Effects of one-month withdrawal of ventilatory support in hypercapnic myotonic dystrophy Type 1

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*FJO and JCB contributed equally to this study.
# RT and JLP share responsibility of this study

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Summary at a Glance

Withdrawal of noninvasive ventilatory support in myotonic dystrophy patients with chronic hypercapnia produced no change in QOL nor somnolence. Small deteriorations were seen in nocturnal oxygenation and daytime CO₂, but without changes in respiratory drive nor lung function. This suggests the benefits of ventilation support in this group are uncertain.

Keywords: Hypercapnia, Myotonic Dystrophy, non-invasive ventilation, Quality of Life, Respiratory Failure,

Short Title: NIV in Myotonic Dystrophy Type 1
ABSTRACT

**Background and objective:** The benefits of domiciliary Noninvasive Ventilation (NIV) in Myotonic Dystrophy type 1 (DM1) are unclear. We sought to determine the effects of elective discontinuation of ventilatory support for 1 month in DM1 patients receiving NIV for chronic hypercapnic respiratory failure.

**Methods:** At baseline, 12 patients underwent polysomnography, and assessment of subjective (Epworth Sleepiness Scale) and objective (Oxford Sleep Resistance Test) sleepiness, fatigue (Fatigue Severity Scale), respiratory function including muscle strength, ABG, hypercapnic ventilatory response (HCVR), BP, peripheral arterial tonometry (PAT) and pulse wave velocity (PWV). They also completed the SF36. Testing was repeated (Visit 2) 1 month after elective cessation of NIV and again (Visit 3) 1 month after NIV reintroduction.

**Results:** No changes were seen in SF36, sleepiness or fatigue, respiratory function, muscle strength nor HCVR. Likewise there were no changes in BP, PAT or PWV. Mean nocturnal SaO₂ deteriorated off NIV and improved on resumption (Mean±SD 95.02 ± 1.90, 92.23 ± 3.61 and 95.08 ± 2.28%, p=0.006 change visit 1 to visit 2, 0.009 visit 2 to visit 3). Daytime PaCO₂ was 43.13 ± 4.20, 46.28 ± 2.25, and 43.87 ± 2.85 mmHg, p=0.056 and 0.017 over the same intervals.

**Conclusion:** DM1 patients derive little benefit in symptoms or quality of life from NIV. Nocturnal and diurnal ventilatory function deteriorates slightly off NIV for 1 month, but this does not appear to be due to changes in HCVR or respiratory function.
function. HCVR changes may be of primary CNS origin given stability on or off NIV.

**Clinical trial registration**: NCT00745238 at clinicaltrials.gov

**Keywords**: Hypercapnia, Myotonic Dystrophy, non-invasive ventilation, Quality of Life, Respiratory Failure,

**Short Title**: NIV in Myotonic Dystrophy Type 1

**Abbreviations**

%TST<90%; Percentage of Total Sleep Time spent at oxygen saturation <90%

A-aO₂; alveolar-arterial oxygen gradient

ABG; Arterial Blood Gas

ArI; Arousal index

BMI; Body Mass Index

BP; Bodily Pain domain of SF36

CO₂; Carbon Dioxide

DBP; Diastolic Blood Pressure

DM1 Myotonic Dystrophy Type 1

EEG; Electroencephalogram

EPAP; Expiratory Positive Airways Pressure NIV setting

ESS; Epworth Sleepiness Scale

FEV₁; Forced Expiratory Volume in 1 second
FRC; Functional Residual Capacity
FSS; Fatigue Severity Scale
GH; General Health Perception domain of SF36
HCVR; Hypercapnic Ventilatory Response
IPAP; Inspiratory Positive Airways Pressure NIV setting
MH; General Mental Health domain of SF36
MWT; Maintenance of Wakefulness Test
N1/N2/N3; Non REM stage 1/2/3 sleep
NIV; Noninvasive Ventilation
OSLER; Oxford Sleep Resistance Test
PaCO₂; Arterial partial pressure of carbon dioxide
PaO₂; Arterial partial pressure of oxygen
PAT; Peripheral Arterial Tonometry
PF; physical functioning domain of SF36
PSG; Polysomnogram
PWV; Pulse Wave Velocity
QOL; Quality Of Life
RE; Role Limitation due to Emotional Problems domain of SF36
RF; respiratory failure
RP; Role Limitation due to Physical Problems domain of SF36
RR backup; ventilator backup respiratory rate
RV; Residual Volume
SB; Spontaneous Breathing
SBP; Systolic Blood Pressure
SF; social functioning domain of SF36
SF36; Medical Outcomes Study 36 item short form health survey
SNIP; Sniff Nasal Pressure
TLC; Total Lung Capacity
TST; Total Sleep Time
VC; Vital Capacity
VT; Vitality domain of SF36
INTRODUCTION

