady state (pH 7.35–7.45); 3) documented on room air; 4) taken in an outpatient setting.

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

$$\text{A-a gradient} = P_{AO_2} - P_{aO_2} = (\text{Age} + 10)/4 \quad [14]$$

The P_{AO_2} was calculated using the measured P_{aO_2} by:

$$P_{AO_2} = (\text{Age} + 10)/4 + P_{aO_2}$$

The RQ was then calculated by rearranging the alveolar gas equation:

$$RQ = P_{aCO_2}/[150.15 - (\text{Age} + 10)/4 - P_{aO_2}]$$

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 motor neurone disease 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±SD, if normally distributed, or median and interquartile range or range if non-normally distributed. Chi-squared test and Fisher's exact test were 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 the continuous variables body mass index (BMI), time, vital capacity and age, and the 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, Chicago, IL, USA) was used for analysis and statistical significance was considered at $p<0.05$.

Results

A total of 807 CHRF patients were treated with long-term NIV from 1990 until 2020. 180 patients had extrinsic restrictive lung diseases and met the inclusion criteria for hypercapnia demonstrated by ABGs (figure 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).

Table 2 shows that despite similar pH, P_{aCO_2} and bicarbonate levels on ABGs across all groups, the P_{aO_2} and arterial oxygen saturation (S_{aO_2}) were considerably higher in both neuromuscular groups compared to the non-NMD group.
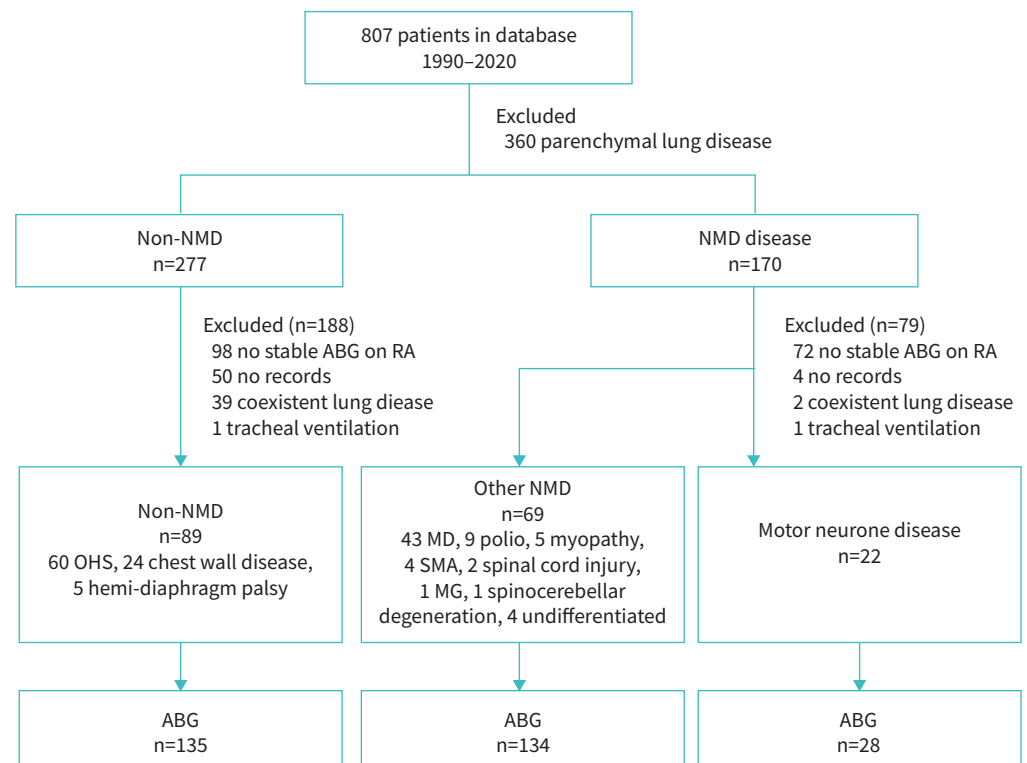
FIGURE 1 Flow diagram. NMD: neuromuscular disease; ABG: arterial blood gas; RA: room air; OHS: obesity hypoventilation syndrome; MD: muscular dystrophy; SMA: spinal muscular atrophy; MG: myasthenia gravis.

