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The role of non-invasive ventilation in the management of type II respiratory failure in patients with myotonic dystrophy

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Take Home Message
Commencing patients with myotonic dystrophy on non-invasive ventilation appears to reverse respiratory failure despite poor adherence with ventilation

Abstract

Type 1 myotonic dystrophy (DM1) causes sleep disordered breathing and respiratory failure due to a combination of obstructive sleep apnoea, reduced central drive and respiratory muscle weakness. Non-invasive ventilation (NIV) is commonly used for treating respiratory failure in neuromuscular disease, however, there have been few studies assessing the role of NIV in DM1. The aim of this retrospective service evaluation was to investigate the impact of NIV adherence on hypercapnia and symptoms of hypoventilation in patients with DM1. Data on capillary pCO_2, lung function, adherence to NIV and symptoms of hypoventilation were obtained from the records of 40 patients with DM1. Mean capillary pCO_2 significantly reduced from 6.81±1.17 kPa during supervised inpatient set-up to 5.93±0.82 kPa after NIV set-up ($p<0.001$). NIV adherence reduced from 7.8 (range: 1.0-11.0) h/24h during supervised inpatient set-up to 2.9 (0-10.4) h/24h in the community. Overall 72% of patients used NIV <5/24h during follow-up, including 11% who discontinued NIV completely. There was no correlation between adherence to NIV and changes in capillary pCO_2. Patients who reported symptomatic benefit (50%) had higher adherence than those who did not feel benefit ($p<0.05$). In conclusion, in patients with Myotonic Dystrophy with type II respiratory failure maintaining adherence is challenging.

1. Introduction

Type 1 myotonic dystrophy (DM1) is an autosomal dominant disease caused by a CTG trinucleotide repeat expansion in the dystrophia myotonica protein kinase (DMPK) gene on chromosome 19. It is the most common muscular dystrophy in adults of European ancestry, with prevalence of DM1 ranging from 10-18/100,000.[1, 2]. The clinical features of DM1 include progressive myotonia and muscle weakness, as well as variable multisystem involvement such respiratory failure, cataracts, cardiac conduction abnormalities, daytime somnolence and cognitive defects. Respiratory failure occurs due to a combination of respiratory muscle weakness, reduced central drive, insensitivity to carbon dioxide (CO_2), upper airway obstruction, and reduced chest wall compliance.[3, 4] Chronic hypercapnia contributes to excessive daytime somnolence, headaches, confusion, and eventually coma and death. Somnolence and sleep disorders are very common in DM, and may be primarily related to a central nervous system process affecting the sleep-wake cycle. Chronic hypercapnia exacerbates somnolence due to other causes.[5, 6]

Our clinical experience suggests that patients with DM1 receive little benefit from using non-invasive ventilation (NIV) and have poor adherence to NIV therapy. There have been few studies assessing the use of NIV in DM1, and results from these are somewhat conflicting. A recent 10- year follow-up study found that patients who started NIV within a year of meeting local criteria for NIV initiation and who had good adherence to treatment had a lower risk of death and significant events, such as invasive ventilation.[7] The criteria for initiation of NIV were symptoms of hypercapnia (dyspnoea, morning headaches, sleep disturbance, diurnal sleepiness) combined with pCO_2 >6 kPa, or nocturnal arterial oxygen desaturation. Sleepiness was considered a symptom of either sleep disordered breathing or

hypoventilation. Polysomnography was not performed to explore central hypersomnolence as a cause of sleepiness. An earlier study showed a sustained reduction in pCO_2 in capillary blood two years after initiation of NIV, with the majority of patients reporting increased alertness and improvement in shortness of breath after initiation of NIV.[8] Similar symptomatic benefit was reported from a study in Portugal, however the majority of patients in this study were started on NIV based on symptoms of hypoventilation rather than hypercapnia, and follow-up daytime blood gases were not affected by NIV.[9] All three of these studies reported issues with adherence to NIV in DM1, with approximately a third of patients averaging less than 5 hours per day. Finally, withdrawal of NIV for 1 month was found to cause an increase in pCO_2 and deterioration of nocturnal oxygen saturation, but this was not associated with worsening of symptoms of nocturnal alveolar hypoventilation or quality of life.[10]

We performed a retrospective service evaluation of patients with DM1 patients to investigate the impact of NIV on pCO_2 measured by capillary blood gas, symptoms of alveolar hypoventilation and adherence to NIV.