Myotonic Dystrophy type I (DM1) is an autosomal dominant disorder caused by a triple repeat expansion gene coding for a protein kinase on chromosome 19q13.3. Clinical manifestations include myotonia, weakness, hypercapnic respiratory failure (T2RF), sleep disorders including sleep-disordered breathing, fatigue and sleepiness, endocrinopathies, and cardiac conduction disturbances. T2RF is a common consequence of respiratory muscle weakness in progressive neuromuscular diseases, often first occurring in sleep. Nocturnal noninvasive ventilation (NIV) has become the standard of care in such patients. Carbon dioxide (CO2) retention in sleep and progressive daytime T2RF are prevented or controlled and NIV has been shown to improve or normalise Hypercapnic Ventilatory Responsiveness (HCVR) over a period of 1-2 weeks. In these patients NIV also prolongs life, and improves sleep fragmentation, somnolence and quality of life.

By contrast, in DM1 there is a poor correlation between the severity of respiratory muscle weakness, and the occurrence and severity of T2RF. It has been proposed that RF in these patients is due to primary abnormalities in respiratory control at medullary level rather than secondary to nocturnal CO2 retention. Similarly, daytime somnolence is often reported in DM1 patients in the absence of identifiable sleep disorder, and reportedly fails to improve with treatment of sleep issues. This lack of symptomatic improvement may be one reason why
DM1 patients have been reported to tolerate NIV poorly.\textsuperscript{4, 12} It therefore appears that both T2RF and daytime somnolence are primary CNS manifestations of DM1, rather than related to sleep breathing disorders, suggesting that the benefits of NIV in this population are uncertain.

We conducted a pilot 1 month open label NIV withdrawal study in DM1 patients with T2RF treated with NIV, measuring arterial blood gases (ABG), HCVR and respiratory muscle function, sleep quality, subjective and objective sleepiness, and quality of life (QOL). We also evaluated markers of cardiovascular risk, since uncontrolled sleep-disordered breathing is associated with an elevated risk of cardiovascular disease.\textsuperscript{13}
METHODS

Patients

Stable DM1 patients undergoing NIV for at least 6 months for treatment of chronic T2RF were recruited from the clinics of the University Hospitals of Grenoble and Lille and Raymond Poincaré Hospital, Garches, France. The study was limited to patients who had daytime PaCO$_2$ 45-55 mmHg at NIV initiation. Daily NIV usage between 4-12 hours over the preceding month was required. Exclusion criteria were the presence of any other respiratory condition potentially causing T2RF, episode of acute or acute-on-chronic RF or any change in NIV settings during the preceding month, and high cardiovascular risk factors such the treating physician felt withdrawal of NIV was unsafe. All patients signed informed written consent, the study was approved by local institutional ethics committees, and was conducted according to the amended Declaration of Helsinki.

Protocol

Full in-laboratory nocturnal polysomnography (PSG) was conducted on the patients’ usual NIV settings. Studies were staged and scored according to standard criteria.$^{14, 15}$ The following morning ABG were taken from the radial artery in sitting posture at least 1 hour after cessation of NIV. Patients completed the Epworth Sleepiness Scale (ESS),$^{16}$ and the Fatigue Severity Scale (FSS).$^{17}$ Daytime sleepiness and attention were also objectively
monitored using a single session of the Oxford Sleep Resistance Test (OSLER).\textsuperscript{18} This test has been validated against direct EEG measures of sleep onset and sleepiness,\textsuperscript{19} and we have previously demonstrated that a single 40 minute session is as sensitive as 3 sessions in detecting daytime somnolence.\textsuperscript{20} All patients had assessment of spirometry, plethysmographic lung volumes, and muscle strength by sniff nasal pressure (SNiP) according to ATS/ERS standards. HCVR was assessed by the Read method.\textsuperscript{21}

Vascular endothelial function was evaluated by measurement of flow mediated vasodilatation using peripheral arterial tonometry (PAT) (EndoPAT, Itamar Medical, Caesarea, Israel).\textsuperscript{22} Arterial pulse wave velocity (PWV) was also measured (Complior SP, Artech Medical, Pantin, France)\textsuperscript{23} as an index of arterial stiffness. PAT index and PWV are strongly predictive of cardiovascular events and all cause mortality.\textsuperscript{22, 23}

Patients also completed the Medical Outcomes Study 36 item short form health survey (SF36) QOL questionnaire.

