Slow Wave Sleep in Patients with Respiratory Failure

David Wang [a,b]*; Amanda J Piper [a,b]; Keith K Wong [a,b,d]; Brendon J Yee [a,b,d]; Nathaniel S Marshall [a,d]; Derk-Jan Dijk [a,c]; Ronald R Grunstein [a,b,d].

[a]Woolcock Institute of Medical Research, University of Sydney, Glebe point Rd, Glebe, 2037 NSW, Australia; [b]Department of Respiratory & Sleep Medicine, Royal Prince Alfred Hospital (work was conducted), Camperdown, Sydney 2050, Australia; [c]Surrey Sleep Research Centre, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK, [d]NHMRC- funded Centre for Integrated Research and Understanding of Sleep (CIRUS)

✉ **Correspondence to:** Dr. David Wang

Department of Respiratory & Sleep Medicine,

Royal Prince Alfred Hospital,

Camperdown, Sydney 2050, Australia.

Ph: 0061-2-9114 0446 Fax: 0061-2-9114 0014

Email: david.wang@sydney.edu.au

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ABSTRACT

Background: Slow wave sleep (SWS) has been theorised as reflecting a homeostatic sleep process and is considered a state of recuperation. SWS is reduced in Obstructive Sleep Apnea (OSA) patients, but SWS has not been specifically studied in respiratory failure patients. The aim of this study is to investigate SWS in predominantly hypercapnic respiratory failure patients.

Methods: We analyzed sleep and arterial blood gas records of all 97 respiratory failure patients who underwent polysomnography and bilevel non-invasive ventilation (NIV) treatment in our laboratory from 2008 to July 2009. We also analyzed 32 initial diagnostic study data from these 97 patients.

Results: The 97 patients had an average age of 58±15 (SD) years. Total sleep time was 320.3±82.8 (SD) minutes of which 32.9%±15.4(%) was spent in SWS. This high percentage SWS correlated positively with awake arterial CO_2 pressure (PCO_2) in both the 97 treatment studies (r=0.35, p=0.001) and the 32 initial diagnostic studies (r=0.40, p=0.025). The relationship was particularly apparent in patients with obesity hypoventilation syndrome or overlap syndrome. Statistical modelling identified three significant predictor variables for SWS across both diagnostic and NIV nights: PCO_2, arousal index and female gender.

Conclusions: Patients with respiratory failure have a high percentage of EEG assessed SWS which is in part determined by disease specific variables such hypercapnia as well as by traditional SWS determinants such as sleep fragmentation and gender.

INTRODUCTION

Slow wave sleep (SWS) is regulated accurately in response to sustained wakefulness and has been theorised as reflecting a homeostatic sleep process.[1] SWS is thought to contribute substantially to the recuperation from the effects of sustained wakefulness. [2-4] As a result stimulation of SWS via medications and devices has been attempted in the hope of producing more restorative sleep.[5-7]

SWS is identified on the basis of the presence of slow waves with an amplitude greater than 75 microvolts in the electroencephalogram (EEG). SWS declines markedly with age; whereas in adults aged between 40-54 approximately 18.2% of sleep time consist of SWS, this drops to around 15.8% in adults aged 61-70.[8] In patients with severe obstructive sleep apnea (OSA), SWS is significantly reduced secondary to increased sleep fragmentation.[8] For instance in 93 of our severe OSA patients (average 46 years), mean SWS was 11%.[9] In contrast, in our department, increased SWS% has frequently been observed clinically in patients with hypercapnic respiratory failure. This phenomenon is not easily explained by current understanding of factors affecting sleep architecture in sleep-breathing disorders.[10] A few studies of patients with nocturnal respiratory failure have quantified SWS but none have reported this phenomenon.[11-14] Interestingly, previous animal studies have shown that hypercapnia, acute or chronic, can lead to slowing of EEG in eels [15], rats [16], rabbits [17], and dogs [18]. Extreme hypercapnia can produce an isoelectric EEG in cats[19] and this has also been observed in a single case report in humans.[20]

We hypothesise that respiratory failure patients will have greater SWS% than normative age-matched controls from previously published studies[8] and that SWS% in respiratory failure patients will be positively correlated with hypercapnia.