2. Methods

2.1. *Patients*

Adult patients with DM1 were identified from the Manchester University NHS Foundation Trust (MFT) North West Ventilation Unit database. Patients with DM2 or other types of myotonia, and those who had never been started on NIV were excluded from the review. Patients with a diagnosis of DM1 who had been started on NIV as stable elective admissions between the years 2005-2018 were included in the study.

2.2. Data collection

Retrospective data on capillary blood gas pCO_2, lung function (FEV1 and FVC) at baseline, daily use of NIV (hours), ventilator settings, and symptoms of alveolar hypoventilation (daytime somnolence and headaches) were obtained from electronic patient records, clinic letters, and patient notes. All blood gas measurements were ear lobe capillary samples taken whilst not on NIV. Patients who reported symptomatic improvement after starting NIV, including more energy, reduced somnolence, fewer headaches, and better sleep were classed as having initial benefit of NIV treatment. Data was grouped into episodes, with the first episode being admission to our ventilation unit for NIV set-up. The second episode was discharge from the unit following NIV set-up, and following episodes were follow-up consultant-led clinic visits. The indication for NIV set up were either: (1) symptoms of alveolar hypoventilation; (2) capillary pCO_2 >6.5 kPa. Patients with symptoms of alveolar hypoventilation and a pCO_2 <6.5 kPa on admission for NIV set-up were pre-designated as the symptom control group. Patients with a pCO_2 >6.5kPa, with or without symptoms of alveolar hypoventilation, were pre-designated as the respiratory failure group. Patients were divided into low (<1 h), medium (1-5 h) and high (>5 h) adherence groups based on the average hours of NIV documented at follow-up appointments.

2.3. Statistical analysis

Statistical analysis was performed using GraphPad Prism version 7 (GraphPad Software Inc, San Diego, CA). Statistical significance was set at 0.05. Parametric data are presented as

mean ± standard deviation, non-parametric data are presented as median (range). Linear regression and Spearman rank correlation were used to analyse correlation between hours of NIV and pCO_2 levels. T-test and Mann-Whitney U test were used for comparing results from patients for whom NIV was indicated and not indicated. One-way ANOVA and Kruskal Wallis tests were used to analyse effect of adherence category (low, medium, high) on pCO_2 and other variables. Chi squared test was used to analyse the relationship between NIV use and variables including: male gender, number reporting symptomatic benefit, discontinuation of NIV or death.

3. Results

3.1. Patient characteristics on admission for NIV set-up

40 patients (20 male) with a mean age of 47.8 ± 12.6 years, who were commenced on NIV between the years 2005-2018, were included in the study (table 1). The mean capillary pCO2 on admission for set up on NIV was 6.8 ± 1.2 kPa. There was a significant reduction in mean pCO_2 on discharge to 5.9 ± 0.8 kPa ($p<0.001$). Non-invasive ventilation was used for a median duration of 7.8 (range 1.0-11.0) hours per day during the index admission to establish patients onto NIV. Mean IPAP was 15.9 ± 4.5 cmH_2O and EPAP 4.1 ± 1.3 cmH_2O. There was no correlation between capillary pCO_2 on discharge and NIV adherence ($p=0.93$), or between capillary pCO_2 and IPAP or EPAP ($p=0.120$ and $p=0.388$, respectively).

