The Impact of Obstructive Sleep Apnoea/Hypopnoea and Its Treatment with Continuous Positive Airway Pressure on the Outcome of Stroke

Chung-Yao Hsu

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Declaration

I hereby declare that this thesis is of my own composition, and that all assistance has been duly acknowledged. The studies in this thesis constitute work carried out from December 2000 to December 2003. The thesis complies with the stipulations set out for the degree of doctor of philosophy by the University of Edinburgh. The results presented here have not previously been submitted for any other degree or qualification.

Chung-Yao Hsu

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For more than 1,500 working days in Edinburgh, I moved from one hospital to another to recruit patients and, from one home to another to visit them. Without all of you this thesis would not be possible.

Chung-Yao Hsu

Abstracts

Background: The prevalence of sleep-disordered breathing (SDB) in stroke is high. One study showed SDB had a negative impact on the functional capacity of stroke patients on discharge and another that SDB was associated with a higher mortality rate. However, these findings are disputed. The impact of SDB in stroke patients on cognition and health-related quality of life is also not clear. The one randomized controlled trial of nasal continuous positive airway pressure (CPAP) in stroke patients with SDB showed CPAP improved wellbeing but not other outcomes. I hypothesised that: (1) SDB is related to stroke outcome and (2) treatment of SDB in stroke patients with CPAP would improve functional outcome.

Methods: There are three parts of the thesis: (1) a study of the prevalence of SDB after stroke; (2) a randomized controlled trial (RCT) of CPAP after stroke and (3) a longitudinal cohort study to investigate the impact of SDB on outcome after stroke. On day 14-19 after stroke, recruited patients underwent a limited sleep study using a validated system (Embletta PDS, Medcare Flaga, Iceland). Baseline assessments were performed on the morning following the sleep study. On day 21-25 following stroke, patients who had $(A+H)\cdot h^{-1} \geq 30$ with $< 30\%$ of central events were randomized to 8 weeks of CPAP treatment with Autoset T (ResMed, SanDiego USA) or conservative treatment for SDB. All outcomes were recorded in the 8^{th} week after randomization or 3 months after stroke for non-randomized patients. All recruited patients received follow-up at six months after stroke. If available, patients also received 12 months and 18 months follow-up until the last recruited patient had had his 6 months follow-up. The Nottingham Extended ADL Index (EADL) was chosen as the primary outcome measure. Secondary outcome measures included: Subscales of EADL, NIH Stroke Scale (NIHSS), Barthel Index (BI), Stanford Sleepiness Scale (SSS), Addenbrooke's Cognitive Examination (ACE) and Mini-Mental State Examination (MMSE), Hospital Anxiety and Depression Scale (HADS), MOS Short Form 36 Health Survey (SF-36) and ambulatory blood pressure - measured with Spacelabs 90207 (Spacelabs, Redmond, USA).

Results: We screened 658 patients with recent strokes and excluded those with dementia, confusion, severe dysphasia or insufficient hand function to use CPAP. Only 96 of 658 patients remained eligible of whom 25 declined to give informed consent. 71 patients were thus successfully recruited for overnight limited sleep study 14-19 days following stroke. Sixty-six patients with adequate recording were included in the study: 45 men and 21 women, median age 74yrs. The sleep study showed 50% of patients had more than 30 apnoeas + hypopnoeas per hour in bed [expressed as $(A+H)\cdot h^{-1}$]. Pulse oximetry alone had lower sensitivity (70%) but high specificity (90%) to predict $(A+H)\cdot h^{-1} \geq 30$. A combination of age, body mass index, snoring and excessive daytime sleepiness based on logistic regression model is useful as a screening tool at the bedside (sensitivity = 85%, specificity = 70%) to predict $(A+H)\cdot h^{-1} \geq 30$ in stroke before referring patients for overnight sleep study. Interaction of lowest oxygen saturation and lowest heart rate is independently associated with stroke during sleep in patients with $(A+H)\cdot h^{-1} < 30$ ($p = 0.023$). Patients with $(A+H)\cdot h^{-1} \geq 30$ more often had their stroke during daytime than patients with $(A+H)\cdot h^{-1} < 30$ ($p = 0.006$). Thirty patients who had $(A+H)\cdot h^{-1} \geq 30$, with < 30% central apnoea or Cheyne-Stokes respiration, proceeded to a randomized controlled trial starting from the 4th week after stroke with 15 patients randomized to CPAP and 15 to conservative treatment for SDB. Conventional stroke treatment was maintained in all patients. Duration of treatment was 8 weeks and blind outcome assessment was performed at 3 months and 6 month after stroke. The result showed compliance with CPAP was poor with mean 1.40 hours and median 0.16 hours per night. There was no statistically significant difference in the outcomes, sleepiness and ambulatory blood pressure with CPAP therapy. Increased length of keeping CPAP was correlated with higher score of language subscale in the Addenbrooke's Cognitive Examination (Spearman's rho = 0.544, $p = 0.036$) and lower score in the depression subscale of the Hospital Anxiety and Depression Scale (HADS, Spearman's rho = -0.538, $p = 0.039$). All 66 patients with adequate sleep studies received longitudinal follow-up at 3, 6 12 and 18 months following stroke. The patients with $(A+H)\cdot h^{-1} \geq 30$ had a trend to worse functional capacity in both Barthel Index and Nottingham Extended ADL Index (EADL) than patients with $(A+H)\cdot h^{-1} < 30$ but there was only a statistically

significant difference in the mobility subscale of EADL. The negative influence of $(A+H)\cdot h^{-1} \geq 30$ on functional capacity and health-related quality of life following stroke was only statistically significant in patients with mild stroke (NIH Stroke Scale, NIHSS < 7) at both 3 and 6 months, lesser emotional distress (HADS < 8) at both 3 and 6 months and lesser cognitive impairment (Mini Mental State Examination ≥ 28) at 6 months after stroke in subgroup analysis. The difference of Modified Rankin Scale between groups was significant at 6 months after stroke ($p = 0.026$). There was no difference in cognitive or emotional outcome. No significant difference of mortality rate was noted.

Conclusions: We focused on a group of patients with mild to moderate stroke (median NIHSS = 6) within a narrow time span (14-19 days) and confirmed a high prevalence of SDB in stroke. CPAP compliance was a major problem but might be enhanced by selecting patients with higher functional capacity, higher cognitive function especially language and less depression in the acute or subacute phase of stroke. We also found that sleep-disordered breathing had little or no effect on cognitive and emotional outcomes, health-related quality of life and mortality in stroke patients. Many other factors resulting from brain damage or complications of stroke have stronger influences on stroke outcome than SDB.

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List of Tables and Figures

List of Abbreviations and Definition of Terms

Abbreviations	Definition of Terms
$(A+H)\cdot h^{-1}$	Apnoeas and Hypopnoeas per Hour in Bed
ABP	Ambulatory Blood Pressure
ACE	Addenbrooke's Cognitive Examination
ADL	Activities of Daily Living
AHI	Apnoea Hypopnoea Index
BI	Barthel Index
BMI	Body Mass Index
CPAP	Continuous Positive Airway Pressure
EADL	Nottingham Extended ADL Index
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
HADS	Hospital Anxiety and Depression Scale
MMSE	Mini Mental State Examination
MRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
ODI	Oxygen Desaturation Index
OSAH	Obstructive Sleep Apnoea/Hypopnoea
OSAHS	Obstructive Sleep Apnoea/Hypopnoea Syndrome
RDI	Respiratory Disturbance Index
SDB	Sleep-Disordered Breathing
SSS	Stanford Sleepiness Scale
SF-36	MOS Short Form 36

Chapter 1 Obstructive Sleep Apnoea/Hypopnoea Syndrome: A Critical Review

1.1 Introduction

Sleep-disordered breathing (SDB) comprises apnoeas and hypopnoeas during sleep. This includes obstructive (obstructive sleep apnoea and hypopnoea, OSAH), central (central sleep apnoea) and mixed events (mixed sleep apnea). Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) means OSAH plus excessive daytime sleepiness (EDS) with or without daytime or nighttime symptoms including unrefreshed sleep, and choking and suffocating episodes during sleep. Sleep apnoea and hypopnoea are measured by a validated device incorporating at least the following sensors: (1) nasal pressure or oral thermistor; (2) thoraco-abdominal movement; (3) finger pulse oximetry. The examples of obstructive, central and mixed apnoea and hypoponoea taken from present study conducted by myself are shown to help explain this (Figure 1.1, P. 35).

The Epworth Sleepiness Scale (ESS) is a commonly used measure of subjective EDS. It asks how likely (scored 0-3) they are to fall asleep in eight situations. A total ESS score of more than 10 is considered significant for subjective EDS. The multiple sleep latency test (MSLT) is a commonly used measure of objective EDS. Individual sleep latencies across four to five naps are averaged to generate mean sleep latency (MSL). A MSL of less than 10 minutes is considered significant for objective EDS.

The obstructive sleep apnoea/hypopnoea syndrome is almost always associated with snoring, a sound made by vibration of soft tissue in the upper airway during inspiration. Snoring is usually associated with decreased airflow through either the nose or mouth and when this decrease is total, obstructive sleep apnoeas occur.

Obstructive sleep apnoea/hypopnoea syndrome and snoring are more common in men than in women and in adults than in children. The diagnosis of SDB is made through overnight recording of breathing during sleep. Consequences of SDB include impairment of cognitive function, mood and health-related quality of life. Nasal continuous positive airway pressure (CPAP) is the mainstay in treating OSAHS but conservative treatment, oral appliance and surgery are useful in certain clinical situations.

1.2 Diagnostic criteria of sleep apnoea and hypopnoea

According to the report of American Academy of Sleep Medicine [1999], an episode of apnoea is defined as cessation of airflow for 10 or more seconds. An episode of hypopnoea is defined as one of the following three features: (1) reduction of airflow to < 50% of the baseline; (2) reduction of airflow to > 50% of the baseline associated with desaturation (> 3%); (3) reduction of airflow to > 50% of the baseline associated with electroencephalographic arousals. Apnoea/hypopnoea Index (AHI), i.e. Respiratory disturbance index (RDI), is calculated as the total number of apnoeas and hypopnoeas per hour of sleep. The severity of sleep apnoea is further classified as mild ($5 < AHI \leq 15$, moderate ($15 < AHI \leq 30$) and severe ($AHI > 30$). Oxygen desaturation index (ODI) is calculated as the total number of oxygen desaturations per hour of sleep. The definition of desaturation varies from 2% to 4 % drop from the baseline oxygen level recorded by pulse oximetry.

We could not absolutely define whether events were central or obstructive in this study as we recorded neither respiratory muscle EMG nor oesophageal pressures. However as is reported later in the thesis (chapter 4.4.2) very few events had the respiratory pattern of central events, the large majority being obstructive in pattern. As obstructive apnoeas can be confidently diagnosed from the respiratory pattern, it is likely that the vast majority of the events we recorded were obstructive.

1.3 History of Sleep-disordered breathing

Pickwickian syndrome is named after Mr. Pickwick, the central character in The Posthumous Papers of the Pickwick Club written by the famous British writer, Charles Dickens. This syndrome is so named because of the "fat and red-faced boy in a state of somnolency" named Joe. This boy is thought by some possibly to have had the Prader-Willi syndrome:

> *After a "most violent and startling knocking" is heard, Mr. Lowton hurries to the door. "The object that presented itself to the eyes of the astonished clerk was a boy--a wonderfully fat boy--.... standing upright on the mat, with his eyes closed as if in sleep. He had never seen such a fat boy, in or out of a travelling caravan; and this, coupled with the utter calmness and repose of his appearance, so very different from what was reasonably to have been expected of the inflicter of such knocks, smote him with wonder.*
>
> *"What's the matter?" inquired the clerk.*
>
> *"The extraordinary boy replied not a word; but he nodded once, and seemed, to the clerk's imagination, to snore feebly."*
>
> *Joe suddenly awakens. When asked why he knocked "like forty hackney-coachmen," Joe replies:*
>
> *"Because master said, I wasn't to leave off knocking till they opened the door, for fear I should go to sleep."*
>
> *Joe, we have learned, "goes on errands fast asleep and snores as he waits at table." He sleeps through cannon fire, and is hard to rouse: "Be good enough to pinch him, sir--in the leg, if you please; nothing else wakes him."*

In history, snoring was reported to be caused not only by exogenous factors such as excessive drinking or eating but also by endogenous factors such as old age, body features or illness affecting the nose [Esser 2002]. In a famous Roman comedy, "Miles Gloriosus" (204 BC), the cellarer's assistant to the captain and his colleague Palaestrio talk about their fellow slave Sceledrus:

> *Lucrio: He (Sceledrus) is slurping in his sleep.*
>
> *Palaestrio: What (should it mean), he is slurping?*
>
> *Lucrio: He is snoring, that was what I intended to say:*
>
> *But since it is almost the same whether you snore or slurp –*
>
> *Palaestrio: Listen, so Sceledrus is sleeping inside?*
>
> *Lucrio: Not his nose, that is calling all the louder. He stealthily has touched the goblet.*

This paragraph emphasized that the acoustic phenomenon of snoring was similar to slurping sounds. Snoring was not only recorded in ordinary people but also in emperors including those who were large with a well-fed neck (Emperor Claudius) or were moderately built (Emperor Ortho).