A plot of arterial S_{aO_2} and P_{aCO_2} (figure 2) shows a clear group of patients with NMDs that have coexistent hypercapnia and normoxia. 37 (54%) out of 69 other NMD and eight (36%) out of 22 motor neurone disease patients demonstrated normoxia with hypercapnia on at least one ABG, while no non-NMD patients displayed this phenomenon (difference in proportions, Chi-squared 61.33; p<0.001).

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 (figure 3).

From the alveolar gas equation there were 33 (11%) ABGs with a calculated RQ below the physiologic range and one (0.3%) ABGs 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 ($F_{(1,189)}=19.05$;

TABLE 1 Demographic details of the three groups				
	Non-NMD	**Other NMD**	**Motor neurone disease**	**p-value**
Patients n	89	69	22	
Age years	61±14.0	44±16.8	64±12.0	<0.001
Female	50 (56)	15 (22)	6 (27)	<0.001
BMI kg·m^{-2}	42.2±16.97	25.7±7.44 (n=55)	23.5±6.20 (n=19)	<0.001
Vital capacity % predicted	54±19.5 (n=85)	32±18.8 (n=64)	62±19.7 (n=21)	<0.001

Data are presented as mean±SD or n (%), unless otherwise stated. NMD: neuromuscular disease; BMI: body mass index.

TABLE 2 Mean values of arterial blood gases for the three groups				
	Non-NMD	**Other NMD**	**Motor neurone disease**	**p-value**
Patients	89	68	22	
pH	7.39±0.02	7.39±0.02	7.39±0.02	0.7
P_{aO_2} mmHg	60.0±7.33	75.2±12.37	76.5±9.46	<0.001
P_{aCO_2} mmHg	52.7±5.15	51.6±4.69	54.0±5.82	0.1
S_{aO_2} %	90.0±3.68	94.4±2.55	94.6±1.89	<0.001
HCO_3^- mmol·L^{-1}	32±5.8	30±2.5	32±3.7	0.08
Base excess mmol·L^{-1}	5.5±3.63	4.4±2.00	5.9±2.64	0.04

Data are presented as n or mean±SD, unless otherwise stated. NMD: neuromuscular disease; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{aO_2}: arterial oxygen saturation; HCO_3^-: bicarbonate.

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 motor neurone disease patients and other NMD patients compared with non-NMD patients (estimated marginal mean 0.99, 95% CI 0.94–1.03; 0.86, 0.76–0.96; and 0.73, 0.63–0.83, respectively; p<0.001 for both comparisons) (figure 4).