The respiratory failure group comprised 23/40 patients. The mean pCO_2 in the respiratory failure group was 7.5 ± 1.2 kPa on admission and this significantly reduced to 6.1±1.0 kPa on discharge ($p<0.001$). In the 17/40 patients with a pCO_2 <6.5kPa on admission (symptom control group), the mean pCO_2 was 5.9 ± 0.34 kPa on admission and 5.7 ± 0.4 kPa on

discharge (p=0.05). In the respiratory failure group (n=23) mean pCO_2 reduced from 7.4 ± 1.2 on admission to 6.1 ± 1.0 on discharge (p<0.001). Patients in the respiratory failure group were set up with significantly higher IPAP than patients in the symptom control group (17.9 ± 4.4 cmH_2O vs 13.2 ± 2.9 cmH_2O, respectively, p<0.001).

	All patients (n=40)	Respiratory failure (n=23)	Symptom control only (n=17)	p
Age at admission	47.8 ± 12.6	47.1 ± 10.8	48.9 ± 15.0	0.666
Gender (male)	20 (50%)	11 (48%)	9 (53%)	0.749
pCO_2 at admission (kPa)	6.8 ± 1.2	7.5 ± 1.2	5.9 ± 0.34	**<0.001**
pCO_2 on discharge (kPa)	5.9 ± 0.8	6.1 ± 1.0	5.7 ± 0.40	0.095
Hours of NIV	7.8 (1.0-11.0)	8.0 (1.0-11.0)	7.0 (1.0-11.0)	0.825
IPAP (cmH_2O)	15.9 ± 4.5	17.9 ± 4.4	13.2 ± 2.9	**<0.001**
EPAP (cmH_2O)	4.1 ± 1.3	4.1 ± 1.3	4.0 ± 1.2	0.752
PS (IPAP-EPAP)	11.8 ± 4.2	13.8 ± 3.9	9.2 ± 2.9	**<0.001**
FEV1 (% predicted)	67 ± 19	62 ± 20	70 ± 20	0.106
FVC (% predicted)	67 ± 20	62 ± 20	70 ± 20	0.145

Table 1. Patient characteristics on index admission for NIV set-up

	All patients (n=36)	Respiratory failure (n=20)	Symptom control only (n=16)	p
Average pCO_2 at follow-up (kPa)	6.1 ± 0.7	6.3 ± 0.7	5.8 ± 0.6	**0.012**
Hours of NIV	2.9 (0-10.4)	1.8 (0-9.7)	3.2 (0.3-10.4)	0.484
Number of follow-up visits	5 (1-18)	7 (1-18)	5 (1-14)	0.464
Months between visits	4.7 (0.3-17.7)	4.4 (0.3-17.7)	4.9 (1.2-8.0)	0.796
Stopped NIV	14 (39%)	7 (35%)	5 (31%)	0.813
Felt benefit	18 (50%)	8 (40%)	10 (63%)	0.180
Somnolence at follow-up	23 (64%)	13 (65%)	10 (63%)	0.877

Table 2. Patient characteristics at follow-up

3.2. Adherence to NIV and pCO_2 levels during follow-up

Patient characteristics at follow-up are presented in table 2. The number of follow-up appointments patients had varied between 0-18, depending on when NIV was started, the frequency of appointments, and if the patient had died, been discharged or lost to follow-up. Follow-up is structured with an initial post discharge consultant led review occurs within 4 months. Following discharge with NIV they are supported by access to the multi-disciplinary team and advice over the telephone. Consultant led reviews occur at 6 monthly intervals. Additional reviews are arranged on as required basis if patients are having difficulty tolerating NIV. Following discharge from hospital one patient in the symptom control group returned their ventilator within a month, one patient died, and two were lost to follow-up. Thus 36 patients attended for outpatient follow up. At the first follow-up visit the mean capillary pCO_2 was 6.0 ± 0.8 kPa in the symptom control group and 6.2 ± 0.8 kPa in the respiratory failure group (p=0.130). There was no significant change in pCO_2 between discharge from the unit and the first follow-up visit (p=0.382), even though NIV adherence at the first follow-up was significantly lower than during admission (p<0.001). At the first follow-up visit median NIV adherence was 2.0 (0-11) h per day, 4.3 (0-10) h in the symptom control group and 1.6 (0-11) h in the respiratory failure group (p=0.146). There was no correlation between change in capillary pCO_2 from discharge and NIV adherence at the first follow-up visit (p=0.334) (figure 1). In total 4/36 (11%) had discontinued NIV completely, and 24/36 (67%) had an average NIV adherence <5h per day.

