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VALUE OF PERIODIC TRANSCUTANEOUS DAYTIME CARBON DIOXIDE MONITORING IN SCREENING FOR RESPIRATORY FAILURE IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT

Background: There is no single test currently available, which can predict respiratory failure in patients with amyotrophic lateral sclerosis (ALS) with high sensitivity and specificity. This study explores the potential use of transcutaneous carbon dioxide (PtcCO2) monitoring in early detection of respiratory failure in ALS.

Methods: This is a prospective observational cohort study consisting of 50 consecutive patients with ALS. The participants underwent 3 monthly assessments for symptoms of respiratory failure, forced vital capacity (FVC) and PtcCO2 monitoring. Once respiratory failure was clinically suspected by the treating physician, further follow-up was stopped. The presence of respiratory failure was confirmed with an overnight capnometry.

Results: Symptoms of respiratory failure were the most powerful tool, alerting the physician to the possibility of respiratory failure. All the patients where respiratory failure was confirmed on overnight capnometry had symptoms of respiratory failure. 37% of these patients had FVC of > 50% predicted and only 13% had daytime hypercapnia. None of the patients had daytime hypercapnia without any other marker of respiratory failure. There was statistically significant difference between the day time PtcCO2 and median overnight PtcCO2 (p=0.0002).

Conclusions: This study has emphasised the importance of symptom history as a screening tool to suspect respiratory failure in ALS. Once again, the limitations of FVC in predicting respiratory failure is demonstrated in this study. A normal daytime PtcCO2 may be falsely reassuring and day time hypercapnia is a late finding which implies established respiratory failure.

KEY WORDS: Amyotrophic lateral sclerosis Neuromuscular respiratory failure Transcutaneous partial pressure of carbon dioxide

INTRODUCTION:

Regularly screening for evidence of respiratory failure is an important facet in the management of amyotrophic lateral sclerosis (ALS)[1]. Currently there is no single test which can predict respiratory failure with high sensitivity and specificity. Moreover, no test of respiratory muscle strength has significant positive predictive power to predict hypercapnia in the ALS patients with significant bulbar weakness[2]. Standard current practice is to screen patients for symptoms of respiratory failure and supplement this with one or more respiratory function tests. Forced vital capacity (FVC) is the most commonly used respiratory function test in many ALS clinics for this purpose. ALS patients with respiratory failure can benefit from non-invasive ventilation (NIV) which has been shown to improve survival as well as quality of life[3]. Although the precise timing for NIV initiation for

maximum benefit has not been established in a clinical trial, once a patient with ALS reaches the stage of respiratory failure the average survival is only few months without respiratory support. Therefore, for important prognostic and therapeutic implications early detection of respiratory failure is important. Since the first ever manifestation of impaired ventilation is nocturnal hypercapnia, a simple and non-invasive test to monitor partial pressure of carbon dioxide in the blood on a regular basis would be very useful in clinical practice[4]. The transcutaneous carbon dioxide (TOSCA) monitor allows transcutaneous measurement of the partial pressure of carbon dioxide (PtcCO2) along with oxygen saturation (SpO2), with a probe attached to the ear lobe[5]. To our knowledge, there are currently no studies on the potential benefit of transcutaneous carbon dioxide monitoring to screen for respiratory failure in patients with ALS. We hypothesized that if $PtcCO_2$ is recorded at regular intervals during follow up clinical assessments, it may help in the early diagnosis of respiratory failure.

MATERIAL AND METHODS

Study design: This is a prospective observational cohort study consisting of 50 consecutive ALS patients.

Aims of the Study: This study aims to determine whether PtcCO2 is a sensitive test for screening for early type II respiratory failure compared to symptom history or FVC.

Research Hypothesis: Periodic measurement of $PtcCO_2$ in the clinic, using this non-invasive method may help in the early detection of type II respiratory failure in patients with ALS. We hypothesized that during the follow-up assessments we will identify some patients with a raised $PtcCO_2$ (and hence respiratory failure) but otherwise having no symptoms of respiratory failure and a preserved FVC. This may allow us to conclude that periodic recording of $PtcCO_2$ in otherwise asymptomatic patients is potentially a useful measure for early detection of respiratory failure in both limb and bulbar onset ALS.