1.4 The upper airway and sleep-disordered breathing

The upper airway can be divided into four parts:

- Nasopharynx
- Velopharynx or retropalatal oropharynx
- Oropharynx
- Hypopharynx

They are covered by mucosa, muscular layer and fat tissue. There are three factors in determination of the patent upper airway: (1) anatomical structures; (2) dilator muscular activity; (3) neuromuscular reflex. The pathophysiology of obstructive sleep apnoea/hypopnoea syndrome is based on both abnormal calibre and muscle tone of the upper airway [Arens and Marcus 2004].

1.4.1 Anatomical structure of upper airway

Changes of anatomical structure can cause obstruction of the upper airway. Adenoid hyperplasia in children and enlarged palatal tonsils, tongue base and lingual tonsil in both children and adults can cause SDB which might benefit from surgical removal of excessive tissues.

Apart from pathology of anatomical structures, other neck structures also play a role. There was significantly 42% greater volume of fat tissue in the anterolateral segments of the neck (52% greater if the fat within the jaw line was analyzed) measured by magnetic resonance image (MRI) in nine nonobese male patients with OSAHS than in nine nonobese, nonsnoring male controls [Mortimore *et al.* 1998]. Even when controlled for BMI and neck circumference the percentage of neck fat are increased in patients with OSAHS in comparison with controls. A study on body fat had similar findings.

1.4.2 Muscle tone of upper airway

There are 20 or more muscles surrounding the upper airway. The upper airway dilator muscles which are closely related with OSAHS can be classified into four groups:

- Soft palate muscles
- Tongue muscles
- Hyoid muscles
- Muscles of posterolateral pharyngeal wall

During wakefulness with quiet nasal breathing, these muscles show phasic inspiratory activity. The muscle tone of upper airway decreases from light sleep to deep NREM sleep to reach the minimum in REM sleep [Trudo *et al.* 1998].

A study compared the mechanics of paralyzed pharynx between normal control (oxygen desaturation index, ODI ≤ 5, n = 17), mild sleep-disordered breathing (SDB; ODI between 5 and 20, n = 18) and severe SDB (ODI ≥ 20, n = 22) [Isono *et al.* 1997]. There was an exponential pressure-area relationship of the passive velopharynx and oropharynx. There was a substantial difference between airways of patients with SDB and those of controls. Active negative pressure was required to close the upper airway in normal subjects whereas the upper airway was closed even at atmospheric pressure in patients with SDB.

Upper airway dimensions are enlarged by reflex contraction and activity of the upper airway muscle [Kobayashi *et al.* 1996]. In the experimental animal model, increased reflex was seen under the effect of induced negative pressure of upper airway simulating the situation in SDB [Eastwood *et al.* 1998]. In clinical studies applied to patients with SDB, the reflex contraction of upper airway dilator muscles are accentuated through the daytime which can compensate for anatomical narrowing of the upper airway [Mezzanotte *et al.* 1996]. The reflex is absent in some of the dilator muscles during episodes of sleep apnoea. This means sleep can suppress the reflex. One of the possible explanations is that hypoxaemia resulting from SDB

might cause brain stem neuronal dysfunction and impair reflex contraction of the upper airway during sleep.

1.5 Diagnosis of sleep-disordered breathing

1.5.1 Polysomnography

Overnight polysomnography (PSG) including EEG, EOG, EMG, nasal/oral airflow, respiratory movement and pulse oximetry conducted in a sleep laboratory has been considered to be the gold standard for the diagnosis of SDB. The clinical guidelines which have been reviewed and proposed by the American Academy of Sleep Medicine show that PSG is routinely indicated for the diagnosis of SDB [1997]. But, there has been no good evidence to show that concomitant recording of sleep electrophysiology in terms of EEG, EOG and EMG is of diagnostic value for SDB [Douglas *et al.* 1992].

The variability of AHI was assessed by recruiting 243 patients referred for the diagnosis of SDB [Le *et al.* 2000]. Repeated PSG was conducted in 27 of 101 patients who had AHI $\geq$ 20 but did not receive nasal CPAP treatment and 142 patients who had AHI < 20. The first PSG showed significantly lower AHI and less severe oxygen desaturation although the correlation between the 1st and 2nd AHI was highly significant. Bland-Altman plots showed the difference between the 1st and 2nd AHI increased in the higher AHI group. Variability of AHI was also found between technologists in different sleep laboratories or centres [Collop 2002]. The AHI was compared with total sleep time. There was a significant higher coefficient of variation (mean divided by standard error) in AHI than in total sleep time. The higher the AHI scored, the more the variability. AHI also varies night-to-night.

As there is increasing demand of PSG required in diagnosing patients with SDB the split-night study is developed based on a positive technician-attended partial night PSG conducted in a sleep laboratory with CPAP titration initiation on the second half of the night. A case control study comparing 46 split-night patients with 92 matched full-night patients was conducted in the sleep centre of Edinburgh University [McArdle *et al.* 2000]. There was no significant difference between split and full night titration in the outcomes of therapy measured by nightly CPAP use,

frequency of nursing intervention, frequency of clinic visit and post-treatment Epworth Sleepiness Scale. The median time from referral to treatment was less for the split-night patients than for full-night patients. The Kaplan-Meier analysis showed there was no difference between the groups in long-term CPAP compliance with a follow-up median of 22 months for split-night and 27 months for full-night studies.

Polysomnography is not always available for the diagnosis of SDB because of:

- Rapidly increased number of patients being referred.
- PSG is time-consuming and not cost-effective.
- Some geriatric, paediatric and severely ill patients are not suitable for PSG.

1.5.2 Portable sleep study

Portable sleep study is also employed to reduce the cost and resource required to diagnose patients with SDB. Recently, many portable devices have become available for home study which can reduce cost compared with expensive in-lab polysomnography [Douglas 2003]. Portable devices are usually used for unattended or semi-attended limited sleep studies in stroke patients to made diagnosis of SDB more feasible. There are many types of portable sleep study devices. One is full unattended polysomnography, which is the same as an in-laboratory device apart from portable function [Fry *et al.* 1998]. Another is limited sleep study, which is usually focused on cardiorespiratory signals. Nasal airflow, chest and abdominal respiratory movement and oximetry are three basic and minimal sensors in portable limited sleep study [Douglas 2003].

The benefits of portable sleep study are:

- Saving cost over conventional in-lab PSG
- Saving time of long waiting list for in-lab PSG
- Saving labour work and personnel
- Possibly reduced first night effect as may sleep better at home with fewer monitors

- More available to disabled or hospitalized patients who need to be excluded sleep-disordered breathing

The limitations of portable sleep study are:

- Inability to diagnose broad range of sleep disorders such as periodic limb movement disorder
- Inability to diagnose upper airway resistance syndrome – if it exists [Douglas 2000]
- Difficulty in distinguishing central from obstructive sleep apnoea
- Possibly more artefacts and technical failure

The pros and cons of an in-lab full polysomnography and a portable limited sleep study were summarized and compared in Table 1.1 (P. 34).

A practice parameters for the use of portable sleep study in the assessment of SDB was proposed by Standards of Practice Committee of the American Sleep Disorders Association [Ferber *et al.* 1994]. Evaluation studies for SDB were classified into four levels:

- Level I: Standard PSG with full signal channels
- Level II: Comprehensive portable PSG with full signal channels
- Level III: Modified portable PSG, minimum of four signal channels, including ventilation, heart rate/ECG and oxygen saturation.
- Level IV: Continuous single- or dual-bioparameter recording, minimum of one signal channel

Only level II and level III of unattended portable recording are accepted for the diagnosis and assessment of therapy for SDB. Portable sleep study is recommended by the American Academy of Sleep Medicine only in the following situations [1994]:

- Patients with severe clinical symptoms of obstructive sleep apnoea when standard PSG is not available and initiation of treatment is urgent.
- Patients unable to be studied in the sleep laboratory.
- Follow-up studies when a diagnosis has been established by standard PSG.

There was no loss of diagnostic accuracy in SDB when the signals of EEG and EMG were omitted [Douglas, Thomas, and Jan1992]. ECG or heart rate is a good adjunctive monitor. Portable devices with at least two cardiorespiratory signals are not only as convenient as pulse oximetry but rated at higher levels (level II and III) than pulse oximetry alone (level IV) for the diagnosis of SDB by the American Academy of Sleep Medicine [1994].

1.5.3 Pulse oximetry

Pulse oximetry is commonly used in the hospital to detect hypoxaemia, as a screening device for cardiopulmonary diseases and a commonly used device in stroke units for casual or regular measurements. Continuous measurement using oximetry in stroke is less frequent. SDB Oximetry is a component of polysomnography, but is also used extensively either alone or in conjunction with other sensors in the diagnosis of SDB. The diagnostic value of oximetry in SDB is controversial. In a large European study described in the previous section, simple overnight oximetry was used as a screening test and was analyzed before applying and scoring polysomnography. There, the predictive value of oximetry could be looked at in isolation [Deegan and McNicholas 1996]. The results showed although the odds ratio of absolute number of $\geq 4\%$ dips in %SaO2 in predicting AHI ≥ 15 was as high as 21 (95% CI = 10 - 45) only one third (32.4%) of patients could be correctly categorized into SDB or non-SDB using clinical features and oximetry data (absolute number of $\geq 4\%$ dips in SaO2 + lowest SaO2) alone. High diagnostic accuracy was reported (sensitivity and specificity > 90%) to predict SDB with cut-off point of AHI at 15/hr [Vazquez *et al.* 2000]. However, relatively low sensitivity was found in not only patients with minimal daytime sleepiness [Hussain and Fleetham 2003] but also in patients with moderately and severe SDB who could benefit from treatment [Douglas, Thomas, and Jan1992]. Pulse oximetry, along with clinical features or with a more specified index, for instance, Δ index derived from changes of SaO2 by certain intervals over time calculated by an extra programme [Levy *et al.* 1996], is useful as a screening instead of diagnostic package to decide which patient needs further sleep study [Deegan and McNicholas1996].

In a more recent study 30 patients who were suspected to have SDB (snoring with or without witnessed apnoea) but denied excessive daytime sleepiness (ESS score < 10) underwent overnight polysomnography [Hussain and Fleetham2003]. Significant SDB (AHI > 15) was found in 40% of them and all had 2% oxygen desaturation index (ODI) < 10. The 2% ODI had a sensitivity of 33%, specificity of 88% and negative predictive value of 67% if the cut-off point was set at 6. The sensitivity increased by decreasing the cut-off point of ODI but this decreased the specificity. Another recent study recruited 424 patients to determine the role of obesity affecting the predictive value of oximetry for SDB [Nakano *et al.* 2004]. The sensitivity of oximetry was lower in the normal-weight group than in the over-weight and obese groups. The specificity was lower in the obese group than in the normal-weight group. Oximetry might be more useful by applying a different cut-off point according to BMI. Another recent study used spectral analysis as an adjunctive to oximetry (n = 233). Power density of oxygen saturation was calculated and the presence of peak at spectrum of 30-70s was determined [Zamarron *et al.* 2003]. The results showed spectral analysis for the presence of peak had higher sensitivity (78%) and specificity (89%) than the predictive value in pulse oximetry.