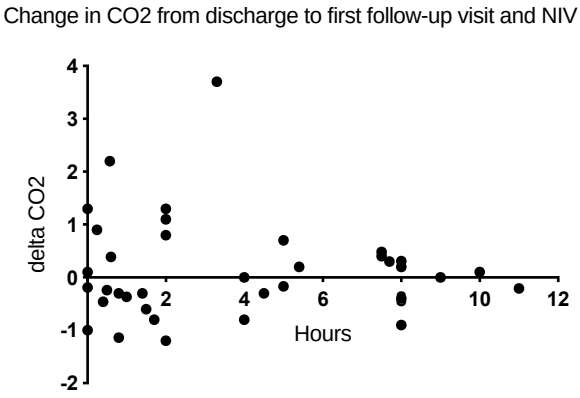

Figure 1. Relationship between NIV adherence and change in capillary CO_2 at the first follow-up visit.

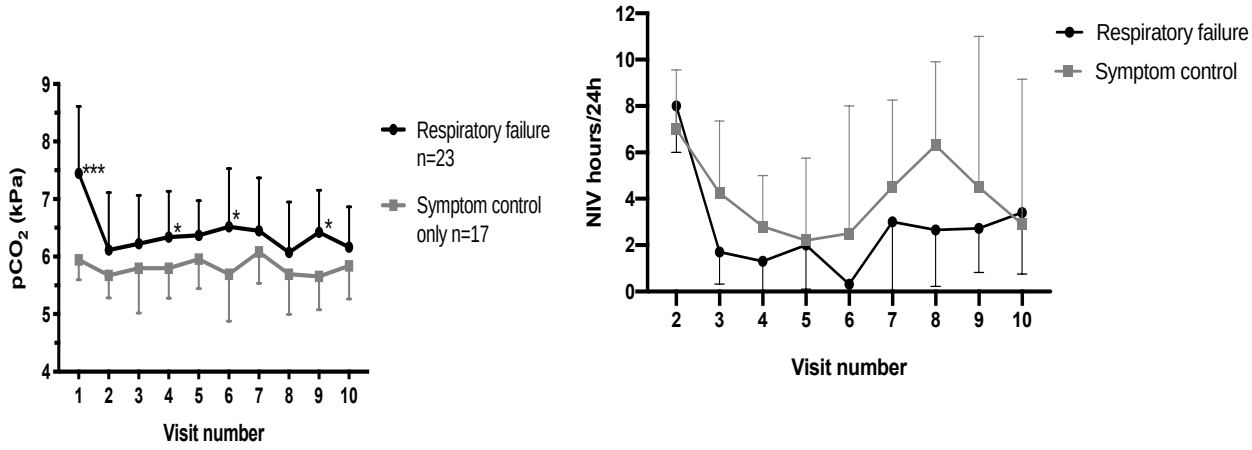

Figure 2a. Changes in pCO_2 levels at admission for NIV set-up (visit 1), discharge (visit 2), and follow-up (visits 3-10). Graph shows mean ± SD. ***(p<0.001), *(p<0.05)
Figure 2b. Changes in NIV hours/24h at discharge (visit 2) and follow visits. Graph shows mean ± SD .