Noninvasive ventilatory support was then electively ceased for 1 month, following which the whole test battery was repeated (Visit 2). NIV was then recommenced for a further month, followed by reassessment of the test battery, with PSG on the patient’s usual NIV settings (Visit 3).

**Statistical analysis**
All statistics were conducted using NCSS 2007 (Kaysville, UT, USA). Evolution of change across visits was evaluated by repeated measures ANOVA, and by Friedman’s test for non-normally distributed data. Post-hoc testing utilised student-t tests. P<0.05 was taken to indicate statistical significance. All data are reported as mean±SD.
RESULTS

Sixteen patients were recruited. However, in one, the treating physician considered it unsafe to withdraw NIV, and 3 declined further participation after visit 1. Table 1 gives epidemiological, anthropometric and baseline respiratory data of the remaining 12, as well as sleep-disordered breathing indices collected off NIV at visit 2.

All patients tolerated NIV withdrawal without ill effects. There was no significant change in any SF36 domain between visits (Table 2).

There were no changes in sleep architecture, but oxygenation during sleep deteriorated off NIV (Table 3, Figure 1A). Mean ESS and FSS scores were within normal limits of $\leq 11$ and $\leq 5$ respectively,\textsuperscript{16, 17} (Table 3) though 42% reported abnormal ESS and 55% abnormal FSS scores. Mean OSLER results were just outside normal limits of $\geq 26.1$ minutes, and 45% recorded abnormal results.

Neither subjective nor objective assessments of daytime fatigue and somnolence changed across visits (Table 3).

There was no significant change in any parameter of respiratory function testing, (Table 4). However, there was a significant change in PaCO$_2$. (Table 4, Fig 1B). Post-hoc testing showed the change after 1 month off ventilation narrowly failed to reach significance ($p=0.056$) but there was a significant reduction on recommencing NIV ($p=0.017$). Similarly both bicarbonate (HCO$_3$) ($p=0.007$) and base excess ($p=0.022$) rose slightly but significantly from V1 to V2, with changes in the opposite direction from V2 to V3 ($p = 0.0003$ and 0.0004 respectively).
There was no change in the slope of the HCVR, which at all times was at or below the lower limit of normal (Table 4, Fig 1C).

Similarly, there was no change in arterial blood pressure (Table 4), in arterial stiffness measured by PWV, nor endothelial function measured by PAT (Table 4).
DISCUSSION

This study examined the effects of 1 month of NIV withdrawal in subjects with DM1 and chronic T2RF. There was no change in sleep architecture or fragmentation during NIV withdrawal or after its reintroduction, but nocturnal oxygen saturations worsened without NIV. There was a small increase in diurnal PaCO₂ which just failed to reach statistical significance, but there was a significant decrease on recommencing NIV, with accompanying small but significant changes in both bicarbonate and base excess. Conversely, there was no change in lung function nor muscle strength, and no change in HCVR across visits. QOL and daytime sleepiness were also unchanged, as were blood pressure and other indices of cardiovascular risk.

Hypersomnolence is reported to be extremely prevalent among DM1 patients.¹⁰ Five subjects (42%) reported excessive daytime sleepiness as assessed by ESS ≥ 11, whereas 55% reported abnormal Fatigue Severity Scale results, comparable to previous reports in DM1 patients not on NIV.¹¹, ²⁴, ²⁵ The OSLER test was designed to mimic the test conditions of the maintenance of wakefulness test (MWT), with which it correlates closely.¹⁹ The lower limit of normal for sleep latency in the MWT has been defined as 26.1 minutes,²⁶ and by this criterion 45% of our DM1 subjects demonstrated pathological sleepiness, again comparable to the previous literature.¹⁰, ¹¹ Our figures relate to patients already on treatment with NIV, but the high prevalence of somnolence in these treated patients, and the fact that there was no significant change on ceasing nor recommencing NIV,
agree with the previous literature, in that both subjective and objective sleepiness are prevalent in this population, but that the presence of these symptoms bears little relationship to sleep-related breathing disturbances, and may be a primary CNS manifestation of DM1,\textsuperscript{10} possibly related to abnormal cytokine regulation,\textsuperscript{27} or brainstem structural changes.\textsuperscript{28}

Similarly, while patients in general reported low scores in all domains of the SF36 when compared to French population norms\textsuperscript{29} consistent with previous reports,\textsuperscript{30} there was no change in any domain during NIV withdrawal or after recommencement. This absence of effect of NIV on quality of life in DM1 has not previously been reported.