1.5.4 Predictive value of clinical and anthropometric features

Comparison of clinically detected and screen-detected OSAHS showed 93% of women and 82% of men who had moderate to severe OSAHS have not been clinically diagnosed [Young *et al.* 1997a]. There is also a discrepancy between AHI and self-reported SDB-related symptoms in the general population. One study recruiting 129 patients [Dealberto *et al.* 1994] and another study recruiting 2,148 patients [Duran *et al.* 2001] who had obstructive sleep apnoea/hypopnoea (OSAH) both showed breathing pauses during sleep and habitual snoring were significantly associated with OSAH but daytime sleepiness was not. Many predictive models for SDB derived from sleep questionnaires were developed and published with variable results. One study using three specific questions about snoring found sensitivity was high (90%) only in men and specificity was high (90%) only in women [Bliwise *et al.* 1991]. Another study found the predictive value of SDB-related symptoms was even

lower than measurement of neck circumference [Davies *et al.* 1992]. The other study revealed that self-reported sleep apnoea, neck circumference, age, and a tendency to fall asleep unintentionally were all significant positive predictors of apnoea index which explained 41.8% of the variability [Pillar *et al.* 1994]. The sensitivity of the model for predicting SDB (AI > 10) was 92.2% but specificity was only 18.2%. A study focused on a morphometric model including body mass index, neck circumference and oral cavity measurements was published later [Kushida *et al.* 1997]. Oral cavity measurements for palatal height, maxillary intermolar distance and mandibular intermolar distance were obtained by placing the caliper tips between the oral cavity structures to be measured, carefully removing the caliper, and measuring the distance between the caliper tips with a ruler. The morphometric model had a sensitivity of 97.6% (95% Cl = 95% - 98.9%), a specificity of 100% (95% Cl = 92% to 100%), a positive predictive value of 100% (95% Cl = 98.5% - 100%), and a negative predictive value of 88.5% (95% Cl =77% - 96%).

According to a study of 594 patients to predict AHI by clinical variables of snoring, nocturnal choking, excessive daytime sleepiness, impotence and witnessed apnoea are distinctive between patients with SDB and without [Hoffstein and Szalai 1993]. A further regression model showed interaction between BMI and age, male sex, witnessed apnoea and abnormal pharyngeal examination can explain 36% of variance in AHI ($r = 0.3585$, $p = 0.0004$). Subjective impression from the examining physician has a sensitivity of 60% and a specificity of 63% in predicting SDB (AHI > 10). One hundred and fifty-two patients had overnight PSG in a large European study and 52% of them had AHI ≥ 15 [Deegan and McNicholas1996]. A stepwise multiple linear regression analysis showed alcohol consumption, BMI and age were significantly associated with AHI in men. However, age and neck circumference were the only two factors in women. After controlling for BMI and age, waist circumference correlated more closely with AHI than neck circumference in men, while the opposite was true in women.

A questionnaire-based study which generated a cut-off point of symptoms score based on a regression model to predict SDB could be more accurate than

questionnaire alone [Flemons *et al.* 1994]. In this study they found positive likelihood ratio (LR+) for predicting SDB was as high as 5.17 (95% CI: 2.54 to 10.51) and post-test probability was 81%. Recently a computer-based artificial neural network (ANN) was suggested as a good alternative to the regression model for prediction of SDB but this needs extra software and training [El Solh *et al.* 1999].

A clinical decision rule was made according to 837 patients who were referred to a university sleep centre [Rodsutti *et al.* 2004]. Multiple logistic regression analysis showed age ≥ 60 (Odds Ratio, OR = 8.8), male (OR = 4.5), snoring (OR = 2.5), stop breathing (OR = 2.4) and BMI (OR = 0.9) were significantly associated with SDB defined as AHI ≥ 5. The scoring scheme was developed using estimated coefficient of the five significant variables. Data from the other 243 patients were used in the validation phase. The area under the curve (AUC) by receiver operating characteristic (ROC) analysis was high (AUC = 0.789). This decision rule might be useful in prioritizing patients who are on the waiting list of polysomnography.

1.6 Epidemiology of habitual snoring and sleep-disordered breathing

In the past decade snoring and sleep-disordered breathing (SDB) have been noted for their diversity of epidemiological and clinical consequence. Hospital-based studies are biased by recruiting patients at sleep clinics or wards who are more likely to have SDB than the general population recruiting for epidemiological studies. A community-based large cohort study is the best model used to calculate the prevalence of snoring and obstructive sleep apnoea.

1.6.1 Prevalence of snoring and SDB in adults

The Wisconsin sleep cohort study [Young *et al.* 1993] which recruited 602 employed men and women aged 30 to 60 years showed the prevalence of SDB defined by apnoea/hypopnoea index (AHI) ≥ 5 was 24% in men and 9% in women. Four percent of men and 2% of women had both SDB and daytime hypersomnolence. The prevalence of habitual snoring was 44% in men and 28% in women and self-reported hypersomnolence was 16% in men and 23% in women.

A large population survey by computer-assisted telephone interview for non-institulized residents in the UK was completed with 4972 subjects [Ohayon *et al.* 1997]. Habitual snoring was noted in 40% of the population (48% in men, 34% in women) and breathing pauses was noted in 3.8% of the population (5.4% in men, 2.4% in women). Logistic regression analysis showed snoring and breathing pauses was significantly associated with middle age, male gender, higher body mass index and daytime sleepiness. .

1.6.2 Age

Sleep problems are common in the elderly, particularly for SDB. A large cohort study [Ancoli-Israel *et al.* 1991] randomly selected 427 elderly individuals in the community (mean age = 72.6 years) for overnight limited sleep study (respiratory and

EMG signals, wrist activity). One hundred of 420 valid data (24%) had AHI ≥ 5, including 20% of women and 28% of men. They followed most subjects (only 4 lost) for 8-12 years [Ancoli-Israel *et al.* 1996]. Although there was a tendency that subjects with higher AHI had higher mortality rate AHI was still not an independent risk for mortality.

In the Cardiac Health Study (CHS) which recruited 5,201 subjects, aged 65 or older [Enright *et al.* 1996] 13% of men and 4% women had witnessed sleep apnoea according to single questionnaire. The prevalence of apnoeas and hypopnoeas in the older age (age 60-70) appears to be 2-fold higher than the prevalence in middle age (age 40-49) in men for AHI ≥ 5 and 3-fold higher in women in the Spanish Cohort Study [Duran, Esnaola, Rubio, and Iztueta2001]. Difference of prevalence between ages was found in both sexes with an odds ratio of 2.2 for each 10-year increase. In the Sleep Heart Health Study (SHHS), the prevalence with AHI ≥ 15 was 1.7-fold higher in older (age 60-99) compared to younger (age 40-60) participants [Young *et al.* 2002].

1.6.3 Gender

The prevalence of sleep-disordered breathing is different between males and females. In the Wisconsin Sleep Cohort Study snoring and symptomatic SDB was twice as common in middle-aged men than women [Young *et al.* 1993]. A large-sampled (n = 4,648) community-based questionnaire survey showed snoring as a problem was reported by 14.6 % of men and 6.7% of women with a male to female ratio of about 2:1 ($p < 0.001$) [Larsson *et al.* 2003]. A total of 1166 out of 1745 patients referred to a sleep centre had SDB based on either in-lab overnight polysomnography (PSG), nap PSG or home PSG which showed male to female ratio of 4.9: 1 [Quintana-Gallego *et al.* 2004]. The possible underlying mechanisms which discriminate men from women for the higher prevalence of SDB are:

- Craniofacial morphology: In a study recruiting 347 patients with SDB and 101 control subjects the most atypical craniofacial and upper airway

abnormalities was shown in male patients with SDB and class I skeletal subtype, measured by cephalometry [Lowe *et al.* 1996].

- Neck fat volume: One study showed men had more severe sleep apnoea than women at the same degree of obesity, measured by BMI [Millman *et al.* 1995]. Another study showed men had larger total neck soft tissue than women. This difference was made up by non-fat soft tissue as there was no significant difference in volume of fat [Whittle *et al.* 1999]. Both studies might indicate that men have more prominent upper body obesity due to fat deposition than women and that this results in upper airway narrowing.
- Pharyngeal collapsibility: Men have markedly greater pharyngeal collapsibility than women in response to external applied loads during NREM sleep [Pillar *et al.* 2000].
- Sex hormone: In the Wisconsin Sleep Cohort Study the prevalence of SDB (AHI $\geq$ 5) increased across menopausal categories: 10.8% (n = 498), 18.4% (n = 125), 27.0% (n = 37) and 29.1% (n = 375) of pre-menopausal, peri-menopausal, peri-menopausal/post-menopausal and post-menopausal women respectively [Young *et al.* 2003]. The adjusted odds ratio of SDB (AHI $\geq$ 15 vs. AHI < 5) was 1.07, 3.13 and 3.49 in peri-menopausal, peri-menopausal/post-menopausal and post-menopausal groups.

1.6.4 Obesity

Obesity has been associated with SDB in many hospital-based cross-sectional studies. In the longitudinal follow-up of the Wisconsin Sleep Cohort Study a 10% weight gain predicted a 32% increase in AHI and on the contrary, 10% weight loss predicted a 26% decreased in AHI [Peppard *et al.* 2000a].

1.7 Clinical features of obstructive sleep apnoea/hypopnoea syndrome

The major nighttime symptom of SDB is snoring. Others include choking or gasping during sleep, recurrent awakenings from sleep and unrefreshing sleep. The major day time symptom of SDB is EDS. Others include fatigue and impaired concentration and cognitive functions which have been reported by the American Academy of Sleep Medicine [1999]. The symptoms of SDB probably result from a combination of (1) sleep fragmentation: frequent awakenings and arousals during sleep; (2) change of sleep architecture: increased light sleep (stage I and II), decreased slow wave sleep (stage III and IV) and rapid eye movement (REM) sleep; (3) nocturnal hypoxaemia.

1.7.1 Night-time symptoms

Habitual snoring was reported in 40 % of the British population including 50% of men and 35% of women [Ohayon, Guilleminault, Priest, and Caulet1997]. This questionnaire-based study showed breathing pauses were only reported in 2.5% of the sample including 5.4% of men and 2.4% of women. Further logistic regression showed snoring was significantly associated with married men aged 35-64 and obesity. Breathing pauses was significantly associated with men aged 35-44, non-restorative sleep, and certain medical illness including thyroid disease, chronic obstructive pulmonary diseases and anxiolytic medications.

A laboratory-based study supported the above findings and showed habitual snoring, bed partner reports of nocturnal gasping or choking episodes, increased neck circumference and hypertension were weak but significantly associated with SDB (AHI > 10) diagnosed by nocturnal PSG ($R^2 = 0.34$) [Flemons *et al.* 1994].

1.7.2 Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is the key daytime feature of SDB which may result from both sleep fragmentation and sleep deprivation. The mean Epworth Sleepiness Score (ESS) of community-based normal sleepers collected from Australian workers was 4.6 (SD = 2.8) out of a maximum of 24 [Johns and Hocking 1997]. The mean ESS in patients with SDB was 15 ± 6 rated by patients themselves and 14 ± 6 rated by their partners [Engleman *et al.* 1996a], about 3-fold higher than normal subjects.

Among 195 Asian patients with SDB (89% male) 52% had severe EDS with mean sleep latency in Multiple Sleep Latency Test (MSLT) < 5 minutes and 35% had moderate EDS with mean sleep latency in MSLT 5-10 minutes [Seneviratne and Puvanendran 2004]. The differential diagnosis of excessive daytime sleepiness includes:

- Narcolepsy
- Idiopathic hypersomnolence
- Klein-Levin syndrome
- Periodic leg movement disorder
- Medications: sedative, withdrawal from stimulants
- Circadian rhythm sleep disorders
- Psychiatric disorders
- Malingering

1.7.3 Cognitive functions

Impaired vigilance including focused and sustained attention and executive function are two major neuropsychological deficits in SDB which suggest frontal lobe dysfunction plays an important role [Beebe *et al.* 2003]. A case-control study was performed to examine semantic memory, using the California Verbal Learning Test, and executive function, using Verbal Fluency Test and Wisconsin Card Sorting Test, in SDB [Salorio *et al.* 2002]. They found patients with SDB had impaired word

recall but preserved word retention in one category and impaired letter fluency but preserved category fluency in the other. These findings support the major problem in SDB being executive dysfunction probably resulting from damage of the frontal lobes.

Two studies were performed which focused on the relationship between neuropsychological assessment and nocturnal polysomnography. One study showed deficit of sustained attention, a frontal lobe dependent parameter, was associated with nocturnal hypoxemia and was not easily reversed by nasal CPAP treatment [Valencia-Flores *et al.* 1996]. The other study designed for the elderly with SDB showed verbal delayed recall in Hopkins Verbal Learning Test was associated with both sleep fragmentation and oxygen desaturation. However, constructional abilities in Visual Motor Integration was strongly associated with oxygen desaturation [Aloia *et al.* 2003].