METHODS

The study was conducted at the clinical sleep laboratory of Royal Prince Alfred Hospital, a teaching hospital of the University of Sydney. We retrieved sleep and arterial blood gas (ABG) data from all the respiratory failure patients who underwent polysomnography (PSG) with administered bilevel non-invasive ventilation (NIV) therapy in our centre from January 2008 to July 2009. Most of these respiratory failure patients were being screened for other research protocols conducted at our department (SSWAHS ethics approval number:

OHS X03-0022), and all patients signed written informed consent before the sleep studies, allowing de-identified data to be used for research audit purposes.

Our clinical criteria for selection of NIV required that patients have daytime hypercapnia [arterial CO_2 pressure (PCO_2) >45 mmHg] and/or frequent hypoventilation with significant oxygen desaturations during the initial diagnostic PSG studies. A total of 97 patients (49F, 48M) were included in the study. Firstly, we did cross-sectional analyses for the 97 NIV studies. Secondly, from 32 of these 97 patients, we were able to retrieve initial diagnostic (pre-treatment) PSG and ABG reports of tests conducted in our laboratory. Sleep data before and after NIV intervention were compared in this subset. Diagnostic PSG studies conducted in other laboratories were not included in the subset to maintain data standardisation.

Polysomnography: In-laboratory PSG was performed using either Compumedics E series data acquisition system (Compumedics; Victoria, Australia) or Alice 4 & 5 diagnostic sleep system (Respironics, USA). Each PSG study included four channels of EEG, two channels of electrooculogram, chin electromyogram (EMG), leg EMG, electrocardiogram, nasal air pressure, percentage oxygen saturation (SpO_2), snoring and body position. Continuous transcutaneous $PaCO_2$ ($PtcCO_2$) was also recorded for the NIV PSG studies. However, the measurement was not calibrated according to blood gas value. The data were therefore only used to indicate trend and were not used for final statistics. EEGs were low-pass filtered at 35 Hz and high-pass filtered at 0.3 Hz. The PSG studies were manually scored by experienced sleep scientists. Sleep staging was scored according standard Rechtschaffen and Kales criteria using 30 sec epochs as the scoring unit.[21] According to these criteria stage 3 is scored when 20-50% of an epoch consists of slow waves with an amplitude greater than 75 micro volt. Stage 4 is scored when more than 50% of an epoch consists of slow waves. Stages 3+4 together constitute SWS. Respiratory events were scored according to Chicago criteria [22], but no respiratory effort-related arousal events were marked. Sleep arousals were scored according to the American Sleep Disorder Association (ASDA) task force criteria.[23]

ABG: As a standard procedure in Royal Prince Alfred Hospital, arterial blood samples are taken for all the potential respiratory failure patients between 4-6 pm before PSG sleep studies.

Statistical methods

Descriptive data were expressed as mean ± SD unless otherwise stated. Unpaired t-tests and Mann-Whitney U tests were used for between group comparisons where appropriate. Within patient comparisons were compared by paired t-tests. Associations were tested by either Pearson's or Spearman's tests as appropriate. Stepwise multiple linear regression analyses were used to identify factors associated with SWS. ANOVA was used to test between subject effects among the subtypes of respiratory failure patients. In the subset with PSGs done with and without NIV, predictors of SWS% were compared between the two nights using a random intercept linear mixed model. Analyses were performed using SPSS 17. A $p < 0.05$ was considered as significant.