There was no change in static lung function testing or tests of respiratory muscle strength between visits. This is consistent with data from other neuromuscular diseases, which have not shown changes with introduction or cessation of NIV.\textsuperscript{3, 31} This has been taken to indicate that relief of respiratory muscle fatigue is not a significant factor in amelioration of T2RF in these patients.\textsuperscript{3}

Previous studies of patients with other forms of neuromuscular or chest wall diseases have shown variable effects on blood gases on withdrawal of NIV.\textsuperscript{32-35} While all have shown deterioration in nocturnal ventilation, sleep quality and symptoms, changes in arterial blood gases were not seen in earlier studies after 1\textsuperscript{32} nor 2\textsuperscript{34} weeks, though in the case of the study by Hill et al,\textsuperscript{32} some patients resumed NIV before 1 week because of intolerable symptoms. More recent studies have reported frequent, sometimes marked deterioration in ABG and in
symptoms after NIV withdrawal for a maximum of 2 weeks. By contrast, in the current study there were no changes in QOL, fatigue or daytime sleepiness with NIV withdrawal or reinstitution. There was a small deterioration in daytime PaCO₂, which just failed to reach statistical significance, and in nocturnal gas exchange as measured by mean SaO₂. Significant improvements were seen in both daytime PaCO₂ and nocturnal SaO₂ on recommencing NIV.

Current theory regarding the mechanism of efficacy of NIV assigns a primary role to the reversal of the blunting of respiratory drive due to recurrent nocturnal CO₂ retention. Hypercapnic patients initiated on nocturnal NIV demonstrate improvements in HCVR within days, with further improvements over subsequent weeks, in concert with improvements in PaCO₂. Furthermore there is a significant relationship between changes in HCVR and changes in diurnal PaCO₂ over a longer timeframe. By contrast in our DM1 subjects there was no change in HCVR, either on NIV withdrawal or on its reintroduction, remaining at or below the lower limit of normal. This supports the previous suggestions of a difference in the mechanisms of RF between DM1 and other forms of neuromuscular disease, whereby the blunted respiratory drive is predominantly of primary CNS origin. This is further supported by neuropathological evidence of reduced density of catecholaminergic neurons in medullary respiratory centres in DM1 patients with a history of chronic RF.
in ventilatory drive? We did detect a small increase in both bicarbonate and base excess after 1 month off NIV, and a decrease with recommencement. Bicarbonate and base excess are calculated rather than measured values, and should therefore be treated with some caution. However this does suggest some minor renal bicarbonate retention in response to nocturnal hypoventilation. Nevertheless this was insufficient to produce changes in HCVR, in contrast to other disorders in which the changes in HCVR slope on commencement of ventilation have been pronounced. 6, 7 It is also possible that the changes in PaCO₂ may in part have been a carryover effect from the previous night. ABG were taken in the morning, at least one hour after cessation of NIV. However this may not have been sufficient time for the changes in PaCO₂ during sleep to wear off.

We also evaluated markers of cardiovascular risk; PWV and PAT, as well as arterial blood pressure. There is evidence that sleep disordered breathing contributes to risk of cardiovascular disease, primarily due to repeated nocturnal hypoxemia.13 However we could not demonstrate any changes in these risk factors with NIV withdrawal.

Our study has limitations. Primarily these relate to the small sample size, patient selection and relatively short study duration. However, to our knowledge this is both the largest and the longest domiciliary NIV withdrawal study yet reported in any population. It is likely that with greater numbers the PaCO₂ change between Visit 1 and Visit 2 and changes in %TST<90% and PaO₂ would have been
significant. However this would not have substantively changed the study conclusions. By contrast, the results for all other parameters suggest that large numbers of patients would have been required to reach statistical significance, assuming no change in mean or variance. For example for FVC (%pred), the parameter with the next lowest p value in Tables 3 and 4, we calculated it would have required a sample size of >300 patients to reach statistical significance. Therefore we believe the likelihood of type II error due to insufficient sample size is small.