Cognitive deficits in SDB result from two major factors. One is sleep fragmentation and excessive daytime sleepiness which have stronger influence on attention, vigilance and memory. The other is nocturnal hypoxemia which has stronger influence on executive and constructive functions. Short-term nasal CPAP therapy for a couple of weeks seems to improve those related with sleep fragmentation but has limited effect on those related with nocturnal hypoxemia [Ferini-Strambi *et al.* 2003].

An animal study examined the isolated effect of hypoxia on cognitive functions by controlling sleep fragmentation [Gozal *et al.* 2001]. Chronic episodic hypoxia was induced mimicking SDB by adjusting oxygen concentration in a designed chamber which accommodated rats. Sleep architecture was controlled by cortical EEG and nuchal EMG recordings. Morris water maze was then used to study cognitive functions. After that, rats were sacrificed for neuropathology of hypoxic brain damage. The results showed rats exposed to 14 days of hypoxia (n = 18) had significantly more difficulty learning the location of a hidden platform than did controls (n = 19). The neuropathology showed cellular changes over time within CA1

hippocampal region and cortex associated with cognitive functions. These findings might explain learning and memory impairment found in patients with SDB.

The other animal study developed two systems, sleep-induced hypoxia or sleep fragmentation without hypoxia, to two strains of mouse: DBA/2J strain with largest ventilatory response to hypoxia and A/J with smallest ventilatory response to hypoxia obtained in previous study [Rubin *et al.* 2003]. The results showed genetic factors determine individual susceptibility to cognitive deficits in SDB. This finding raises the possibility that individuals with low hypoxic sensitivity might be at a greater risk for hypoxia-related injury.

A prospective study conducted in the sleep centre of Edinburgh University which recruited 150 patients with OSAHS showed nocturnal sleep variables only weakly correlated with daytime sleepiness (lowest SaO2 vs. MWT, rho = 0.19) and cognitive functions in terms of Trail making B (vs. lowest SaO2, rho = -0.17), PASAT 4-s test (vs. 2% Desaturation, rho = -0.17) and performance IQ (vs. AHI, 2-4% desaturation and lowest SaO2, rho = -0.17 to -0.23) [Kingshott *et al.* 1998]. Another prospective study was conducted in the same sleep centre which recruited 15 normal subjects. It showed that one night of sleep fragmentation induced by repeated brief auditory simulation resulted in decreases in mean sleep latencies in the multiple sleep latency test (MSLT) and maintenance of sleepiness test (MWT) with big effect sized ($\geq$ 0.75). The effect of sleep fragmentation on attention-based cognitive scores including Trail Making-B and PASAT 4-s tests was smaller but still significant (effect size $<$ 0.75) [Martin *et al.* 1996]. This means at least some cognitive deficits in OSAHS may be a secondary consequence of sleep disruption.

1.7.4 Health-related quality of life

MOS Short Form-36 Health Survey (SF-36) is the most commonly used generic measure for health-related quality of life in patients with SDB [Moyer *et al.* 2001]. In the Wisconsin Sleep Cohort Study SDB was associated with significant impairment in 6 of 8 domains in SF-36 after adjusting for confounders in 760 individuals. These

domains were mental health, social roles, role functioning due to physical problems, physical functioning, vitality and general health perceptions [Finn *et al.* 1998].

SF-36 is also one of the most sensitive assessment tools to evaluate changes of quality of life in patients with SDB before and after nasal CPAP treatment. In a randomised controlled trial conducted by Oxford research group, SF-36 revealed substantially lower scores in patients with SDB whereas nasal CPAP treatment showed significant improvements demonstrated by medium to large effect sizes in the energy/vitality dimension (0.98), mental summary score (0.76) and physical summary score (0.57) [Jenkinson *et al.* 1997].

The Functional Outcome of Sleep Questionnaire (FOSQ) was developed specific to the impact of EDS on multiple activities of daily living in the areas of physical, mental and social functioning [Weaver *et al.* 1997]. It consists of 35 items in 5 domains: activity level, vigilance, intimacy and sexual relationships, general productivity and social outcome. It has been widely used for both research and clinical purposes and showed significant changes of clinically meaningful effect size after CPAP treatment.

The Sleep Apnea Quality of Life Index (SAQLI) was developed in Calgary to specifically identify the impact of sleep apnoea and nasal CPAP treatment on health-related quality of life [Flemons and Reimer 1998]. It consists of 40 items in 5 domains: role functioning, social interactions, emotional functioning, symptoms, and treatment-related symptoms. The correlation between SAQLI rating of change score and SF-36 vitality domain change score was good ($r = 0.81$, $p = 0.0002$).

1.7.5 Mood

Many studies found an association between SDB and depressive symptoms. About 25-50% of patients with SDB have depression. Depression is one of the major factors affecting quality of life in patients with SDB.

One study applied Zung self-rated depression scale and SF-36 to 66 Japanese patients with severe SDB (AHI > 20/h, SaO2 < 80% and EDS) and 34 controls

[Akashiba *et al.* 2002]. Depression measured by self-rated Zung Depression Scale significantly correlated with subscales of general health, role physical, role emotional, mental health and vitality in SF-36 but EDS was not correlated with Zung self-rated depression scale. A randomized controlled trial conducted in our department has shown that the beneficial effect of CPAP was stronger in the depressive subscale than the anxiety subscale of HADS [Engleman *et al.* 1994a]. The beneficial effect of CPAP in mild SDB was also shown in the depressive subscale of HADS instead of anxiety subscale [Engleman *et al.* 1997]. This means depression in SDB can be treated in non-stroke patients. Depression measured by the Beck Depression Inventory also significantly correlated with self-reported sleep quality measured by the Insomnia Severity Index in 135 patients referred to an American sleep centre for polysomnographic evaluation of SDB [Wells *et al.* 2004].

Fatigue is a common symptom in SDB. A study on 60 patients with SDB (mean age = 49.1, AHI = 48.8 and BMI = 29.5) found that, after severity of sleep apnoea was controlled, significantly more fatigue measured by the fatigue-inertia subscale of the Profile of Mood State (POMS) was seen in patients with higher depression measured by Centre for Epidemiological Studies Depression Scale (CES-D)[Bardwell *et al.* 2003]. Multivariate analysis suggested depression was significantly associated with fatigue in patients with SDB.

1.7.6 Comments

The evidence that SDB causes daytime sleepiness [Young *et al.* 1993], cognitive impairment [Salorio *et al.* 2002], reduces quality of life [Finn *et al.* 1998] and impairs mood [Akashiba *et al.* 2002] is based on cross-sectional case-control studies with adjustment for confounding factors in multivariate analysis. This evidence is further strongly supported by many well-designed randomized controlled trials which show CPAP treatment can significantly improve sleepiness, vigilance, quality of life and mood [Engleman *et al.* 1998;Engleman *et al.* 1999;Engleman *et al.* 2002]. Thus SDB can cause impairment of daytime functions rather than just being an associated factor.

1.8 Treatment of obstructive sleep apnoea/hypopnoea syndrome

1.8.1 An overview

A good treatment for SDB should have the following merits:

- Lowering apnoea hypopnoea index (AHI) and eliminate abnormal sleep-related physiological markers, e.g. desaturation, arousals
- Improving sleepiness and daytime function
- Well-tolerated by patients

1.8.1.1 Literature review

I did a comprehensive literature review including studies conducted in the University of Edinburgh from 1 September 1999 to 31 May 2000. Searches were performed on MEDLINE, OVID and Cochrane Library with the following search terms:

- Sleep-disordered breathing (SDB)
- Sleep-related breathing disorder
- Obstructive sleep apnoea (OSA)
- Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)
- Interventions
- Drug treatment
- Continuous positive airway pressure (CPAP)
- Compliance
- Oral appliances
- Mandibular repositioning device (MRS)
- Uvulopalatopharyngoplasty (UPPP)
- Surgery

1.8.1.2 Evidence-based medicine

Evidence-based literatures were obtained from "Cochrane Review" which is a generic term for a systematic review performed under the auspices of the Cochrane Collaboration.

Evidence-based medicine has been developed to determine the best medical care for patients. Meta-analysis based on randomized controlled trials (RCT) which should be adherent to original protocol with "intention-to-treat" analysis is the core of evidence-based medicine. If a trial is not randomized, it might have "selection bias". If it is not a controlled trial, it might have "regression to mean" effect and if there is no placebo, it might have "placebo effect".

When we take a look at the results we not only concern ourselves with statistical significance (p value) but clinical significance. One of the considerations is "effect size" defined as mean divided by standard deviation which is independent of sample size. When the p value is significant, effect size might still be small (<0.5) if the sample size is large enough. When the p value is not significant, effect size might be big if the sample size is inadequate (Type II error with low statistical power). The other consideration is, even though the p value is low and effect size is big we should explain the result very carefully if the only difference is in a subscale of a total scale or if the difference has little clinical value.

1.8.2 Continuous positive airway pressure for obstructive sleep apnoea/hypopnoea syndrome

1.8.2.1 Studies in Edinburgh University

A series of randomized placebo-controlled crossover trial for four weeks conducted in the sleep centre of Edinburgh University based on an intention-to-treat analysis supports the role of nasal CPAP as a safe and effective treatment for SDB.

Thirty-four patients with SDB (median AHI = 28) completed the first study published in 1994 [Engleman *et al.* 1994a]. Mean nightly CPAP usage was 3.7 ± 0.4 hours. The study showed CPAP improved objective daytime sleepiness measured by multiple sleep latency test (MSLT), cognitive functions including vigilance, mental flexibility and coding efficiency. CPAP also improved energetic arousal, mood and health-related quality of life in moderate to severe SDB.

Thirty-four patients with mild SDB (median AHI = 10) completed the study published in 1999 [Engleman *et al.* 1999]. Mean nightly CPAP usage was 3.2 ± 2.4 hours. The study showed CPAP improved general symptoms of SDB, subjective sleepiness measured by Epworth Sleepiness Scale (ESS), cognitive functions including vigilance, coding efficiency, mood and health-related quality life even in mild SDB.

1.8.2.2 Cochrane review

Twelve randomized controlled trials (RCT) including the University of Edinburgh studies were recruited in a Cochrane review for continuous positive airway pressure (CPAP) treatment in middle-aged patients (age = 36-71) with mild to severe SDB (AHI = 5-129) [White *et al.* 2002]. All but three were randomized cross-over studies. Four studies used inactive oral medication [Engleman *et al.* 1994a; Engleman *et al.* 1996a; Engleman *et al.* 1997; Engleman *et al.* 1999] and two used sham CPAP as placebo [Dimsdale *et al.* 2000;Jenkinson *et al.* 1999]. Two studies compared CPAP with conservative treatment [Ballester *et al.* 1999;Lojander *et al.* 1996], one with a positional therapy device [Jokic *et al.* 1999] and another three with oral compliances [Clark *et al.* 1996;Ferguson *et al.* 1996;Ferguson *et al.* 1997].

The meta-analysis showed CPAP significantly improves subjective and objective daytime sleepiness, Nottingham Health Profile part 2, General Health Questionnaire (GHQ-28), depression component of Hospital Anxiety and Depression Scale (HADS) and MOS Short Form 36 (SF-36) in the domains of vitality, physical role, bodily pain and mental health. Nocturnal mean arterial blood pressure (MAP) was also significantly reduced by CPAP.

1.8.2.3 Predictors of effectiveness

Prediction of daytime functions by sleep fragmentation, architecture and nocturnal oxygenation is limited [Kingshott *et al.* 2000]. The study showed improvement of daytime functions was not well predicted by pretreatment arousal or apnoea hypopnoea index in patients with SDB. Patients with more severe baseline hypoxaemia had a greater improvement in the Maintenance of Wakefulness Test (MWT), quality of life, SDB symptom ratings, reaction time, attention and visuomotor speed but could only explain not more than 22% of the observed variance in response.

1.8.2.4 Auto-titration continuous positive airway pressure (auto-CPAP)

Traditional CPAP delivers a fixed pressure. The individual pressure might need change according to sleep stages, body positions or alcohol consumption on a nightly basis and changes of body weight on a long-term basis.

Continuous positive airway pressure with auto-titration mode has the following benefits: (1) it can save beds and time of in-hospital manual titration if the titration is done at home [Massie *et al.* 2003]. (2) It has variable pressure during the night so it can adjust itself to fit the condition of patients at that particular night in long term use. The pressure needed for elimination of obstructive sleep apnoea could be variable according to different situations, for example, when patients have nasal stuff or other medical situations.