RESULTS

NIV study

The 97 patients could be categorized into 6 subtypes according to the cause of the disease: a) 24 neuromuscular disease-related; b) 13 lung disease related; c) 14 overlap syndrome (COPD plus OSA); d) 19 obesity hypoventilation syndrome (OHS); e) 22 chest wall restriction; f) 5 disordered control of breathing. In detail, the lung disease related subtype consists of 8 COPD, 2 COPD with pulmonary fibrosis, 1 with bronchiectasis, and 2 with cystic fibrosis. The diagnosis of lung disease was initially made on the basis of clinical history and pulmonary function testing months to years prior to the sleep study. Arterial blood gases and spirometry were routinely performed during the afternoon prior to the PSG. COPD was defined as FEV_1/FVC ratio <70%, with severity based on percent of predicted FEV_1 (GOLD criteria, www.goldcopd.com); the disordered control of breathing subtype consists of 2 with congenital central hypoventilation syndrome, 2 with sustained brain stem damage, and 1 with abnormal ventilatory control of unknown cause. Hypoventilation is defined by an awake daytime CO_2 > 45mmHg or during sleep a sustained fall in SpO_2 > 4% from baseline values accompanied by a rise in $PtcCO_2$> 8mmHg. OSA was defined by apnea hypopnea index (AHI) > 10/hour. Only 7 out of the 97 patients (7%) had normal initial pre-NIV awake PCO_2 < 45 mmHg, including 6 with neuromuscular diseases and 1 with chest wall restriction (PCO_2 = 44 mmHg).

Sleep and PCO_2 data are shown in Table 1. Seventy-seven of the 97 patients studied (79.4%) had SWS greater than 20%. This high SWS% was related to increases in both stage 3 and 4, with the highest value of stage 4 sleep (65%) observed in a 58-year old patient with overlap syndrome. Out of the 97 NIV studies, 19 (20%) were initial NIV titration studies and had mean SWS of 37.5%, while the other 78 (80%) were long-term NIV review studies (Review studies assess adequacy of the ventilation settings after at least one year continuously using NIV following initial titration study) with a mean SWS of 31.8%. Females had significantly more SWS than males (Mean difference=25.6 mins, p=0.024) after correction for PCO_2, disease subtype, Arousal Index (ArI), and potential interactions of subtype & PCO_2.

The overall SWS% was positively correlated with awake daytime PCO_2 (r=0.35, p=0.001, see Figure 1) and with % Total sleep time with SpO_2 below 90% (%T90) (rho=0.22, p=0.035). We stratified the 97 patients into the six subtypes and found that the correlations between SWS% and PCO_2 were only significant in Overlap syndrome and OHS subtypes (Table 2). Using univariate ANOVA, we found a significant interaction between subtype*PCO2 when SWS was the dependent variable (F=3.25, p=0.01). Because of this interaction we had to test the 6 subgroups separately. We also tested correlations between Stage 4% and PCO_2 separately in each of the 6 subgroups. Again, the correlations were only apparent in Overlap syndrome (r=0.65, p=0.015) and OHS (r=0.47, p=0.05) subtypes.

We conducted a stepwise multiple linear regression (backward deletion) to explore significant predictors for the increased SWS time. SWS time was the dependent variable with BMI, Gender, Subtype of Overlap or OHS present or absent, Age, ArI, AHI, SpO_2 nadir, %T90, and awake PCO_2 as independent variables. There were three significant predictors, explaining 22% of the variance of SWS time: PCO_2 (t=3.03, p=0.003), ArI (t=-2.78, p=0.007) and Gender (t=-2.2, p=0.03). We repeated this analysis with stage 4 as the dependent variable and found the same significant predictors albeit in a different order: ArI (t=-3.14, p=0.002), PCO_2 (t=2.68, p=0.009) and Gender (t=-2.65, p=0.01).

The increased SWS time was negatively correlated to sleep latency (r=-0.22, p=0.34) and positively correlated to sleep efficiency (r=0.44, p<0.001), suggesting an overall increase in sleep drive with the SWS

increase. However, the best predictor for the increased SWS time, PCO_2, did not correlate to either sleep latency or sleep efficiency ($p>0.5$).