Regarding trial duration, it is unknown whether the observed ABG changes would have been progressive over a longer period of withdrawal. Measurable changes in nocturnal pCO₂ may precede frank daytime RF by many months in slowly progressive neuromuscular disease.³, ³⁸ On the other hand, the studies of NIV initiation⁶, ⁷ and withdrawal³³, ³⁵ cited above suggest ABG and HCVR changes occur more rapidly in other neuromuscular disease populations with established respiratory failure. Similarly for cardiovascular risk, the time course of changes in the assessed risk factors is uncertain. Furthermore untreated sleep-disordered breathing may contribute to the risk of sudden death due to arrhythmia in DM1.³⁹, ⁴⁰

It is also possible that respiratory failure and flattening of the HCVR were due to respiratory muscle myotonia⁴¹ or increased respiratory system elastance,⁴² rather than muscle weakness or blunted central respiratory drive. Myotonia of respiratory muscles has been described⁴¹, though its incidence is unknown.
Increased elastance generally only occurs with significant restriction in neuromuscular disease,\textsuperscript{42} which was not present in our patients. While we cannot discount a contribution, we believe it is unlikely either of these factors caused the exceedingly flat HCVR responses seen in our patients.

A further limitation is that safety considerations dictated we only enrolled patients with milder respiratory failure, at least at the time of initial NIV commencement. We do not know whether the same results would be obtained in patients with more severe hypoventilation. Furthermore our patients were necessarily those who were adherent to NIV, and as such may not represent the broad spectrum of DM1 patients, in whom adherence is often difficult to achieve.\textsuperscript{4, 12}

Nevertheless, the results of the current study, in particular the lack of symptomatic benefit from NIV in DM1 subjects, do suggest that the decision to treat or not in this population is different to that in other forms of neuromuscular disease, especially in view of the difficulties with treatment adherence.

In conclusion, both somnolence and respiratory failure appear to be primarily of CNS origin in DM1. We have been unable to demonstrate a benefit from NIV in terms of quality of life in these patients. This suggests that, at least in patients with milder respiratory failure with low arrhythmia risk, delaying initiation of NIV should be considered in DM1 patients.
Acknowledgments

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Disclosure statement

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RT has received research grant support from ResMed, Phillips Respironics and Agir a Dom, and travel grants from Agir a Dom and Novartis.
JLP has received consultancy fees from Vivatech, lecture fees from Vivatech, Resmed, Perimetre, Philips, Fisher and Paykel and Astra-zeneca, travel grants from Agir a Dom and Teva, and research grant support from ResMed, Philips Respironics, Glaxo Smith Kline, and Agir a Dom.

No funder had a role in the study design, in the collection, analysis and interpretation of the data, in the writing of this report nor in the decision to submit it for publication.
FIGURE LEGEND

Figure 1: Changes during and after 1 month of NIV withdrawal in mean nocturnal SaO₂ (A), diurnal PaCO₂ (B), and Hypercapnic Ventilatory Response slope (HCVR) (C). Dashed line on panel C indicates lower limit of normal for HCVR.

NIV; Noninvasive Ventilation, SB; Spontaneous Breathing
Table 1: Patient Characteristics (n=12)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.53 ± 10.67</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>27.00 ± 6.62</td>
</tr>
<tr>
<td>Gender</td>
<td>5M / 7F</td>
</tr>
<tr>
<td>NIV use (hr.n⁻¹)</td>
<td>5.01 ± 1.72</td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>96.13 ± 23.41</td>
</tr>
<tr>
<td>IPAP (cmH₂O)</td>
<td>16.8 ± 4.6</td>
</tr>
<tr>
<td>RV (% pred)</td>
<td>113.00 ± 27.78</td>
</tr>
<tr>
<td>EPAP (cmH₂O)</td>
<td>6.0 ± 2.2</td>
</tr>
<tr>
<td>FRC % pred</td>
<td>102.00 ± 30.20</td>
</tr>
<tr>
<td>RR backup</td>
<td>12.8 ± 1.9</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>82.10 ± 25.44</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 17</td>
</tr>
<tr>
<td>VC (% pred)</td>
<td>80.67 ± 24.92</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>FEV₁/VC (%)</td>
<td>81.04 ± 5.84</td>
</tr>
<tr>
<td>Total AHI (hr⁻¹)</td>
<td>14.16 ± 6.87</td>
</tr>
<tr>
<td>SNIP (% pred)</td>
<td>57.11 ± 23.41</td>
</tr>
<tr>
<td>Central AHI (hr⁻¹)</td>
<td>7.09 ± 7.99</td>
</tr>
</tbody>
</table>