The disadvantage of autotitration mode of CPAP is that the machine is more expensive than traditional CPAP. An alternative way is to apply this machine to find out and set up an ideal fixed pressure for subsequent use on conventional CPAP [Series 2000].

It is not yet clear whether auto-CPAP is better than CPAP. Current evidence shows it can be as effective as CPAP but can save time and cost of in-lab CPAP

titration and maintain the minimal necessary pressure in non- stroke apnoeic population. Although auto-CPAP is recommended by the American Academy of Sleep Medicine to be used during attended titration or for unattended treatment of patients with SDB after attended standard or auto-CPAP titration [Littner *et al.* 2002], a few randomized control trials [Stradling *et al.* 1997] have shown that auto-CPAP is promising for naïve CPAP users to initially determine pressure by unattended titration or self-adjusting CPAP treatment. This is more convenient for stroke patients. In long term use it may have advantages in some patients [Massie *et al.* 2003].

1.8.2.5 CPAP acceptance and compliance

In different studies between 5-50% of patients with SDB refuse to use CPAP after a single night of titration and about 10-46% of patients discontinued CPAP in a follow-up period ranged from 2 weeks to 8 years [Engleman and Wild 2003].

Although compliance of CPAP is variable it can be as high as 80-90%. In a European multi-centre study (n = 121) an "effective compliance" (time spent at effective pressure ≥ 4 hours per night and ≥ 5 nights per week) to nasal CPAP was 80% at 3 months in patients with severe SDB (AHI > 50) [Pepin *et al.* 1999]. This finding is compatible with a study conducted in Asia (n = 296) which showed compliance to CPAP was 89% at 3 months with average usage of 5.9 hours per night in patients with AHI of 64.4 ± 34.2 [Sin *et al.* 2002]. A retrospective study conducted in the sleep centre in Edinburgh (n = 1,103) revealed the use of CPAP dropped to around 84% at 12 months and reached a plateau at around 4 years when 68% continue with treatment [McArdle *et al.* 1999].

Patients who refused CPAP were more often female, current smokers and referred by specialists instead of general practitioners [McArdle *et al.* 1999]. An initial problem reported at auto-titration was a predictor to good compliance to CPAP (5.0 hours of CPAP usage in patients with initial problem vs. 2.4 hours in patients without) [Lewis *et al.* 2004].

Intensive support performed by trained sleep nurses incorporating (1) initial CPAP education in patient's home; (2) additional two night of CPAP titration; (3) home visits at 7, 14, 28 days and 4 months, in comparison with standard support (CPAP education, mask fitting in sleep centre and one night of CPAP titration), can improve compliance of CPAP from 3.8 ± 0.4 hours per night to 5.4 ± 0.3 hours [Hoy *et al.* 1999]. In those with randomized controlled trials (RCT) that were under meta-analysis in Cochrane review [Haniffa *et al.* 2004], 24 randomized controlled trials met the inclusion criteria, 13 of them were parallel and 11 cross-over design. The results showed most participants preferred auto-CPAP. Although the effect of auto-CPAP is still unclear there might be a subgroup of patients who respond better to auto-CPAP than others. Intensive support including home visit and cognitive behavioural therapy improved compliance to CPAP. Other interventions showed no significant difference.

1.8.3 Other treatments for obstructive sleep apnoea/hypopnoea syndrome

1.8.3.1 Conservative treatment

As previously described, obesity is associated with the obstructive sleep apnoea/hypopnoea syndrome. Obesity increases either or both submental/ peripharyngeal fat which compromises upper airway dimension or abdominal/ chest wall fat which decreases lung volume and further compromises upper airway dimension [Strobel and Rosen 1996]. In the Wisconsin Sleep Cohort Study an increase of body mass index of 1 SD (5.7 kg/m^2) is associated with 4-fold increase of risk of having AHI more than 5 per hour [Young, Palta, Dempsey, Skatrud, Weber, and Badr1993].

One non-randomised controlled study with a follow-up of 5.3 months showed significant body weight loss by dietary advice from 106 ± 7.3 kg (mean ± SD) to 96.6 ± 5.9 kg was associated with a significant decrease of AHI from 55.0 ± 7.5 to 29.2 ± 7.1 per hour [Smith *et al.* 1985] in 15 patients with moderate to severe obstructive

sleep apnoea/hypopnoea syndrome. There was no significant change in the other 8 patients as weight- and age-matched control. Most of the studies, although in favour of weight loss for improvement of SDB, have been based on uncontrolled trials.

1.8.3.2 Drug treatment

Several medications have been tried to treat SDB including ventilatory stimulants (e.g. medrooxyprogesterone acetate) and psychotropic agents (e.g. protryptyline). According to meta-analysis, there is still no effective drug treatment for SDB [Magalang and Mador 2003;Smith *et al.* 2002;Hudgel 1995].

1.8.3.3 Oral appliance

Oral appliances which advance the mandible and thus widen the retroglossal airway have been shown in randomised controlled trials to be beneficial in snoring [Stradling *et al.* 1998] and in SDB to help sleepiness, sleep and blood pressure [Cistulli *et al.* 2004;Mehta *et al.* 2001].

A comparison between CPAP and oral appliance was also conducted in Edinburgh University. Forty-eight patients with SDB (median AHI = 22/hr) completed the RCT conducted in Edinburgh to compare the effect of CPAP (n = 24) with mandibular repositioning splint (MRS, n = 24) [Engleman *et al.* 2002]. Apnoea hypopnoea index obtained by a home limited sleep study was reduced to 5 or less in 19% of patients on MRS and 34% of patients on CPAP. The mean AHI was 15 ± 16 in CPAP group and 8 ± 6 in MRS group ($p = 0.001$). Patients' effectiveness treatment rating, Symptom Score, Epworth Sleepiness Score (ESS), Functional Outcome of Sleepiness questionnaire (FOSQ), Short Form-36 health survey (SF-36) mental component and health transition score were also significantly higher in the CPAP than in MRS group (effect size = $0.34 - 0.57$, $p < 0.01$). Another direct comparison between oral devices and CPAP also showed better outcomes with CPAP [Barnes *et al.* 2004].

Fourteen randomized controlled trials (n = 553) were included in the meta-analysis in Cochrane review with five studies involving oral appliances vs. control appliances, eight involving oral appliances vs. CPAP and one involving oral appliances vs. surgery [Lim *et al.* 2004]. Oral appliances were not only better than control appliances but also better than surgery in reducing AHI and excessive daytime sleepiness. In comparison with CPAP, although in two small studies, participants preferred oral appliances to CPAP, CPAP was more effective than oral appliance in reducing AHI and improving minimal oxygen saturation.

1.8.3.4 Surgery

No published papers fulfilled the criteria in Cochrane review [Bridgman and Dunn 2000]. The following major problems in the research of surgical intervention for SDB were proposed: (1) inadequate sample size; (2) only p values without confidence intervals were presented; (3) not controlled or randomized controlled trials; (3) follow-up period was as short as 1-2 months [Schechtman *et al.* 1995]. Surgical treatment of obstructive sleep apnoea/hypopnoea syndrome might either cause some dangerous complications like mortality or impaired CPAP use after surgery.

In the practice parameters proposed by the American Academy of Sleep Medicine [1996], there are only two indications for the surgery of SDB: (1) patients with underlying specific surgically correctable abnormality that is causing sleep apnoea including narrow or collapsed retropalatal region and enlarged retrolingual region; (2) patients for whom other non-invasive treatment have been unsuccessful or rejected. Although no study was eligible for formal meta-analysis in Cochrane review, adenotonsillectomy might be helpful in paediatric patients with both significant SDB and adenoid/tonsilar hypertrophy on a individual case basis [Lim and McKean 2003].

1.9 Discussion

Sleep-disordered breathing (SDB) has diverse influences on psychological and cognitive functions. Patients who have SDB suffer from sleep fragmentation, nocturnal hypoxaemia, excessive daytime sleepiness, impaired vigilance, memory, executive function, depression and poor health-related quality of life. Stroke patients who have SDB may therefore have decreased motivation to actively participate in rehabilitation due to sleepiness, emotional or cognitive problems. This might impair multi-dimensional outcomes including physical recovery, functional capacity, cognition, mood and health-related quality of life.

The diagnosis of SDB in stroke is more difficult than that in the usual patients referred to sleep centres. Transport of patients to a sleep centre for overnight polysomnography can be difficult to arrange, especially at relatively short notice given waiting times. Thus portable home study or limited sleep study conducted in the ward seems to be more feasible than full polysomnography for the diagnosis of SDB in stroke. Although major symptoms and signs of SDB and demographic data have limited value in the diagnosis of SDB, a prediction model generated from these variables may play a role as a first line screening tool especially for the physicians who have little knowledge about SDB. Nasal continuous positive airway pressure (CPAP) is also considered the first choice of randomized controlled trial for stroke patients who have SDB. Surgery still has limited evidence, can only be applied on a highly selected basis and is not suitable for acutely ill patients. Oral appliance is less effective in comparison with CPAP in moderate to severe SDB.

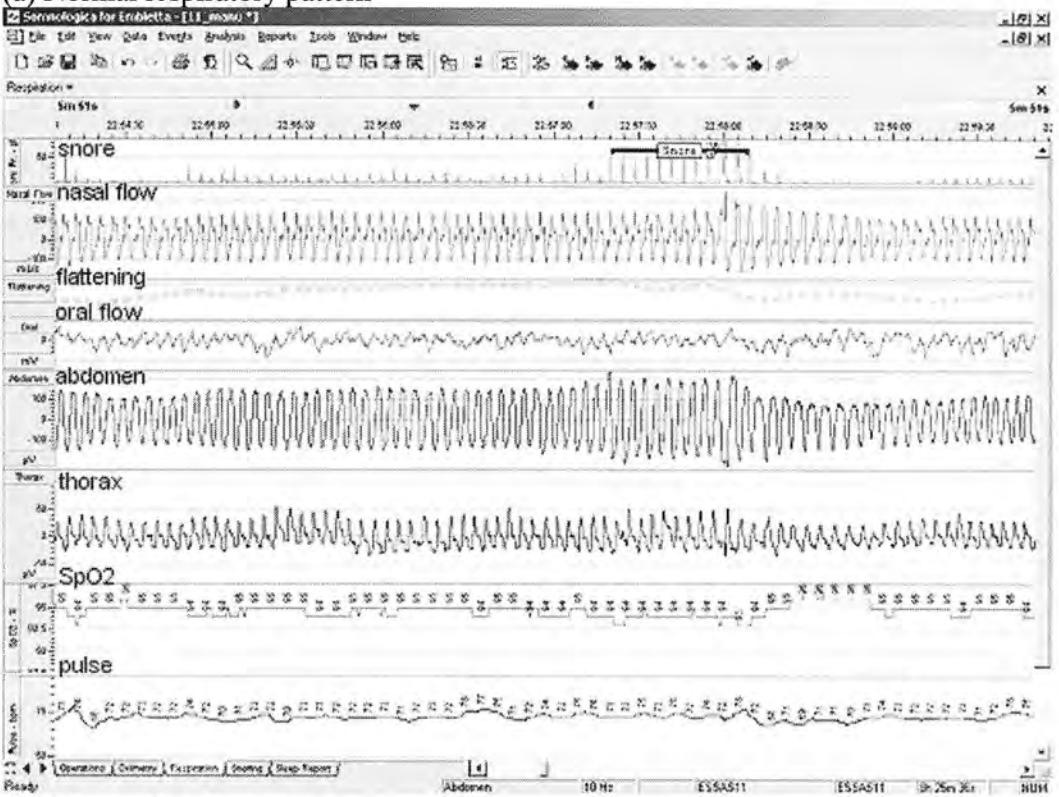
Table 1.1 A comparison of in-lab polysomnography and portable limited sleep study in the diagnosis of SDB

	Polysomnography	Limited sleep study
Level of evidence by APSS	I and II	III and IV
Recording type	In-lab	Portable
Sleep laboratory space	Occupied	Saved
Speed of diagnosis	Faster	Slower
Attendance	Yes	No
Artefacts of the sensors	Less	More
Data loss	Lower	Higher
The 1st night effect	Higher	Lower
Sleep staging	Yes	No
Diagnosis of other sleep disorders	Yes	No
Scoring of SDB	AHI	$(A+H)\cdot h^{-1}$
Split-night study	Yes	No
Cost	Higher	Lower
Patients' preference	Lower	Higher
CPAP use	Higher	Lower