Patients with both Diagnostic and NIV data (n= 32)

Table 3 shows the comparisons of sleep and PCO_2 data before and while on NIV treatment. Before commencing NIV, the 32 subjects had an average age of 60.3 years and SWS% of 23.5% despite high ArI of 33.1/hr. In the initial diagnostic studies fourteen patients (43.8%) had SWS higher than 20%. In the latter NIV studies, 19 out of 32 (59%) were long-term NIV review studies. The application of NIV reduced average ArI from 33.1 to 13.5/hr, AHI from 29.9 to 7.7/hr and PCO_2 from 56.7 to 51.2 mmHg. SWS increased from 23.5% to 33.3% on average. (Table 3) The increase of SWS% was significantly associated with the reduction of ArI (rho=-0.389, p=0.028).

Similar to the NIV study, we found a significant positive correlation between awake PCO_2 and SWS% in the 32 initial diagnostic studies (r=0.40, p=0.025, see Figure 2). Female subjects (n=19) had higher SWS% than the 13 male patients (27.3±24.1% vs. 17.9±15.6%, p=0.16).

To explore the reasons for SWS% increasing from the diagnostic to the NIV night, concurrently with a fall in PCO_2, mixed effects models were fitted to data from n=32 patients with PSG data from both nights analysed. The full model included predictors gender, arousal index, PCO_2, night (diagnostic vs. NIV) and the night*PCO_2 interaction, while the dependent variable was SWS%. There was no significant night*PCO_2 interaction, indicating no difference in the positive relationship between PCO_2 and SWS% between the two nights (p=0.7). Mixed linear regression indicated that PCO_2 (p=0.009), gender (p=0.009) and arousal index (p=0.03) remain significant independent predictors of SWS% across both nights, but night was not a significant predictor. The latter also suggests that the rise in SWS% despite a fall in PCO_2 between diagnostic and NIV nights (Table 3) can be explained by the concomitant improvement in sleep quality as expressed by the fall in arousal index.

DISCUSSION

As we hypothesised respiratory failure patients have much higher proportion of slow wave sleep than a reference normal population.[8] In addition the SWS% was positively associated with daytime hypercapnia. The association was found in both initial diagnostic PSG and in subsequent NIV treatment studies, indicating that the high SWS is not due to a rebound effect from NIV use. The relationship was particularly apparent in OHS and overlap syndrome subtypes which can not be easily explained by our data. The increased SWS may also be a marker of increased overall sleep drive with decreased sleep latency and increased sleep efficiency. Our multiple regression results suggest three mechanisms involved with the increased SWS%.

Hypercapnia

Our 97 patients predominantly had hypercapnic respiratory failure and PCO_2 was the best predictor for the increased SWS time. To our knowledge, this phenomenon has not previously been reported in observational studies, although few clinical studies have reported SWS data in respiratory failure samples.[11-14] In a study conducted in 1976, the authors reported "greater than expected stage 4 sleep" (>11%) in 4 out of 10 chronic ventilatory failure patients which is "surprising for their age group"(48-66 yrs).[11] The 10 patients had an average awake PCO_2 of 57mmHg which is similar to our patient group (mean PCO_2 58±10.9 mmHg). The authors did not discuss this observation further, possibly due to small sample size. In 1982, a study compared sleep architecture in 24 severe COPD patients before and after O_2 therapy with that of age-matched healthy control participants.[14]. Although the exact numerical effect was not reported, a figure showed that compared to the normal participants, the SWS% in "COPD on air" was more than doubled, and the SWS% in "COPD on O_2" was more than tripled. This finding was not discussed.[14] Also in 1982, Calverley and colleagues compared sleep architecture in 20 chronic bronchitis and emphysema patients with 9 healthy controls.[13] Thirteen out of the 20 patients with elevated PCO_2 (mean = 51 mmHg) had an average 11% SWS. The remaining 7 patients with relatively normal PCO_2 (mean = 36 mmHg) had an average SWS of 8% compared with 12% in the controls. No significant difference was found among the three groups possibly due to small sample size and heterogeneous patient groups.[13] Another study reported PSG in 25 out of 117 chronic respiratory failure patients before and after lung transplant.[12] Before transplant the 25 patients averaged 7.8% of stage 4 sleep which dropped to 4.8% after transplant ($p=0.09$). Stage 3 sleep did not change (8.8% to 9.1%). Awake PCO_2 change was not reported but awake SaO_2 was reported to be markedly improved after transplant (91.5±4.7% vs. 96.0±1.85%, $p<0.001$). Overall these 117 patients had an average awake PCO_2 of