Standard protocol approval, registration and patient consent: The study protocol was approved by Bradford research ethics committee, reference 10/H1302/96. Written informed consent was obtained from all patients (or carers of patients) participating in the study.

Study setting and population: The study was carried out at the Sheffield care and research centre for motor neurone disorders. In this clinic patients with ALS are routinely screened for respiratory impairment. A cohort of 50 consecutive patients with ALS, who gave informed consent, was recruited irrespective of the duration of their disease. The exclusion criteria were presence of respiratory failure and inability (due to mental capacity) or unwillingness to give informed consent.

Study tools: Transcutaneous carbon dioxide level ($PtcCO_2$) was recorded using TOSCA 500, operated in accordance with the manufacturer's operating manual. A disposable ear clip was used to attach the sensor from the TOSCA monitor to the ear lobe. A contact gel was applied between the sensor and the skin to facilitate diffusion. The device was operated on a "QUICKSTART" mode which warms the sensor to a temperature of 42°C (increasing the arterial blood supply in the dermal capillary bed below the sensor) and gives the reading in 10-15 minutes. In order to have a consistent approach in screening for symptoms of respiratory failure, a questionnaire consisting of 18 possible symptoms of respiratory insufficiency was designed. A detailed search of the literature did not identify any pre-existing questionnaire which could be used for this purpose. The questionnaire was based on symptoms reported by patients with respiratory muscle weakness (in the literature and clinical experience of the investigators)[6-12]. It was interviewer administered and took 5-10 minutes to complete. The symptoms were divided into three domains i.e., breathing related symptoms, sleep related symptoms and mental/emotional state. This format was partially influenced by the format of the ALS functional rating scale and sleep apnoea quality of life index[13 14]. Each question was answered as yes or no, with one mark awarded for each affirmative answer. The questionnaire was piloted to ensure the questions were easy to understand, clear and open ended. The questionnaire in Table 1 is the final questionnaire developed following some minor amendments in response to the pilot experience. A volumetric spirometer (vitalograph® – Alpha) was used to record FVC. A face mask was used for the patients not able to achieve a tight mouth seal. The spirometer was calibrated daily and the best of three attempts was recorded.

Measurements: On the registration visit, after obtaining an informed consent patients underwent the following assessments:

1. Detailed questioning about the symptoms of respiratory failure (using a standard questionnaire)
2. TOSCA $PtcCO_2$

3. FVC
Only those patients with a normal PtcCO2 (4.6 - 6 kPa) were recruited. At each 3 monthly subsequent visits patients underwent the following assessments:

1. Detailed questioning about the symptoms of respiratory failure (using a standard questionnaire)
2. TOSCA $PtcCO_2$
3. FVC

Once clinically suspected by the treating physician, respiratory failure was confirmed by overnight capnometry (using TOSCA500), at which point the study-specific respiratory assessments were stopped.

Table 1 Screening questionnaire to identify potential patients with respiratory failure

Breathing related symptoms	**Yes**	**No**
Have you noticed any change in your breathing? If yes please specify …… ……		
Is there anything which makes you short of breath (e.g. on walking, eating, bathing, dressing etc?) If yes, please mention the least strenuous activity ……		
Do you get short of breath when lying flat?		
Do you have difficulty coughing?		
Sleep related symptoms		
Have you noticed any change in your sleeping pattern? If yes, please specify ……		
Do you ever wake up feeling short of breath?		
Is your sleep disturbed/interrupted? If yes, please specify why …… How many times do you wake up ……		
Do you get up at night to pass urine more than usual?		
Do you feel refreshed on awakening?		
Do you have early morning headaches?		
Do you feel sleepy during the day (more than usual)?		
Do you fall asleep inappropriately?		
Do you feel drowsy or fight to stay alert during the day?		
Mental/emotional state		
Have you noticed any change in your usual self (e.g. irritable, anxious, low mood etc) If yes, please specify ……		
Do you feel fatigued or lack of energy?		
Do you have poor motivation to do things which you can do?		
Have you lost your appetite?		
Do you find hard to concentrate?		