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

Data on feeding was available for 133 (74%) patients, with six patients having PEG tubes *in situ* (two motor neurone disease, four other NMD). There was no effect of this on RQ ($F_{(2,98.53)}=0.25$; p=0.78). There were 93 (31%) ABGs taken prior to NIV commencement and 202 (68%) taken after at least 1 month of prescribed NIV therapy. There was no effect of NIV on RQ ($F_{(1,227.7)}=0.62$; p=0.43).
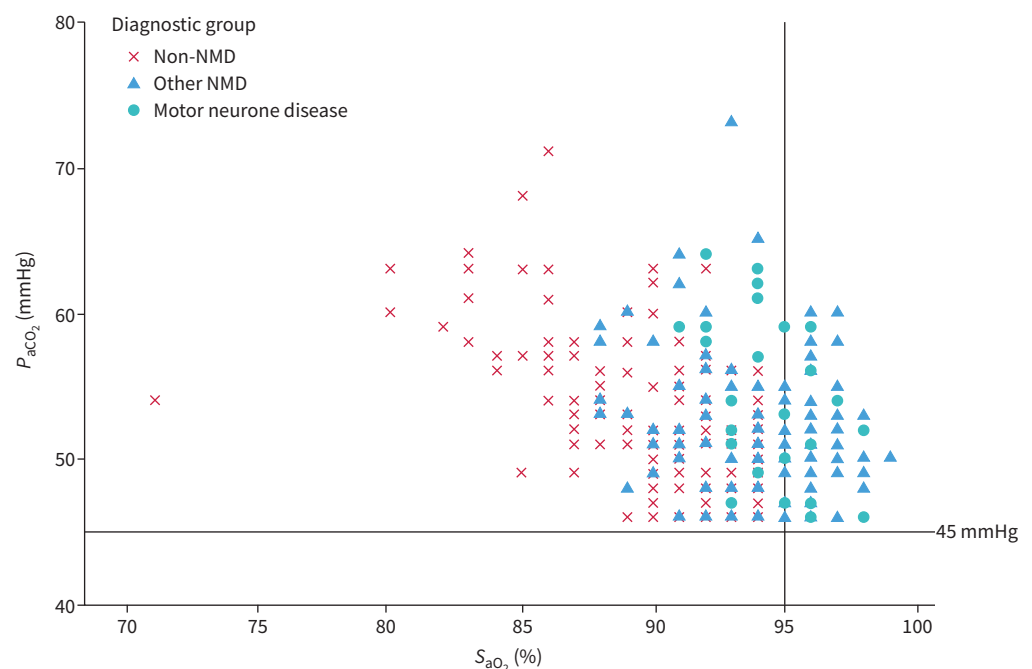

FIGURE 2 Arterial oxygen saturation (S_{aO_2}) and arterial partial pressure of carbon dioxide (P_{aCO_2}) for patients with non-neuromuscular disorders (NMDs), other NMDs and motor neurone disease. Individual arterial blood gases included. Lines at normoxia ($S_{aO_2} \geqslant 95\%$) and hypercapnia ($P_{aCO_2} >45$ mmHg).
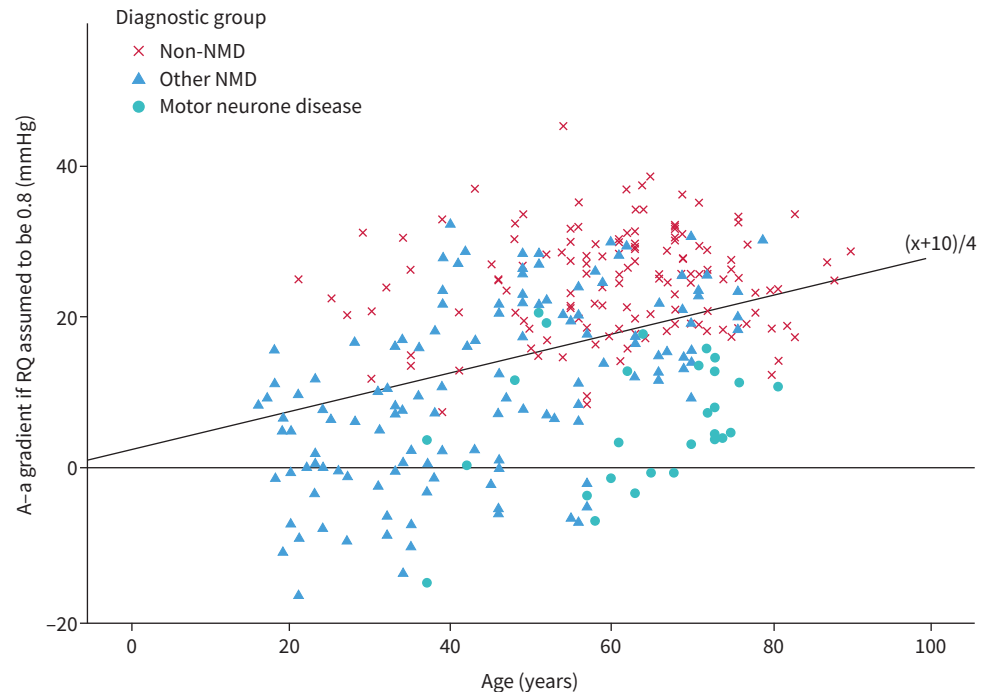
FIGURE 3 The predicted alveolar–arterial (A–a) gradient for patients based on the arterial blood gases if the respiratory quotient (RQ) is assumed to be 0.8. The line is the estimated A–a gradient based on age. NMD: neuromuscular disease.