42±6.6 (28-76) mmHg which is not as hypercapnic as our patient group. Most were prescribed steroids and other drugs which are likely to have reduced SWS. In addition, the lung transplant study patients mainly had cystic fibrosis and emphysema which we would have classified under the lung disease subtype in our study.[12] But our data did not yield a significant association between PCO_2 and SWS in the pure lung disease subgroup. The superior sample size in our study allowed us to investigate the potential effects of patient heterogeneity on the association between hypercapnia and SWS. In addition, the severity of hypercapnia in conjunction with a wide spread in hypercapnia in our patients allowed us greater statistical power to detect effects on SWS than was available to the previous investigators.

Because previous experimental studies in both animals and humans have shown that hypercapnia causes increases in SWS we believe that the biologically plausibility of the clinical association we report here is already established. In a human study $PaCO_2$ levels were manipulated in 18 anesthetized elective surgery patients to achieve hypocapnia ($PaCO_2$=20mmHg), normocapnia ($PaCO_2$=38mmHg) and hypercapnia ($PaCO_2$=50mmHg).[24] Acute hypercapnia ($PaCO_2$=50mmHg) was found to cause a significant decrease of power in the alpha and beta EEG bands, whereas delta and theta power remained unchanged.[24] In contrast, previous animal studies have suggested that both acute[15,16,18] and chronic hypercapnia[17] are associated with increased delta waves in EEG. After giving 30 seconds of 80% CO_2, EEG traces in rats (under light anesthesia with N_2O) were dominated by slow waves.[16] Relative percentage EEG power (Frequency analysis) dropped from 100% to 56.4% by 45 seconds. Thirty seconds after cessation of 80% CO_2, this metric began to recover and 4 minute later recovered to 75%[16] Similar findings have also been reported in dogs[18] and eels[15]. In a chronic hypercapnia model of 13 rabbits (without anesthesia) exposed to an air mixture containing an increasing amount of CO_2 over an eight-week period, arterial CO_2 increased to 60mmHg and mean EEG frequency dropped by 10Hz.[17] The rabbits became extremely apathic and brain edema was confirmed by electron microscope. The authors proposed that the slowing of EEG and the accompanying behavioural change may signal a depression in vital activities caused by chronic hypercapnia.[17] We speculate that the mechanism may also apply to our clinical patients, the large amounts of SWS we found may not represent changes in SWS similar to those caused by sustained wakefulness. The exact biological reason for the increased SWS in our patients is unclear. However, SWS in our patients is associated with the same factors that are associated with SWS in normal people, namely sleep interruption/arousal and gender.

Our findings may also be related to the description of "Paradoxical Delta Activity" during anaesthesia.[25] Although this phenomenon was attributed to noxious stimulation causing cortical arousal[25], substantial variation in PCO_2 may occur in anesthetized patients, especially in those with hypercapnic respiratory failure.

Arousal

Frequent sleep interruption/ sleep fragmentation is an important factor affecting SWS. In our SWS analysis the second most powerful association was the negative association with arousal index. In addition, the comparison of sleep before and after NIV intervention showed a significant negative relationship between the change of arousal index and the change of SWS%. This is not surprising as SWS in severe OSA patients is significantly disturbed by frequent arousals.[8] After implementing NIV, sleep fragmentation was reduced and SWS significantly increased despite a reduction of PCO_2. This may suggest that the dramatic reduction of arousals from the introduction of NIV played a more dominant role than the more minor shift in PCO_2 in determining SWS changes within patients. However, the correlation between patients on any single night of observation is that PCO_2 correlates more strongly with SWS than ArI does.