RESULTS

The characteristics of study participants are summarised in Table 2. The average age was 60 years, 58% were male and participants were predominantly sporadic ALS with limb onset disease. The mean duration between disease onset and study entry was 39 months. 30 patients reached the primary end point. 8 patients died during follow-up without been diagnosed with respiratory failure and 6 patients were lost to follow-up during the course of the study. 6 patients have not reached the primary end point at the time of writing and are likely to be slow progressing atypical forms of ALS. Although we hypothesised that recording transcutaneous PCO2 would be particularly valuable for patients with poor bulbar function, only 6 patients with severe bulbar dysfunction could be recruited during the recruitment time available.
en trials of this test performed namely MIND ALERTNESS in which the participants were directed to play a video game in which he/she had to recognize the direction of the arrows in a given time.

Table 2: Baseline characteristics of the study participants

Parameter	**N (range) [SD]**
Total number	50
Mean (range) age (years)	60 (27-77) [12.3]
Gender (M:F)	29:21
Mean duration of disease (months)*	39 (6-157) [35.7]
Site of onset: Limb onset Bulbar onset Respiratory onset	 41 (82%) 9 (18%) 0
Mean Bulbar Score No. with normal to moderate bulbar impairment (score 7-12) No. with severe bulbar impairment (score 0-6)	10 44 (88%) 6 (12%)
Mean (range) SVC (% predicted)	79% (26-139) [23.3]
Mean (range) $PtCO_2$ (kPa)	5.0 (4.2-5.9) [0.39]

Evidence of respiratory failure

Table 3 summarises the respiratory parameters at the time when respiratory failure was suspected by the clinician and confirmed with an overnight capnometry. These data suggest that the presence of symptoms of respiratory failure is the most powerful tool to predict respiratory failure. FVC and daytime PtcCO2 were insensitive as FVC of > 70% of predicted and daytime $PtcCO_2$ of < 5.0 kPa was observed in patients where respiratory failure was suspected clinically due to presence of symptoms and those who fulfilled the criteria of respiratory failure on nocturnal capnometry (median $PtcCO_2 \geq 6$ kPa).

Table 3: Respiratory parameters when respiratory failure suspected and confirmed by overnight capnometry

Parameter	**N (range)**
Number of patients developing respiratory failure	30 (60%)
Duration from disease onset to the development of respiratory failure (days)	974 (431-3702)
Number of patients with symptoms when respiratory failure suspected	30 (100%)
Number of patients with FVC < 50% when respiratory failure suspected	14 (47%)
Number of patients with FVC 50-70% when respiratory failure suspected	7 (23%)
Number of patients with FVC > 70% when respiratory failure suspected	3 (10%)
Number of patients with $PtCO_2$ > 6.0 kPa when respiratory failure suspected	4 (15%)
Number of patients with $PtCO_2$ > 6.0 kPa without any other marker of respiratory failure	0

	Confirmed respiratory failure	
	Yes (N=30)	No (N=20)
Presence of symptoms	30 (100%)	6 (30%)
FVC		
<50	14 (47%)	4 (20%)
50-70%	7 (23%)	1(5%)
>70%	3 (10%)	11 (55%)
$PtCO_2$		
>6.0 kPa	4 (13%)	0
<6.0 kPa	26 (87%)	12(100%)*

* Values only available for 12 patients

Symptoms of respiratory failure

The most common symptoms (present in at least 1/3rd of the patients at the time of suspected respiratory failure) are reported in table 4. These questions may assist in identifying those at risk and in the decision to investigate a patient further. Cronbach's alpha (α) was calculated as a measure of internal consistency of the responses when respiratory failure was clinically suspected. The Cronbach's α for the analysed cohort of 30 patients was 0.7. A Cronbach's α value between 0.7 and 0.8 is considered as having a strong and positive correlation of the items of a scale.