Discussion

We found that hypercapnia can occur in the presence of normoxia in patients with NMDs. Approximately a third of motor neurone disease and half of other-NMD patients had elevated P_{aCO_2} 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 motor neurone disease 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 CO_2 rather than oximetry alone in this group of patients.

The implications for this normoxia–hypercapnia paradox are far reaching. In motor neurone disease, there is a median 12-month delay from onset of first symptom to diagnosis [15, 16], which occurs at the midpoint of the disease pathway, delaying the only available disease-modulating pharmacotherapy, riluzole, and access to clinical trials [15]. 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 S_{pO_2} 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 S_{pO_2} without a direct measure of CO_2 may further delay the diagnosis of respiratory involvement and institution of therapy proven to improve quality and length of life [4].

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 P_{aCO_2} ⩾45 mmHg to be an indication to commence NIV; however, direction surrounding when to do an ABG is variable. The United Kingdom NICE guidelines for motor neurone disease suggest an ABG if S_{pO_2} <94% in the absence of lung disease [1]. Neither the EFNS nor the AAN recommend CO_2 measurement [5, 6]. The section on ABGs in the 2002 American Thoracic Society/European Respiratory Society guideline on respiratory muscle testing [17] suggest that daytime hypercapnia is unlikely unless respiratory muscle strength testing is reduced to <40% or predicted vital capacity <50%. This was updated in 2019 and did not include ABGs [18]. The 2019 motor neurone disease position statement by the Canadian Thoracic Society recommended CO_2 measurement by ABG, CBG or transcutaneous CO_2 (tc_{CO_2}) monitoring when hypercapnia was "suspected by symptoms" [19].
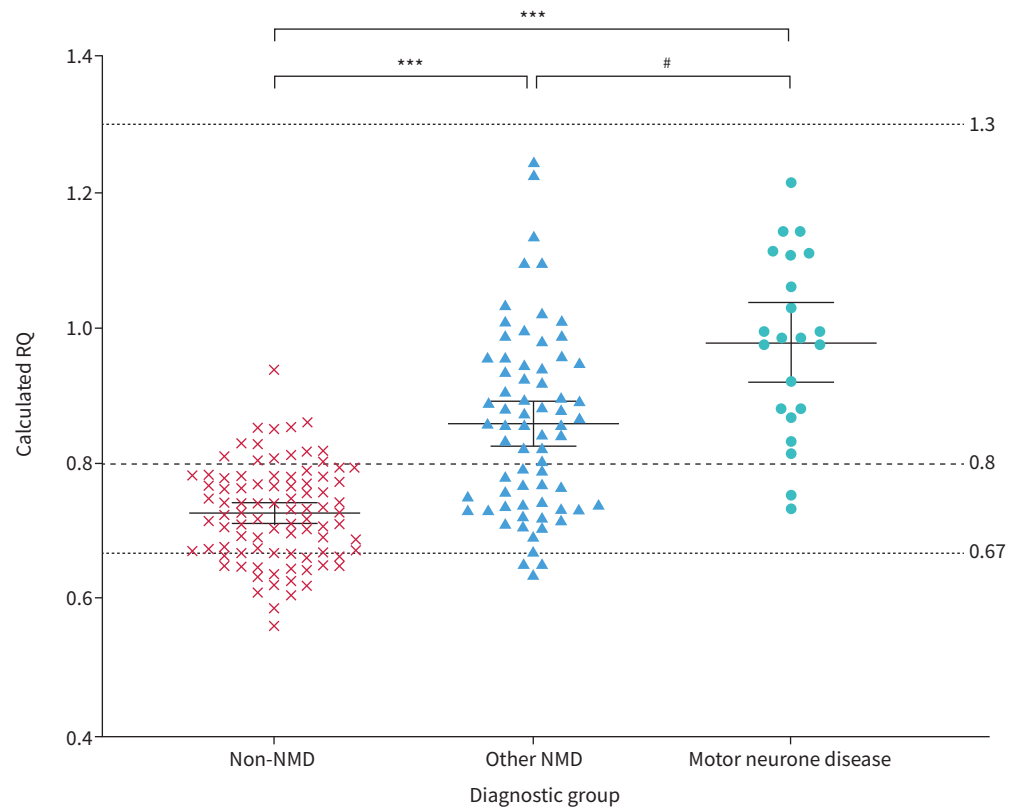
FIGURE 4 Mean (95% CI) calculated respiratory quotient (RQ) for each patient by mixed-model analysis by diagnostic group. RQ 0.8 and the physiological range of RQ (0.67–1.3) are presented. NMD: neuromuscular disease. ***: p<0.001; #: p=0.001.
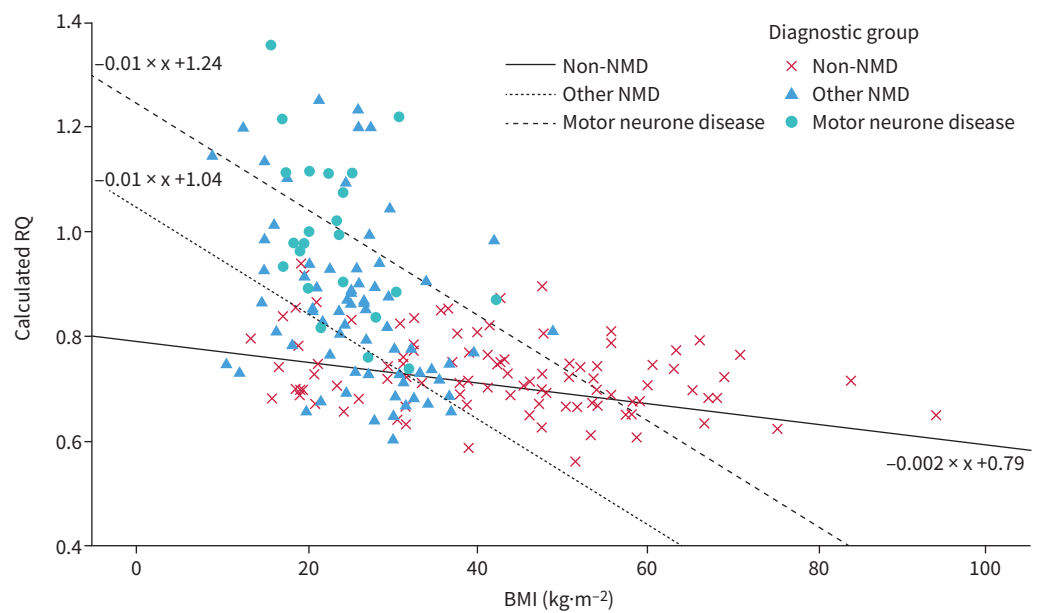

FIGURE 5 Effect of body mass index (BMI) (kg·m^{-2}) on respiratory quotient (RQ) for each of the diagnostic groups: non-neuromuscular disease (NMD), other NMD and motor neurone disease.