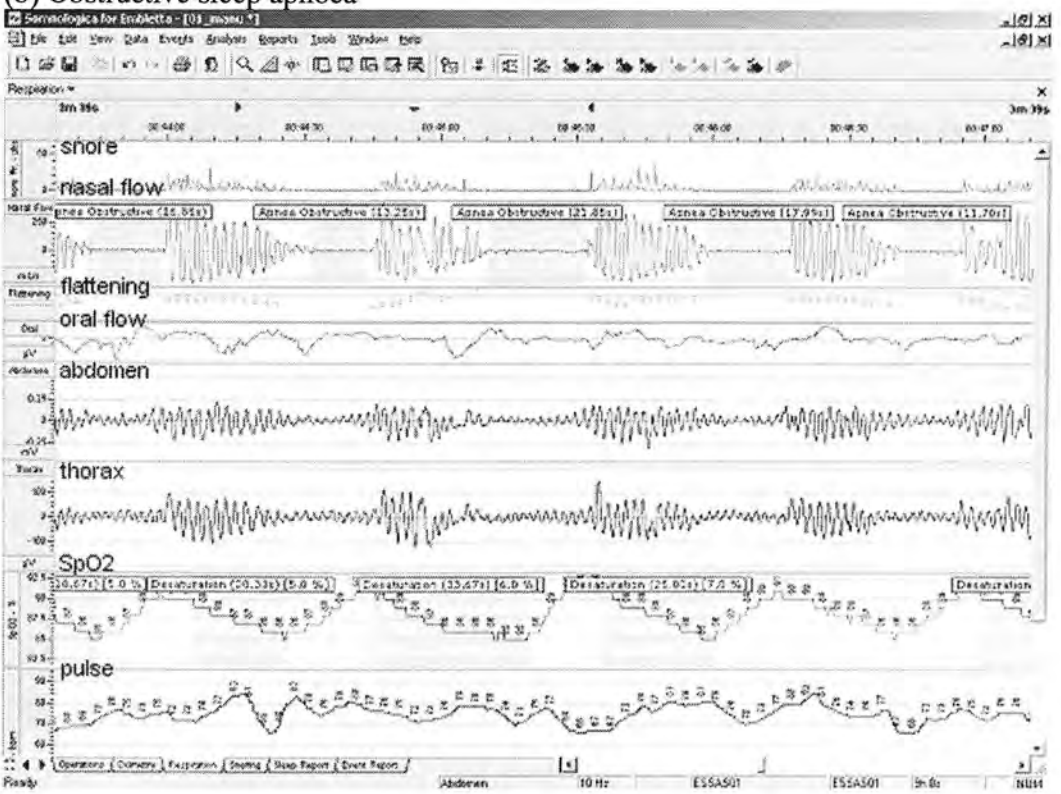
APSS: The Associated Professional Sleep Societies (USA)

Figure 1.1 Demonstration of respiratory events during sleep

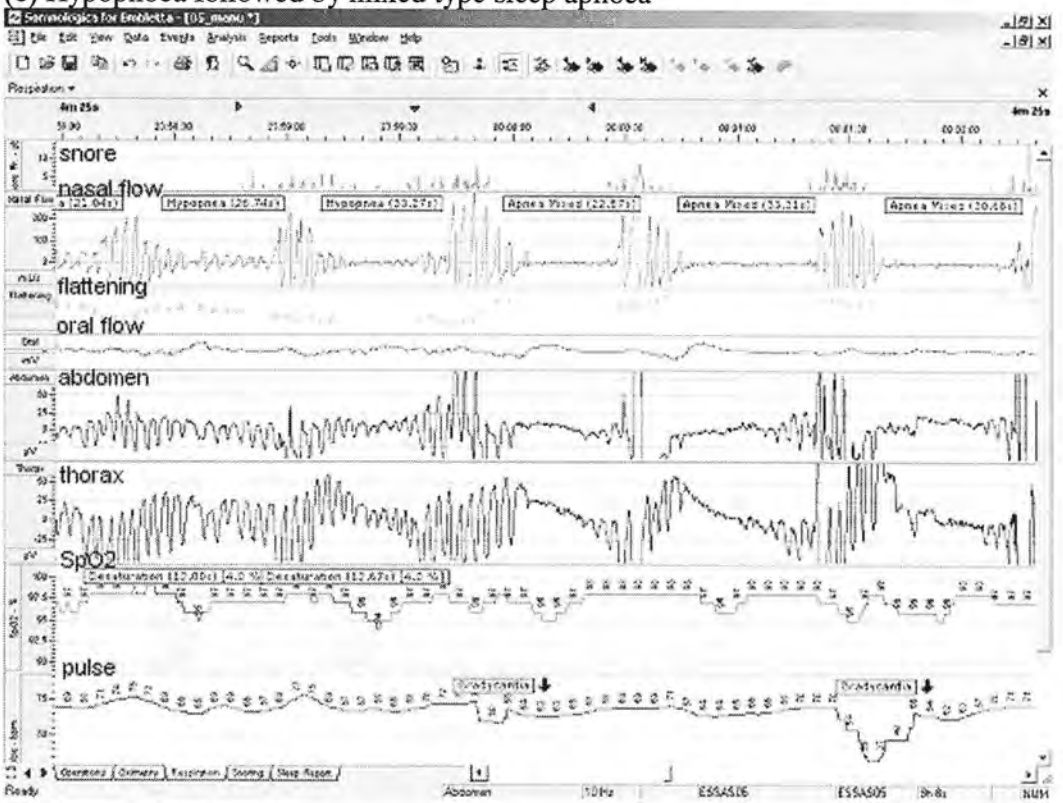
(a) Normal respiratory pattern



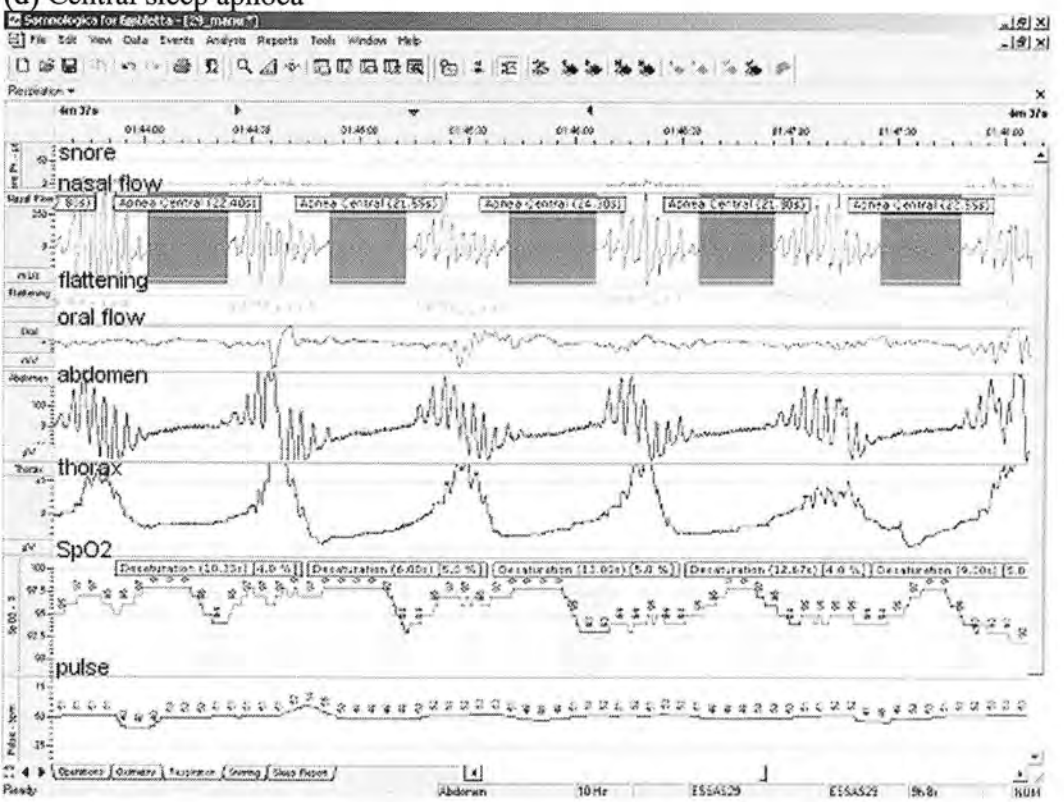
(b) Obstructive sleep apnoea



(c) Hypopnoea followed by mixed type sleep apnoea



(d) Central sleep apnoea



Chapter 2 Obstructive Sleep Apnoea/Hypopnoea Syndrome and Cardiovascular Diseases: A Critical Review

2.1 Introduction

Patients with sleep-disordered breathing (SDB) experience sleep fragmentation and nocturnal hypoxemia which might result in haemodynamic oscillations and inflammatory changes of blood vessels. These draw the attention that SDB not only has an influence on night time and daytime functions but also might be involved in the initiation and progression of cardiovascular diseases. The cardiovascular systems are mainly innervated by the autonomic nervous system (ANS). The ANS transmits impulses from the central nervous system to peripheral organs. The ANS largely consists of: (1) sympathetic division which is responsible for "flight or fight"; (2) parasympathetic division which is responsible for "rest and digest". Autonomic control of heart rate and blood pressure are two major functions related with sleep and SDB. Several factors have been regarded in the pathogenesis of cardiovascular diseases:

- Hypertension, diabetes and hyperlipidemia
- Atherosclerosis, thrombosis and coagulopathy
- Genetic and behavioural characters

Two major endpoints of cardiovascular diseases are coronary artery diseases in terms of angina pectoris and acute myocardial infarction and cerebrovascular diseases in terms of transient ischaemic attack and stroke.

In the beginning of this chapter I will be reviewing the association of SDB and risk factors of stroke in terms of hypertension, coronary artery disease, cardiac arrhythmia, diabetes, atherosclerosis, thrombosis, hypercoagulability, cerebrovascular reactivity and cerebral blood flow. Then I will be reviewing the possible links between SDB and stroke related to the hypothesis and studies of my thesis including diagnosis and epidemiology of SDB in stroke, CPAP treatment for SDB in stroke and impact of SDB on the outcome of stroke.

2.2 Baroreflex sensitivity

Baroreflex sensitivity (BRS) is defined as the slope of linear regression of RR intervals on the electrocardiogram (ECG) versus systolic blood pressure (SBP). The steeper the slope, the higher the BRS indicating a stronger vagal reflex. The flatter the slope, the lower the BRS indicating a weaker vagal reflex and a higher sympathetic reflex. BRS can be studied by the sequence method. For example, sequences of four or more consecutive beats where both pulse interval and SBP progressively increased or decreased are identified. BRS is calculated as slope of each sequence (msec/mmHg). A study showed stroke patients with impaired cardiac BRS (n = 63) had a significantly higher mortality rate (28% vs. 8%) than those with normal BRS (n = 61) over a median follow-up period of 1,508 days [Robinson *et al.* 2003].

An animal model of SDB was performed in three dogs by a permanent side-hole tracheotomy and monitoring of electroencephalography (EEG), ECG and SBP [Brooks *et al.* 1999]. No change of BRS was found 1 to 2 months before induction of sleep apnoea, during 1 to 3 month of sleep apnoea and during the recovery period of 1 month after cessation of sleep apnoea.

Clinical studies were also performed for BRS. An earlier case-control study showed both cardiac and muscle sympathetic BRS were depressed in patients with SDB in comparison with controls [Carlson *et al.* 1996]. More strict criteria were used in a later study which recruited 11 normotensive men free of any other diseases, with newly diagnosed SDB, without medication and never been treated for sleep apnoea [Narkiewicz *et al.* 1998]. Baroreceptor activation was induced by phenylephrine infusion and baroreceptor deactivation was induced by nitroprusside infusion. There was no significant difference between patients and controls in BRS. The patients with SDB showed partial response in sympathetic activity (change of muscle sympathetic nerve activity, MSNA divided by change of mean arterial blood pressure, MAP) to deactivation of baroreceptor.

A non-randomized trial showed eight middle-aged obese men with congestive heart failure and SDB had nocturnal BRS improved on the second night of CPAP trial [Tkacova *et al.* 2000]. A similar trial showed BRS decreased in 29 normotensive patients with SDB in comparison with 11 age-matched normal controls and CPAP treatment for at least three months in 10 patients with increased BRS [Bonsignore *et al.* 2002]. Baroreceptor sensitivity was reduced even in non-apnoeic snorers and this was corrected by CPAP [Gates *et al.* 2004]. The heart rate variability can be obtained by spectral analysis of R-R interval (RRI). The R-R high frequency (HF) component reflects mostly vagal modulation and the R-R low frequency (LF) component reflects both sympathetic and vagal modulation [Monti *et al.* 2002]. Another non-randomized trial focused on heart rate variability showed CPAP treatment increased the high frequency power of RRI and improved vagal heart rate control in patients with moderate to severe SDB. Although compliance to CPAP was poor, the degree of improvement increased with degree of compliance [Khoo *et al.* 2001].