Explanation of abbreviations: TLC; Total Lung Capacity, RV; Residual Volume, FRC; Functional Residual Capacity, FEV₁; Forced Expiratory Volume in 1 second, VC; Vital Capacity, BMI; body mass index, SNIP Sniff Nasal Pressure, NIV use; mean usage of NIV in hours/night over 9 months preceding study, IPAP; Inspiratory Positive Airways Pressure NIV setting, EPAP; Expiratory Positive Airways Pressure NIV setting, RR backup; ventilator backup respiratory rate (breaths/min), SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, AHI; Apnea/Hypopnea Index.
Table 2 Evolution of Quality of Life (SF36) during and after NIV withdrawal

<table>
<thead>
<tr>
<th>SF36 Domain</th>
<th>Visit 1 (NIV)</th>
<th>Visit 2 (SB)</th>
<th>Visit 3 (NIV)</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>50.91 ± 24.78</td>
<td>42.85 ± 30.06</td>
<td>50.00 ± 26.36</td>
<td>0.16</td>
</tr>
<tr>
<td>RP</td>
<td>54.55 ± 31.26</td>
<td>43.18 ± 37.23</td>
<td>56.82 ± 29.77</td>
<td>0.11</td>
</tr>
<tr>
<td>BP</td>
<td>64.64 ± 20.75</td>
<td>57.73 ± 23.80</td>
<td>62.09 ± 25.65</td>
<td>0.71</td>
</tr>
<tr>
<td>GH</td>
<td>44.40 ± 19.16</td>
<td>42.70 ± 20.27</td>
<td>37.70 ± 21.39</td>
<td>0.33</td>
</tr>
<tr>
<td>VT</td>
<td>45.00 ± 21.91</td>
<td>35.91 ± 17.29</td>
<td>40.00 ± 9.75</td>
<td>0.18</td>
</tr>
<tr>
<td>SF</td>
<td>71.59 ± 19.44</td>
<td>59.09 ± 25.67</td>
<td>70.45 ± 25.17</td>
<td>0.12</td>
</tr>
<tr>
<td>RE</td>
<td>66.66 ± 36.52</td>
<td>66.67 ± 39.44</td>
<td>57.57 ± 33.65</td>
<td>0.85</td>
</tr>
<tr>
<td>MH</td>
<td>68.73 ± 17.14</td>
<td>69.45 ± 19.45</td>
<td>67.27 ± 19.08</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Explanation of Abbreviations: NIV; Noninvasive Ventilation, SB; Spontaneous Breathing, PF; physical functioning, RP; role limitation due to physical problems, BP; bodily pain, GH; general health perception, VT; vitality, SF; social functioning, RE; role limitation due to emotional problems, MH; general mental health.
Table 3: Evolution of PSG parameters and somnolence during and after NIV withdrawal

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>p(ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1/N2 sleep %</td>
<td>66.37 ± 12.13</td>
<td>64.94 ± 6.94</td>
<td>64.21 ± 7.49</td>
<td>0.27</td>
</tr>
<tr>
<td>N3 sleep %</td>
<td>13.12 ± 9.06</td>
<td>14.25 ± 4.52</td>
<td>13.02 ± 8.32</td>
<td>0.91</td>
</tr>
<tr>
<td>REM %</td>
<td>22.36 ± 8.40</td>
<td>20.66 ± 5.14</td>
<td>22.51 ± 6.21</td>
<td>0.66</td>
</tr>
<tr>
<td>TST (min)</td>
<td>331.42 ± 66.47</td>
<td>361.90 ± 51.23</td>
<td>359.67 ± 64.39</td>
<td>0.29</td>
</tr>
<tr>
<td>Ar I (/hr sleep)</td>
<td>9.82 ± 6.69</td>
<td>13.38 ± 7.40</td>
<td>6.33 ± 187.11</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean SpO2</td>
<td>95.02 ± 1.90</td>
<td>92.23 ± 3.61</td>
<td>95.08 ± 2.28</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Nadir SpO2</td>
<td>85.90 ± 3.28</td>
<td>78.10 ± 8.90</td>
<td>84.40 ± 7.31</td>
<td>0.13</td>
</tr>
<tr>
<td>%TST &lt;90%</td>
<td>2.32 ± 5.38</td>
<td>18.17 ± 22.27</td>
<td>2.16 ± 4.82</td>
<td>0.05</td>
</tr>
<tr>
<td>Epworth</td>
<td>9.33 ± 5.93</td>
<td>10.58 ± 6.17</td>
<td>9.67 ± 5.88</td>
<td>0.38</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.91 ± 1.50</td>
<td>4.99 ± 1.39</td>
<td>4.42 ± 1.31</td>
<td>0.34</td>
</tr>
<tr>
<td>OSLER (min)</td>
<td>25.43 ± 16.52</td>
<td>27.38 ± 16.43</td>
<td>28.06 ± 15.88</td>
<td>0.97</td>
</tr>
</tbody>
</table>