Overall patients had 5 (1-18) follow-up visits over 2.6 (0.0-10.0) years, with visits every 4.7 (0.3-17.7) months. There was no correlation between adherence to NIV and frequency of follow-up visits (p=0.131), and no significant difference in the frequency of visits between the respiratory failure and symptom control groups (11.1 (1-17) months and 12.5 (3-16) months respectively, p=0.771). During follow-up 14/36 (39%) patients stopped using NIV, and two of these were restarted on NIV at a later date. Of the patients who stopped using NIV, 9/14 were in the respiratory failure group. Patients in the respiratory failure group retained a higher mean pCO_2 during follow-up than patients in symptom control only group

(6.3 ± 0.7 versus 5.8 ± 0.6 respectively, p<0.05). Changes in mean pCO_2 in the two groups during the first 10 episodes are shown in figure 2a. There was no significant difference in NIV adherence between the respiratory failure and symptom control groups during follow-up (1.8 (0-9.7) h vs 3.2 (0.3-10.4) h respectively, p=0.484) (figure 2b).

2.3. Mortality

10 patients died during follow up, with a mean age of 54.0 ± 8.7 years (table 3). In the patients whom died the mean time from being established on NIV to death was 2.9 (0.1- 5) years after NIV set-up. 4/10 had discontinued NIV, 2 had low adherence to NIV (<2 hours per day), and 1 had high adherence (8 hours per day). Mortality was associated with higher pCO_2 on admission for set up and at follow-up compared with surviving patients (p<0.01 and p<0.005, respectively). Furthermore, mortality was associated with worse lung function at time of NIV initiation (FVC 57 ± 16 % predicted versus 71 ± 20 % predicted, p<0.05).

	Alive (n=30)	**Deceased (n=10)**	**p**
Age of death		54.0 ± 8.7	
Age at admission	45.3 ± 12.9	52.9 ± 9.1	0.074
Gender (male)	15 (50%)	4 (40%)	0.721
NIV indicated	13 (43%)	8 (80%)	**0.044**
pCO_2 at admission	6.6 ± 0.8	7.6 ± 1.6	**0.006**
pCO_2 at follow-up	6.0 ± 0.6	6.7 ± 0.7	**0.004**
Hours of NIV at follow-up	3.4 (0-10.4)	1.6 (0.2-7.9)	0.240
FEV1 (% predicted)	71 ± 19	58 ± 15	0.074
FVC (% predicted)	71 ± 20	57 ± 16	**0.040**

Table 3. Characteristics of patients who have died after being set up on NIV

3.4. Symptoms of alveolar hypoventilation

On admission for NIV set-up 34/40 (85%) of patients reported symptoms of alveolar hypoventilation (daytime somnolence, early morning headaches). In the symptom control group 16/17 patients reported somnolence, 8/17 headaches, and 5/17 dyspnoea. In the respiratory failure group 17/23 patients reported somnolence, 4/23 headaches, and 5/23 experienced dyspnoea.

Half (18/36) of the patients in this study reported feeling some symptomatic benefit from NIV at follow-up (table 4). Those with perceived symptomatic benefit used NIV 4.3 (0.2-10.4) h per day during follow-up, significantly more than those who did not feel benefit at 1.6 (0-8) h per day ($p<0.05$), and also had significantly lower pCO_2 at follow-up (5.8 (4.9-7.8) and 6.1 (5.5-7.7), respectively, $p<0.05$). There was no significant difference in pCO_2 at admission between the two groups ($p=0.707$). Patients who felt benefit of NIV reported excessive daytime somnolence at follow-up at an equal rate as patients who did not feel benefit.

	Symptomatic benefit (n=18)	**No symptomatic benefit (n=18)**	**p**
Age	48.6 ± 14.4	47.3 ± 11.3	0.750
Gender (male)	9 (50%)	8 (44%)	0.739
Somnolence at admission	16 (89%)	14 (78%)	0.371
Somnolence at follow-up	12 (67%)	12 (67%)	1.000
pCO_2 at admission (kPa)	5.9 (5.1-11.8)	6.9 (5.5-8.6)	0.707
pCO_2 at follow-up (kPa)	5.8 (4.9-7.8)	6.1 (5.5-7.7)	**0.037**
NIV hours at follow-up	4.3 (0.2-10.4)	1.6 (0-8.0)	**0.047**
FEV1 (% predicted)	65 ± 20	69 ± 19	0.623
FVC (%predicted)	65 ± 22	69 ± 19	0.562