All previous studies focused on the cardiac arm of the baroreflex. A study focused on the arm of vascular resistance was conducted [Cooper *et al.* 2004]. It showed breathing with an inspiratory resistance reduced the sensitivity of baroreceptor control for vascular resistance which was calculated as mean arterial pressure divided by mean blood flow velocity. Asphyxia caused an increased set point of the baroreceptor-vascular resistance reflex.

The baroreflex activity is involved in the regulation of blood pressure. In conclusion, the evidence that SDB impairs sympathoinhibitory baroreceptor function was not consistently supported by an animal model and two cross-sectional clinical studies although a few non-randomized clinical trials showed baroreceptor sensitivity can be corrected by CPAP.

2.3 Hypertension

The normal circadian rhythm of blood pressure resembles a sine-cosine pattern. The blood pressure reaches the nadir in the early morning before getting up, then has an early morning surge after getting up. It gradually increases to its peak in the late afternoon with a small early afternoon dipand then gradually declines through the evening to reach its nadir. A study classified elderly hypertensive patients into four groups according to their nocturnal systolic blood pressure (SBP): 97 extreme-dippers with > 20% SBP decrease; 230 dippers with > 10% but < 20% decrease; 185 non-dippers with > 0% but < 10% decrease and 63 reverse dippers with < 0% decrease. The results showed non-dippers, extreme dippers and reverse dippers had higher rate of developing stroke than dippers [Hoshide *et al.* 2002].

Snoring is a heterogeneous diagnostic entity mostly based on history taking and questionnaire survey. Most studies about snoring and hypertension were cross-sectional. The findings were inconsistent after adjusting for confounding factors. More researches have shifted into the association between hypertension and sleep-disordered breathing (SDB) instead of snoring alone. The following questions need to be solved:

- Whether intermittent increased nocturnal blood pressure is a transient phenomenon restricted to sleep?
- Can it be extended to the morning after getting up?
- Can it cause permanent hypertension?

2.3.1 Animal and cross-sectional studies for SDB and sympathetic activity

An experimental was performed on rats for the effect of chronic intermittent hypoxia mimicking SDB on sympathetic activity by intermittently flushing an exposure chamber with 100% nitrogen for 30 days [Greenberg *et al.* 1999]. A significantly increased cervical sympathetic activity and mean arterial blood pressure were noted in hypoxic rats but not in controls. As there was no difference between

groups in baroreflex the authors concluded the influence of chronic intermittent hypoxia on sympathetic activity might be through chemoreflex.

Increased arousals from sleep are the major feature of sleep fragmentation in patients with SDB in comparison with normal subjects [Mathur and Douglas 1995]. Increased arousals not only impair daytime function [Martin *et al.* 1997] but also activate sympathetic activity. An experiment recruited 12 healthy non-obese subjects for concomitant polysomnography and cardiovascular monitoring showed external stimuli can provoke cardiovascular response mediated by arousals and sympathetic activation [Trinder *et al.* 2003]. In comparison with the pre-stimulus state, subjects demonstrated significantly larger responses for heart rate, systolic blood pressure and a measure for peripheral vasoconstriction at arousal to either the orienting stimuli or startle stimuli which had a transient activation without returning to waking state.

An observational study showed there was significantly higher prevalence of hypertension in sleep-fragmented non-apnoeic snorers (arousal index ≥ 10, n = 50) than in non-sleep-fragmented non-apnoeic snorers (arousal index < 10, n = 50) [Lofaso *et al.* 1996]. Further study in six non-apnoeic snorers showed the magnitude of increased systolic, diastolic pressure and heart rate following non-apnoeic non-hypopnoeic events was higher in those with higher grade of arousal defined as longer duration of EEG frequency changes [Lofaso *et al.* 1998].

A case-control study for sympathetic nerve activity using direct multiunit intraneural recordings during wakefulness showed significantly higher sympathetic burst frequency in patients with SDB (n = 10) than in age- and sex-matched controls (n = 10) [Somers *et al.* 1995]. Large oscillations in sympathetic nerve activity and blood pressure synchronous with the apnoeic episodes during sleep were terminated by arousal response of electroencephalography and increased muscle activity. Nasal CPAP treatment in four patients at the same night of recording decreased sympathetic activity and blood pressure.

2.3.2 Population-base cohort studies

From mid 1980's to early 1990's, many cross-sectional and case-control studies were published regarding snoring, SDB and hypertension. There are two major weak points to these studies: (1) lack of controlling confounding factors especially for age and obesity; (2) lack of objective measurement of SDB. Two large population-based prospective cohort studies have been under investigated for SDB and cardiovascular diseases since early 1990's and some results from cross-sectional analysis have been published. One is Wisconsin Sleep Cohort Study and another is Sleep Heart Health Study.

2.3.2.1 Wisconsin Sleep Cohort Study (WSCS)

The aim of the WSCS is prospective investigation of cardiovascular diseases as an outcome of sleep-disordered breathing. Overnight polysomnography was performed and blood pressure was measured by standard sphygmomanometer. Patients were stratified into five groups according to AHI: (1) AHI < 2 (n = 642); (2) $2 \leq$ AHI < 5 (n = 191); (3) $5 \leq$ AHI < 15 (n = 141); (4) $15 \leq$ AHI < 30 (n = 58); (5) AHI ≥ 30 (n = 37). Multiple linear regression revealed AHI was significantly associated with systolic and diastolic BP. Sleep-disordered breathing was supported as a risk factor for hypertension (OR = 1.8 for AHI > 15) with a dose-response linear relationship between AHI and BP [Young *et al.* 1997b]. The magnitude was stronger in the low BMI group.

In total, 709 participants completed follow-up for four years and 184 participants completed follow-up for eight years [Peppard *et al.* 2000b]. The odds ratio for the presence of hypertension in subjects with AHI ≥ 15 at a follow-up for eight years increased to 2.89 after adjusting for baseline hypertension, nonmodifiable risk factors and habits. The presence of hypertension in this study group was 34%.

2.3.2.2 Sleep Heart Health Study (SHHS)

The SHHS is a multi-centre study to determine cardiovascular and other consequences of sleep-disordered breathing. 5,250 subjects were recruited for overnight polysomnography [Nieto *et al.* 2000;Shahar *et al.* 2001]. The first part was a cross-sectional case-control study. The second part was a prospective cohort study. The results of first part study showed there was a strong link between SDB and the prevalence of heart failure (adjusted OR 2.20, CI 1.11-4.37) but weaker links to coronary artery disease (adjusted OR 1.22, CI 0.93-1.59) and stroke (adjusted OR 1.55, CI 0.96-2.50). When some confounders, including variables related with hypertension, cigarette smoking and body mass index were removed from the statistical adjustment for confounders post hoc to avoid "over-adjustment", the odds ratio increased to 1.27 (CI 0.99-1.62) in coronary artery disease and 1.58 (CI 1.08-2.46) in stroke. However, the validity of this approach is questionable. The results can only tell that SDB is an associated factor of congestive heart failure, coronary artery disease and stroke rather than that SDB might cause CHF, CAD and stroke. The prospective cohort study will be completed in August 2008 so the result has not been published yet.

The prediction of SDB is different in older people than in younger adults. The odds ratio of body mass index for an AHI $\geq$ 15 decreased with age and became statistically non-significant at age 80. The odds ratio of self-reported breathing pauses for an AHI $\geq$ 15 decreased with age and became statistically non-significant after age 80 [Young *et al.* 2002].

2.3.2.3 Other epidemiological evidence

A study recruited 2677 adults (aged 20-85) referred to a sleep clinic for evaluation of SDB [Lavie *et al.* 2000]. Hypertension was defined as either taking anti-hypertensive medication or abnormal readings of blood pressure (> 140/90). The study also supported SDB significantly contributed to hypertension independent of all relevant confounders. An increase in 10 in the apnoea/hypopnoea index (AHI)

increased the risk of having hypertension by about 11%. Each 10% decrease in oxygen saturation nadir increased the risk of having hypertension by about 13%.

Another study included young and middle-aged subjects (1000 women and 741 men) randomly selected from a community for overnight polysomnography and blood pressure measurement for hypertension [Bixler *et al.* 2000]. An independent association between SDB and hypertension was stronger in young subjects with normal BMI after adjustment for menopause and hormone replacement therapy.

2.3.3 The effect of CPAP trials on blood pressure

Many early clinical trials for the effect of nasal CPAP on blood pressure control had some weak points: (1) lack of randomized control design; (2) limited sample size. (3) lack of objective report of compliance of CPAP;

Ambulatory blood pressure monitoring is a better predictor for cardiovascular diseases than casual blood pressure measurement. Higher mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) are associated with increased relative risk of cardiovascular diseases [Clement *et al.* 2003]. Hypertensive patients with higher nocturnal blood pressure (non-dippers, i.e. < 10% lower than daytime mean blood pressure) may have a worse prognosis than dippers [Verdecchia *et al.* 1994].

Non-dippers were common in patients with SDB [Akashiba *et al.* 1999;Davies *et al.* 2000]. Ambulatory blood pressure was measured in 38 patients with SDB (AHI = 54 ± 11) before and after CPAP treatment for three days [Akashiba *et al.* 1999]. The average daytime and night time blood pressure decreased significantly after CPAP treatment. Fifteen of 22 patients who were non-dippers before treatment reversed to become dippers. The results were based on a non-randomized uncontrolled trial.

A small randomized controlled cross-over trial of nasal CPAP did not show any effect of CPAP on systolic, diastolic and mean ambulatory blood pressure but the sample size (n = 13) was too small (power 65-95%) to draw any firm conclusions [Engleman *et al.* 1996b]. The effect of four weeks of CPAP on blood pressure in

normotensive patients with SDB was further evaluated by the same research group [Faccenda *et al.* 2001]. Sixty-eight patients completed the trial (median AHI = 35). Ambulatory blood pressure monitoring (ABPM) was used. Although there was no change in systolic blood pressure there was a 1.5-mmHg reduction of diastolic blood pressure in the overall patients on CPAP therapy. In an a priori determined group with more marked nocturnal hypoxaemia, there were significant falls in both systolic (4mmHg) and diastolic (5mmHg) pressure. This is clinically meaningful as 5-mmHg decrease in diastolic blood pressure results in 32% decrease in stroke and 21% decrease in coronary artery disease [MacMahon *et al.* 1990]. The effect of CPAP was independent of baseline blood pressure and more prominent in patients taking antihypertensive medications [Pepperell *et al.* 2002].

2.3.4 Conclusions

Hypertension is the most powerful stroke risk factor. In my reviews, evidence which support the link between SDB and hypertension is stronger. They are mainly based on the cross-sectional parts of two large-scaled prospective cohort studies, WSCS and SHHS after adjusting for confounding factors. Further evidence from final results of a time-consuming longitudinal follow-up is expected.

More promising findings are based on several well-designed randomized controlled trials which definitely support the benefits of CPAP treatment in reducing blood pressure.

2.4 Coronary artery disease

2.4.1 Concomitant sleep and Holter monitoring

Overnight polysomnography, Holter motoring and blood pressure measurement every 30 minutes was performed in 51 patients suffering from coronary artery disease (CAD) and SDB in comparison with 17 controls [Peled *et al.* 1999]. Nocturnal ST-segment depressions occurred during the rebreathing phase of the obstructive apnoeas. Treatment with CPAP significantly decreased ST-segment depression time from 78 to 33 minutes and double product value (systolic blood pressure × heart rate) from 14,137 ± 2,827 to 12,083 ± 2,933.

A similar study with concomitant overnight limited sleep study and Holter motoring was performed in 219 patients (127 men and 92 women) [Mooe *et al.* 2000]. Although there was no difference in oxygen desaturation index (ODI) and AHI between patients with and without nocturnal ST-segment depressions, ST-segment depression occurred within 2 minutes after an apnoea-hypopnoea or desaturation in 12% of patients. Most of these ST-segment depressions were preceded by a series of breathing events.