Table 4: Most common sympztoms at the ztime of suspected respiratory failure

Symptom	No. of patients (n=30)
Shortness of breath on exertion (e.g., walking, eating, bathing, dressing etc)	20 (67%)
Noticed any change in breathing	18 (60%)
Difficulty in coughing	12 (40%)
Sleepy during the day (more than usual)	11 (37%)
Fatigue or lack of energy	10 (33%)
Interrupted sleep	9 (30%)
Loss of appetite	9 (30%)

Relationship between symptoms and daytime carbon dioxide level

Figure 1 illustrates the relationship between the symptoms of respiratory failure and daytime $PtcCO_2$. The study was not powered for such analysis and hence within the limits of small number of patients no relationship between the symptoms of respiratory failure and daytime $PtcCO_2$ is demonstrated at any of the follow-up time points.

Relationship between daytime and nocturnal carbon dioxide levels

Nocturnal transcutaneous capnometry was carried out when respiratory failure was clinically suspected. The difference between daytime $PtcCO_2$ and median overnight $PtcCO_2$ was statistically significant (p=0.0002). Figure 2 illustrates the Bland-Altman plot used for the analysis of agreement between the two methods. Pearson correlation coefficient was 0.656.

DISCUSSION

A crucial aspect in the management of patients with ALS early identification of respiratory compromise. Respiratory muscle weakness is often unmasked during sleep, particularly during rapid eye movement (REM) sleep when the intercostal and accessory muscles of breathing are inactive and the diaphragm carries the work of breathing[9]. A weak diaphragm may fail to allow adequate ventilation and frequent arousals are required as a compensatory mechanism to maintain adequate ventilation, thus reducing total sleep time, REM sleep and the overall quality of sleep. Hence disturbed sleep, due to episodes of hypoventilation, is one of the earliest manifestations of respiratory insufficiency and usually occurs well before daytime hypoventilation and the resulting daytime hypercapnia develops9. The symptoms of "sleep fragmentation" include nocturia, nightmares, unrefreshing sleep and daytime somnolence. Symptoms of CO2 retention include morning headaches, poor appetite, fatigue, cognitive dysfunction and, as a result, poor quality of life. With disease progression, patients may develop exertional dyspnoea, orthopnoea, dyspnoea at rest and anxiety associated with the feeling of breathlessness[1].

In order to objectively assess respiratory function, a variety of invasive and non-invasive, voluntary and involuntary respiratory function tests have been assessed to identify patients with respiratory impairment and plan timely intervention. However, no single respiratory test can reliably confirm or exclude the presence of nocturnal hypoventilation. An FVC of 50% predicts day time hypercapnia with a sensitivity of 53% and specificity of 89%[2], demonstrating the limitations of this test for predicting even late respiratory failure. Moreover, it is a volitional test which is often difficult for the patients with severe bulbar dysfunction to perform. The most appropriate method to screen for respiratory failure in such patients remains unclear. The ideal test would be non-invasive, easy to perform in an out-patient setting and would diagnose early respiratory failure with high sensitivity. This study was planned with the aim to evaluate the value of regular transcutaneous carbon dioxide measurements in the early detection of respiratory failure. It is non-invasive and independent of the subject being tested and findings are easy to interpret (PCO2 > 6.0 kPa = respiratory failure). Although daytime hypercapnia is reported in the literature as a relatively