Table 4. Characteristics of patients with and without perceived symptomatic benefit from NIV

Overall 33/40 (83%) of patients reported excessive daytime somnolence at admission, with median capillary pCO_2 6.5 (5.1-11.8) kPa in those with somnolence, and 6.9 (6-8.6) kPa in those without (p=0.470). On follow-up 24/36 (67%) reported excessive daytime somnolence (table 5). Patients with excessive somnolence used NIV significantly less (1.6 (0-9.7) h per day) than those who did not report somnolence (5.0 (0.3-10.4) h per day, p<0.05). Those with somnolence at follow-up had a median pCO_2 of 6.1 (4.9-7.8) kPa versus those without somnolence 5.8 (4.9-7.0) kPa (p=0.09).

	Somnolence at follow-up (n=24)	**No somnolence at follow-up (n=12)**	**p**
Age	49.3 ± 9.5	42.9 ± 17.7	0.171
Gender (male)	11 (46%)	6 (59%)	0.813
Somnolence at admission	22 (92%)	8 (67%)	0.058
pCO_2 at admission (kPa)	6.6 (5.1-11.8)	6.9 (6-8.6)	0.470
pCO_2 at follow-up (kPa)	6.1 (4.9-7.8)	5.8 (4.9-7.0)	0.097
NIV hours at follow-up	1.6 (0-9.7)	4.8 (0-10.4)	**0.038**
FEV1 (% predicted)	65 (25-102)	69 (32-83)	0.540
FVC (% predicted)	63 (34-111)	69 (27-79)	0.606

Table 5. Characteristics of patients with and without somnolence at follow-up

4. Discussion

We have observed that patients with DM1 have a significant reduction in CO_2 during admission for NIV set-up and this is maintained at follow-up despite an observed marked reduction in adherence to NIV. There was no correlation between the use of NIV and pCO_2

suggesting that the reduction in pCO_2 could not wholly be explained by the use of NIV. A proportion of patients were commenced on NIV for symptoms compatible with alveolar hypoventilation, in the absence of a pCO_2 >6.5kPa. We did not identify a difference between adherence to NIV or improvement in symptoms and pCO_2 levels. A high pCO_2 on admission for set up on NIV was however associated with higher mortality reflecting more advanced respiratory involvement of DM1.

Low adherence to NIV is well recognized in DM. In our hands 72% of patients averaged less than 5 hours a day and over a third discontinued NIV during follow-up. Adherence to NIV did not appear to impact on pCO_2 on follow-up and we noted that in surviving patients pCO_2 normalised irrespective of duration of NIV use. The reasons for low adherence are likely to be multifactorial, and include the lack of observed symptomatic benefit, lack of understanding of the role of NIV, and problems using the NIV machine.[11] The mask can be uncomfortable to wear, especially when sleeping, the ventilators can be perceived as noisy, and travelling with them difficult. Many patients with DM have a degree of cognitive impairment, which may affect their ability to use the ventilators, tolerate masks, and also to understand the reasons for using NIV. Patients may be unable to fit and remove their mask due to weakness in their hands or arms. It is important to engage families and carers early on to ensure effective treatment and good compliance. Facial weakness and deformity may also affect mask fit, making them uncomfortable or causing air leak.

An important factor affecting adherence to NIV is the lack of symptomatic improvement. Whilst NIV has been shown to significantly improve quality of life in patients with motor neurone disease and other neuromuscular conditions, the impact in DM is more complex.[12,

13] Only half of the patients in this study reported symptomatic benefit after staring NIV, and despite initial benefit many patients still experienced lack of energy, somnolence and headaches at follow-up. It is well recognised that these symptoms of alveolar hypoventilation are also characteristic symptoms of the condition itself. However, patients who did report symptomatic benefit had significantly higher adherence with NIV and lower pCO_2 at follow-up. It is not clear whether patients discontinue NIV because of the lack of symptomatic improvement, or due to other factors.