Gender

We also found that female gender is a significant predictor for the increased SWS time in our patients independent of age, AHI, ArI, overnight SpO_2, awake PCO_2 and disease subtype. This is not a new observation as females have long been noted to have greater amounts of SWS and concomitantly greater EEG power in the delta frequency[8],[26,27] _ENREF_28 Our study confirms that this gender effect is still evidence even in the context of severe hypercapnia.

Study limitations

We tried to minimize the retrospective limitation of our study by retrieving initial diagnostic PSG studies and comparing with their latter NIV treatment studies. However, a large proportion of patients commenced NIV on an emergency basis and did not undergo full diagnostic polysomnography. Also, some initial diagnostic PSG studies were not conducted at our laboratory. To maintain high quality standardisation of data, we excluded those studies. Therefore, only 32 out of 97 studies were included in final diagnostic study analyses. We are aware of the pitfalls related to this and therefore verified our findings with the diagnostic studies

using mixed model analysis. In our NIV studies, the $PtcCO_2$ measurements were not calibrated as they were used to indicate trends, and therefore they were not included in our analysis. Instead, we used awake ABG PCO_2 to represent the degree of hypercapnia. We can only speculate that, generally speaking, patients with daytime hypercapnia will be further worse off with sleep depressing respiration and that daytime and night-time hypercapnia are substantively correlated. A potential confounding factor is that some patients were O_2 dependant and the investigations were performed with O_2 supplementation or immediately off oxygen, which could affect PCO_2 and SpO_2 results. Most of our patients were taking different medications and it is nearly impossible to find a medication free respiratory failure group. Nevertheless, none of the related medications has proven effects of increasing SWS which could significantly bias our study results. Our approach of not excluding patients on arbitrary criteria does however have an advantage because we are reasonably confident that these patients represent a general cross-section of our normal respiratory failure population. It is also possible that application of quantitative EEG analysis methods[28] to these data may provide superior resolution compared to standard visual scoring. Another limitation is that the sample size in some of the subtypes was small (due to rarity of the diseases), which limited statistical power. Caution should be exercised in concluding the absence of associations in any given subtype.

In summary, patients with respiratory failure have a paradoxically high amount of SWS. In these patients, SWS is positively correlated to PCO_2, particularly in OHS and overlap syndrome subtypes.

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Legends

Table 1. Sleep and PCO_2 data in 97 NIV study patients. BMI=Body Mass Index; REM=Rapid Eye Movement Sleep; TST=Total Sleep Time; AHI= Apnea Hypopnea Index; T90%= percentage of total sleep time with SpO_2<90%, and same apply to T80%, T75%, T70%.

Table 2. Respiratory failure **s**ubtypes on NIV PSG and PCO_2. OHS=Obesity Hypoventilation Syndrome; AHI= Apnea Hypopnea Index; NIV No.= number of NIV PSG studies; Diag No.= number of Diagnostic PSG studies.

Table 3. The comparisons of sleep and PCO_2 data before and after NIV treatment in 32 patients. REM=Rapid Eye Movement Sleep; TST=Total Sleep Time; S1% = Stage 1 percentage in total sleep time and same apply to S2%, S3%, S4%; AHI= Apnea Hypopnea Index; T90%= percentage of total sleep time with SpO_2<90%, and same apply to T80%, T75%, T70%.

Figure 1. Significant positive correlation between PCO_2 and SWS% in 97 NIV studies (r=0.35, p=0.001; Panel A), the correlation coefficient increased to 0.56 in OL and OHS subgroups only (n= 31, r=0.56, p= 0.001; Panel B). The reference dash line indicates the average SWS% from normative population data [8]. Diagnostic Code: NM=Neuro-Muscular Disease; LD=Lung Disease; OL=Overlap; OHS=Obesity Hypoventilation Syndrome; CWR= Chest Wall Restriction; COB= Control of Breathing.

Figure 2. Significant positive association between PCO_2 and SWS% in 32 initial diagnostic PSG studies (r=0.40, p=0.025). The reference dash line indicates the average SWS% from normative population data [8].