late event[15 16], the benefit of regular transcutaneous PCO_2 measurements has not been systematically assessed previously. There are a number of important lessons learnt in this study. The primary outcome was detection of daytime hypercapnia when it would not have been clinically suspected using other parameters. In the current cohort, no patient was identified to be in respiratory failure on the basis of daytime $PtcCO_2$ alone. Most patients (87%) with other features of respiratory failure and nocturnal hypercapnia, had a normal daytime $PtcCO_2$. This finding suggests daytime compensation of ventilation with the voluntary activation of accessory muscles of breathing and enhanced activation of the respiratory center as a result of improved blood biochemistry. The accessory muscle of respiration and central respiratory drive are both suppressed during normal sleep[9]. Hence, daytime normocapnia may not be considered as indicating the absence of respiratory dysfunction. The importance of symptom history is highlighted in this study. In all the patients who reached the primary endpoint, development of symptoms of respiratory compromise alerted the physicians to the presence of respiratory insufficiency. The most common symptoms identified are listed in Table 4. Based on the most common symptoms, the questionnaire used in this study could be modified further to include only the symptoms listed in Table 4. The resultant questionnaire, with a certain cut-off score, is likely to have a strong positive predictive value in diagnosing respiratory failure. However, such questionnaire would require further validation in diagnosing respiratory failure using a bigger sample size[17]. A difficulty in this regard is in deciding which comparator to use as benchmark of respiratory failure. The best definition of early respiratory failure in patients with neuromuscular disease is nocturnal hypercapnia which requires at least nocturnal transcutaneous capnography, which is time consuming and expensive. Hence, bedside respiratory function tests need to be combined with clinical assessment to select appropriate patients who are most likely to have nocturnal hypercapnia and may benefit from intervention with NIV. Once again, the limitations of FVC in predicting respiratory failure is demonstrated in this study. Three patients with confirmed nocturnal hypercapnia had an FVC of greater than 70% predicted. One patient with an FVC of 95% predicted had 6 symptoms of respiratory failure with a median nocturnal PtcCO2 of 6.27 kPa. Similarly an FVC as low as 38% predicted was not associated with any symptoms of respiratory failure. In conclusion, regular PtcCO2 measurements may not help in early identification of respiratory failure and daytime normocapnia may be falsely reassuring. Special attention should be given to the presence of symptoms of respiratory failure and overnight capnography carried out where clinical suspicion of respiratory failure is high. Demonstration of nocturnal hypoventilation (rising PCO2 and falling SpO2) imply ventilatory failure and the patient may benefit from intervention with NIV.

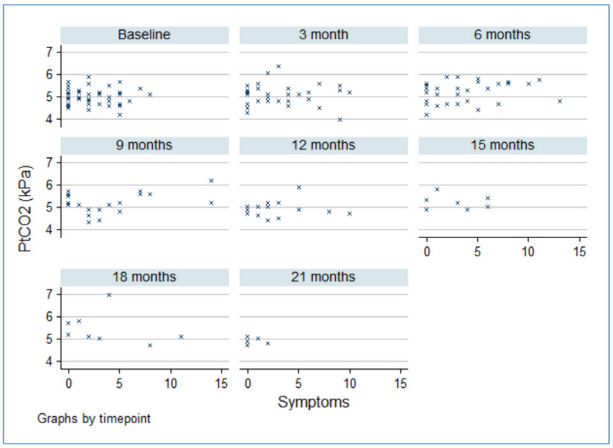

Figure 1: Relationship between number of symptoms and PtcCO2

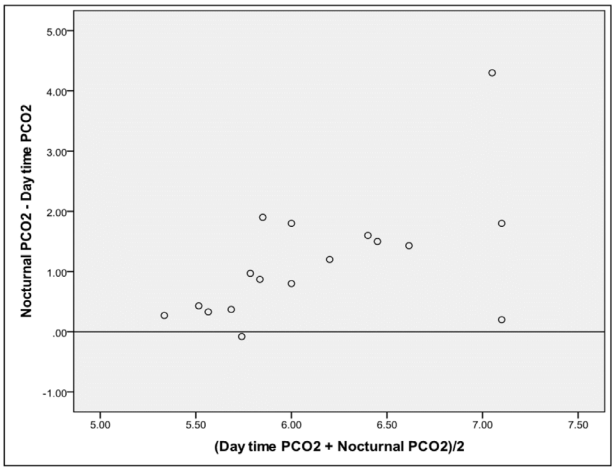

Figure 2: Bland-Altman plot of the difference between the nocturnal and day time PCO2 against the average of the two measurements

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Muhammad K Rafiq; concept, data collection, data analysis, manuscript writing, manuscript review