* post hoc test V1-V2 P=0.006, V2-V3 p=0.009

Explanation of Abbreviations: N1/N2/N3; Non REM stage 1/2/3 sleep, TST; Total Sleep Time, Ar I; Arousal index (per hour of sleep), %TST<90%; Percentage of Total Sleep Time spent at oxygen saturation <90%, Epworth; Epworth Sleepiness Scale, Fatigue; Fatigue Severity Scale, OSLER; Sleep latency on Oxford Sleep Resistance Test.
Table 4: Evolution of lung function, arterial blood gases, hypercapnic ventilatory responses and cardiovascular risk factors during and after NIV withdrawal

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (%pred)</td>
<td>80.67 ± 24.92</td>
<td>78.89 ± 26.74</td>
<td>76.29 ± 25.95</td>
<td>0.13</td>
</tr>
<tr>
<td>SNIP (%pred)</td>
<td>57.11 ± 23.41</td>
<td>55.53 ± 22.57</td>
<td>52.51 ± 26.18</td>
<td>0.30</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.03</td>
<td>7.39 ± 0.01</td>
<td>7.39 ± 0.02</td>
<td>0.37</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>43.13 ± 4.20</td>
<td>46.28 ± 2.25</td>
<td>43.87 ± 2.85</td>
<td>0.02*</td>
</tr>
<tr>
<td>HCO3 (mmol.L⁻¹)</td>
<td>26.08 ± 1.51</td>
<td>27.51 ± 1.51</td>
<td>25.76 ± 1.14</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Base Excess (mmol.L⁻¹)</td>
<td>1.28 ± 1.49</td>
<td>2.39 ± 1.45</td>
<td>0.75 ± 1.15</td>
<td>&lt;0.01‡</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>83.62 ± 15.30</td>
<td>76.88 ± 11.78</td>
<td>80.85 ± 11.33</td>
<td>0.06</td>
</tr>
<tr>
<td>HCVR (L.min⁻¹.mmHg)</td>
<td>1.52 ± 1.53</td>
<td>1.49 ± 1.71</td>
<td>1.30 ± 1.06</td>
<td>0.82</td>
</tr>
<tr>
<td>SBP sitting (mmHg)</td>
<td>120 ± 17</td>
<td>119 ± 18</td>
<td>119 ± 20</td>
<td>0.84</td>
</tr>
<tr>
<td>DBP sitting (mmHg)</td>
<td>70 ± 9</td>
<td>72 ± 11</td>
<td>71 ± 11</td>
<td>0.57</td>
</tr>
<tr>
<td>PAT</td>
<td>1.99 ± 0.40</td>
<td>1.87 ± 0.57</td>
<td>1.93 ± 0.38</td>
<td>0.70</td>
</tr>
<tr>
<td>PWV (m.sec⁻¹)</td>
<td>8.63 ± 1.01</td>
<td>8.90 ± 1.65</td>
<td>8.87 ± 1.49</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* post hoc V1-V2 p=0.056, V2-V3 p=0.017
† post hoc V1-V2 p=0.007, V2-V3 p=0.0003
‡ post hoc V1-V2 p=0.022, V2-V3 p=0.0004

Explanation of abbreviations: FVC; Forced Vital Capacity, SNIP; Sniff Nasal Pressure, HCVR; Hypercapnic Ventilatory Response slope, SBP; Systolic Blood
Pressure, DBP Diastolic Blood Pressure, PAT; Peripheral Arterial Tonometry, PWV; Pulse Wave Velocity
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