Our findings would suggest that NIV does not improve symptoms of alveolar hypoventilation in the absence of daytime hypercapnia. Furthermore adherence to NIV in this setting is very poor. Adherence to NIV in DM1 is extremely variable and does not correlate with changes in pCO_2. We do however observe that initial set up on NIV in patients with significant hypercapnia (pCO_2 >6.5kPa) results in correction of hypercapnia although adherence is not maintained at follow up. Control of hypercapnia >6.5kPa may have an impact on overall survival. 10/40 patients died during follow up and mortality was associated with significant hypercapnia on intial set up and worse lung function as reflected in lower % predicted FEV1 and FVC.

The aetiology of respiratory failure in DM is complex including reduced central drive and CO_2 insensitivity.[4] The ventilatory response to hypercapnia and experience of symptoms related to hypercapnia may be abnormal thereby reducing the impact of NIV use on symptom control. Adherence to NIV use may therefore be reduced. Our observations would support the view that although there was no correlation between NIV use and longer term

control of pCO2 improved adherence to NIV in the presence of daytime hypercapnia (pCO_2 > 6.5) at set up may impact longer term survival as described previously.[7]

This study has a number of limitations and it is recognized that this is a retrospective observational review of a cohort of DM1 patients under consideration of NIV set up. We cannot be certain we have included all patients with DM1 into the study. Variability in the frequency of individual follow up visits has made accurate assessment of changes in pCO_2 and adherence to NIV more difficult. We cannot exclude the impact of the time of day blood gas measurements were taken on the improvement in pCO_2 at time of discharge. As an in-patient changes of ventilator settings are made following overnight monitoring of oximetry and an early morning blood gas measurement. A daytime blood gas measurement is taken prior to discharge typically blood gas measurement was taken with patients not using NIV (although due to the retrospective nature of this study it is possible a small proportion of patients may have been using NIV at the time of blood gas measurement). It is anticipated that the early morning blood gas is taken whilst using NIV and hypercapnia due to alveolar hypoventilation has been corrected. However, poor tolerance and adherence to NIV may contribute to a persistent elevated morning pCO_2, which may subsequently correct wholly or in part during waking hours. However, our control of hypercapnia in the “respiratory failure group” and better adherence to NIV during the in-patient stay would suggest NIV is at least in part correcting hypercapnia initially and resetting central drive. Hypercapnic respiratory failure in DM1 remains multi-factorial. The sustained reduction of PCO2 unrelated to NIV adherence suggests that the initial presentation with elevated PCO2 rise may be related more to impaired central drive and insensitivity to PCO2 rather than other factors including underlying respiratory muscle weakness. In most neuromuscular diseases hypercapnic

respiratory failure is directly related to impaired muscle strength and control of hypercapnic is proportional to the use of NIV. We have not observed this DM1 which may suggest that the initial presentation in respiratory failure is related to blunted central respiratory drive. Additional factors may impact this such as intercurrent respiratory illnesses and medication. Respiratory muscle weakness will compound respiratory failure over time and increase the risk of sudden deterioration. We anticipate a greater dependence and relationship to NIV adherence once this occurs.

In conclusion, the results of this single centre retrospective study show that patients with DM under our care have low adherence to NIV over time, and longer term NIV use does not correlate with daytime pCO_2 levels. The complexity and overlap of symptoms of alveolar hypoventilation with those of myotonic dystrophy may well be contributing to the lack of perceived benefit of NIV and therefore low adherence to use. The benefit of using NIV in DM remains unclear. In the presence of normocapnia (pCO_2 <6.5 kPa) NIV does not appear to offer any benefit and adherence to NIV use is very low. However, in the presence of hypercapnia (pCO_2 >6.5kPa) use of NIV may offer some symptomatic benefit in those who adhere to use. Furthermore, there may be a mortality advantage in using NIV and concentrating efforts to support adherence in this group. There is a need for high quality evidence of the benefits of NIV in DM. Results from our centre suggest long-term adherence to NIV is difficult to achieve and there may be no benefit in initiation of NIV for symptom control in absence of significant daytime hypercapnia.

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