A retrospective assessment of 624 patients from a French motor neurone disease 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 P_{aCO_2} 48 mmHg) [20]. In addition, one in 10 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 tc_{CO_2} monitoring to S_{pO_2} in patients with NMD has emphasised the importance of CO_2 monitoring. A study by NARDI et al. [21], assessing nocturnal gas exchange in 58 patients with NMD, mostly Duchenne muscular dystrophy (DMD), on ventilatory support found that approximately one-third of patients with elevated tc_{CO_2} values did not have substantial oxygen desaturations. Likewise, a study of 72 patients with either NMD (predominantly motor neurone disease) or chest wall disorders identified nocturnal hypoventilation using tc_{CO_2} criteria without associated hypoxaemia in 33% of the cohort [22]. 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% versus 50.5%, p<0.05), yet higher isolated serum bicarbonate levels (24.8 mmol·L^{-1} versus 23.4 mmol·L^{-1}, p<0.01) [23]. Furthermore, a review of 448 ABGs of motor neurone disease patients showed a significant increase in risk of death when P_{aCO_2} >42 mmHg [24]. In addition, bicarbonate elevation without significant P_{aCO_2} elevation occurred in ~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 versus 1.39 years, p<0.001) [24]. These studies lend support to the hypothesis that hypercapnia and normoxia can coexist 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 CO_2 production through either the intake of excess calories where lipogenesis occurs, or a hypermetabolic state [25]. Hypermetabolism, defined as a significant increase in measured resting energy expenditure (REE) relative to predicted REE [12], is known to occur in ~50% of motor neurone disease patients [26]. A recent retrospective study of 48 patients with motor neurone disease calculated RQ from indirect calorimetry, and found that RQ increased as the percentage body-fat decreased [27]. Furthermore, body-fat percentage was positively correlated with BMI [27]. Proposed mechanisms for the presence of hypermetabolism in motor neurone disease patients include excitotoxicity and uncontrolled fasciculations, subthalamic dysfunction, dysregulated autophagy and mitochondrial dysfunction [28]. Hypermetabolism is also thought to occur in DMD due to hypercatabolism of skeletal muscle and increasing basal metabolic rate with age [29].

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 [8], as well as hyperinsulinaemia, glucose resistance and mitochondrial dysfunction in muscular dystrophy type 1 [9]. There is increasing evidence, particularly surrounding altered glucose metabolism [10, 30] in people with motor neurone disease, which may contribute to disease progression [31]. In addition, the majority of the pathogenic genes associated with motor neurone disease have important roles in glucose uptake as well as lipid and carbohydrate metabolism [11]. 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_2 production through the hypermetabolic state and metabolic disturbances seen in NMD is unable to be offset by an appropriate increase in alveolar volume 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 past decade our practice has been to use CBG analysis instead of ABGs in our NMD patients. This led to ~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, while others were taken after ≥1 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 S_{pO_2} on therapy does not preclude hypercapnia, and hence the measurement of CO_2 is required to assess the effect of NIV on gas exchange.

The gold standard for the measurement of RQ is by indirect calorimetry under stable conditions including a minimum of 5 h 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 alveolar gas equation 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 of 0.8. Furthermore, there was no information available regarding muscle mass, and BMI was used as a surrogate for body composition.

Despite these limitations in attempting to explain the coexistence of hypercapnia and normoxia, this study shows clearly 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 CO_2 either directly with blood gases or *via* tc_{CO_2} will miss significant proportions of NMD patients with hypercapnia.

Author contributions: E. Gray: conception and design of study, acquisition of data, analysis and interpretation of data, drafting of manuscript, and approval of manuscript to be published. C. Menadue: conception and design of study, acquisition of data, revision and critical appraisal of manuscript, and approval of manuscript to be published. A. Piper: conception and design of study, revision and critical appraisal of manuscript, and approval of manuscript to be published. K. Wong: analysis and interpretation of data, revision and critical appraisal of manuscript, and approval of manuscript to be published. M. Kiernan: conception and design of study, revision and critical appraisal of manuscript, and approval of manuscript to be published. B. Yee: conception and design of study, revision and critical appraisal of manuscript, and approval of manuscript to be published.

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