2.4.2 Cross-sectional studies

A case-control study recruited 289 patients for the evaluation of CAD [Schafer *et al.* 1999]. All patients had coronary angiography and 209 patients had overnight limited sleep studies. The obstructive sleep apnoea/hypopnoea was found in 30.5% of CAD patients but only in 19.7% of controls. Patients with CAD (n = 223) had significantly higher AHIs than patients without CAD (n = 66). Logistic regression analysis revealed sleep apnoea/hypopnoea defined as AHI ≥ 20 and hyperlipidemia were both independent risk factors associated with CAD.

Another case-control study recruited 62 CAD patients and 62 age-matched controls for overnight polysomnography [Peker *et al.* 1999]. Obstructive sleep

apnoea/hypopnoea defined as AHI ≥ 10) was noted in 19 CAD patients but only in 8 controls. The CAD group had significantly higher AHI than control group. Logistic regression analysis showed current smoking, diabetes mellitus and SDB were independently associated with CAD.

2.4.3 Prospective cohort studies

A prospective cohort study with 392 CAD patients (264 men and 128 women) who completed overnight limited sleep studies entered a longitudinal follow-up for a median period of 5.1 years [Mooe *et al.* 2001]. The risk ratio of combined cardiovascular events and death in patients with AHI ≥ 10 was 1.62. Among them the risk ratio of cerebrovascular disease was higher (3.41) than for myocardial infarction which was not significantly raised (1.02). An oxygen desaturation index (ODI) of > or = 5 and an AHI of > or = 10 were both independently associated with cerebrovascular events (hazard ratio 2.62, 95% CI 1.26-5.46, p = 0.01, and hazard ratio 2.98, 95% CI 1.43-6.20, p = 0.004, respectively).

A 7-year follow-up was conducted on 182 middle-aged patients who were referred to a sleep centre for the diagnosis of SDB [Peker *et al.* 2002]. Patients were divided into two groups on the basis of the results of their overnight limited sleep studies: those with an overnight total ODI ≥ 30 being defined as having sleep apnoea/ hypopnoea (n = 60) and those with ODI < 30 non- sleep apnoea/ hypopnoea (n = 122). The incidence of at least one cardiovascular disease (hypertension, angina pectoris, myocardial infarction, stroke or cardiovascular death) was significantly higher in patients with ODI ≥ 30 (36.7%) in comparison with those below (6.6%). Multiple logistic regression showed SDB at baseline (apnoea index ≥ 5) was an independent predictor for cardiovascular diseases but efficient treatment (ODI < 30 after treatment) was associated with significant reduction of cardiovascular incidence. The bias was CPAP, oral appliance or uvulopalatopharyngoplasty (UPPP) was given depending on the clinical situation. Patients with OD ≥ 30 were completely or partially treated so might not reflect the natural course of SDB.

2.4.4 Clinical trial of CPAP for SDB in CAD

Fifty-four patients with both CAD and SDB were recruited in a study for non-randomized treatment with either CPAP (n = 25) or upper airway surgery (n = 29) [Milleron *et al.* 2004]. Median of follow-up was 86 months in the treatment group and 90 months in the decline group. At least one cardiovascular event occurred during follow-up in 24% of the treatment group but in 58% of the decline group ($p < 0.01$).

2.4.5 Conclusions

Coronary artery disease and stroke share common pathogenesis. In my reviews, the influence of SDB on electrocardiogram (ECG) is shown by some observational studies and a non-randomized trial. There was a few evidence to support the link between SDB and coronary artery disease from case-control studies. Stronger evidence from two prospective cohort studies showed that SDB was an independent risk factor for cardiovascular diseases but not coronary artery disease alone. Randomized controlled trials are needed to support the benefit of CPAP treatment in reducing coronary artery or cardiovascular diseases.

2.5 Atrial fibrillation

A prospective cohort study with one year of follow-up was performed to investigate obstructive sleep apnoea and recurrent atrial fibrillation. Among patients with atrial fibrillation/atrial flutter who were referred for electrical cardioversion 43 patients were identified as having a formal sleep study resulting in the diagnosis of obstructive sleep apnoea [Kanagala *et al.* 2003]. Seventy-nine postcardioversion patients who did not have obstructive sleep apnoea were randomly selected as control. Both the questionnaire and phone interview were performed at 12 months. Patients were considered to have recurrence of AF only if a physician had documented them to be in AF by either clinical or ECG examination. Follow-up was completed in 39 of 43 patients. Twenty-seven of 39 patients either did not receive CPAP treatment or used CPAP inappropriately. Recurrence of AF was significantly higher in these 27 patients (82%) in comparison with CPAP-treated (42%, $p = 0.013$) and control group (53%, $p = 0.009$).

A further case-control study was performed by the same group. They recruited 151 consecutive patients with AF and 312 controls without past or current AF from general cardiology practice. Obstructive sleep apnoea was diagnosed by validated Berlin questionnaire. The results showed that the prevalence of SDB obstructive sleep apnoea was significantly higher in AF (49%) than in control (32%) group ($p = 0.0004$) [Gami *et al.* 2004]. In multivariate analysis, body mass index, neck circumference, hypertension, diabetes and AF remained significantly associated with obstructive sleep apnoea and the odds ratio was largest for AF (2.19, 95% CI = 1.40-3.42, $p = 0.0006$).

On the contrary a recent prospective cohort study did not show the association between SDB and AF [Roche *et al.* 2003]. One hundred and forty-seven patients were recruited for time-synchronized polysomnography and ECG Holter monitoring. Although nocturnal paroxysmal asystole (10.6% vs. 1.2%, $p < 0.02$) and bradycardia (18.2% vs. 4.9%, $p < 0.01$) were more prevalent in patients with SDB increased risk of atrial and ventricular fibrillation was not found. A similar finding was found in

another case-control study. A limited sleep study was performed for 59 patients with lone atrial fibrillation defined as atrial fibrillation without known causes and 56 age-, sex- and cardiovascular morbidity-matched community controls [Porthan *et al.* 2004]. There was no significant difference of percentage of mild, moderate and severe SDB between patient and control groups.

Atrial fibrillation is one of the major risk factors for stroke, particularly embolic brain infarction. In conclusion, the association between SDB and AF is supported by a prospective cohort study which showed patients with SDB had a higher recurrence rate of AF. The shortcoming of this study is that they did not perform a randomized controlled trial of CPAP for SDB in patients with AF. Some other case-control studies including a study with a well-matched control did not support the association between AF and SDB. More prospective cohort studies and randomized controlled trials are necessary.

2.6 Diabetes

More attention has been paid to the link between SDB and glucose intolerance, insulin resistance and diabetes recently. Diabetes, like hypertension, shares some confounders with SDB such as obesity and ageing.

A cross-sectional observational study was performed to investigate whether SDB is an underlying cause of diabetes or glucose intolerance [Meslier *et al.* 2003]. In total, 494 of 595 patients who had both polysomnography and 2-hour oral glucose tolerance test (OGTT) had an SDB defined as AHI $\geq$ 10. After adjusting for age and BMI, AHI was still significantly correlated with post-loading glucose level in OGTT and insulin sensitivity evaluated by the ratio of fasting glucose to fasting insulin. The authors drew a conclusion that SDB is an independent risk factor of glucose intolerance which is usually an initial presentation of diabetes mellitus.

The above conclusion was only weakly supported by the cross-sectional results from the Sleep Heart Health Study with similar methodology. In the first instance, data generated from 4972 community-based subjects who had no cardiovascular risks were published [Resnick *et al.* 2003]. Although significantly more diabetic subjects (23.8%) had AHI $\geq$ 15 than non-diabetic subjects (15.6%), there was no clear association between SDB and diabetes after adjusting for confounders including age, sex, BMI, race and neck circumference. Further analysis showed adjusted odds ratio of fasting glucose intolerance was 1.27 (95% CI = 0.98 – 1.64) in subjects with mild SDB (AHI = 5-14.9) and 1.46 (95% CI = 1.09 – 1.97, AHI $\geq$ 15) in subjects with moderate to severe SDB in comparison with those with AHI < 5 [Punjabi *et al.* 2004].

A non-randomized trial was performed for the effect of CPAP treatment on insulin sensitivity. Forty patients (mean age 54 year-old) with SDB (mean AHI = 43.10 $\pm$ 11.38) received CPAP treatment for three months [Harsch *et al.* 2004]. Improved insulin sensitivity index calculated from the insulin measurements and the

corresponding glucose infusion rates during that period was found after 2 days and 3 months of CPAP treatment in comparison with baseline data ($p < 0.001$).

Diabetes, like hypertension, is a major cause of stroke. In conclusion, the evidence which showed association between SDB and either insulin sensitivity or diabetes is based on cross-sectional studies. It needs to be clarified whether SDB is just a confounding factor for or independently associated with diabetes because SDB was no longer an independent risk factor after adjusting for other confounders in the observational part of Sleep Heart Health Study. The clinical trial of CPAP in this review was biased as it was not a RCT.

2.7 Atherosclerosis

There are many causes of atherosclerosis including hypertension, diabetes, hyperlipidemia, cigarette smoking, elevated plasma homocysteine, infection, genetic factors and oxidative stress. Atherosclerosis is the major cause of ischaemic stroke, especially thrombotic stroke. One of the theories of atherosclerosis, the "response-to-injury" hypothesis was first published in 1973 which emphasized the chronic inflammatory process underlying atherosclerosis [Tegos *et al.* 2001].

A simple evidence of atherosclerosis was found by carotid duplex ultrasonography performed in 23 male patients with severe SDB (AHI > 30 by overnight limited sleep study) and controls matched by age, BMI and vascular risk profiles [Silvestrini *et al.* 2002]. The study showed significant higher ($P < 0.0001$) intima-media thickness (IMT) value of common carotid artery in the apnoeic group (1.43 ± 0.34 mm) in comparison with control (0.98 ± 0.17 mm). This study could not completely rule out the possibility that the difference in IMT could be explained by an imperfect comparison of severity and duration of exposure of vascular risk factors.

2.7.1 Cell adhesion molecules

Adhesion molecules are produced in both endothelial cells and leukocytes including intercellular adhesion molecules-1 (ICAM-1), vascular cell adhesion molecules-1 (VCAM-1), L-selectin and E-selectin. Adhesion molecules increased due to endothelial activation and dysfunction which might result from hypoxia or oxidative stress in patients with SDB [Ohga *et al.* 1999]. Another study revealed that soluble E-selectin and VCAM-1 decreased after CPAP treatment for 3-4 days and ICAM-1 decreased after CPAP treatment for 6 months [Chin *et al.* 2000] but there was no control group.

The expressions of cellular phenotypes of two adhesion molecules in peripheral whole blood monocytes and granulocytes, CD15 and CD11c, were also increased in patients with SDB [Dyugovskaya *et al.* 2002]. The percentage of CD15 ($n = 8$) and

CD11c (n = 8) monocytes was significantly decreased after CPAP treatment for more than 6 months, again with no control group.

2.7.2 Nitric oxide (NO)

Nitric oxide (NO) is continuously released from arterial and arteriolar endothelium and is one of the most important vasodilators of small arteries and arterioles. Deficiency of NO is thought to be involved in the pathogenesis of atherosclerosis [Vallance and Collier 1994].

The serum level of NO was significantly lower in patients with SDB (AHI > 20, n = 30) in comparison with controls (n = 40) and there was a significant negative correlation between NO and AHI, and systolic blood pressure [Ip *et al.* 2000]. There was a significant increase in NO after one night (n = 22) [Ip, Lam, Chan, Zheng, Tsang, Fung, and Lam2000] or two nights (n = 21) of CPAP treatment and remained constant at 5.5 months of follow-up [Schulz *et al.* 2000]. Nocturnal oxygen (1-2 l/min) via nasal prongs for one week can increase serum NO level in patients with SDB (n = 24) in comparison with controls (n = 24) [Teramoto *et al.* 2003a].

2.7.3 Homocysteine

Homocysteine is auto-oxidized into hydrogen peroxide with accompanying free radicals. The role of homocysteine in atherosclerosis is mainly in impairing endothelial function, promoting migration of smooth muscle spindle cells and enhanced platelet aggregation. Excessive homocysteine is usually neutralized by NO. In patients with SDB, NO is reduced so homocysteine is increased.

Plasma homocysteine level was not different between patients with OSAH (AHI ≥ 20) and controls in one study [Svatikova *et al.* 2004] but was significantly higher in patients with both ischaemic heart disease and SDB than control group, SDB-only group and CAD-only group in another study [Lavie *et al.* 2001]. It remained statistically significant after adjustment of covariates including age, BMI, creatinine level, and diabetes.

Treatment with CPAP can effectively lower plasma homocysteine level in a small (n = 16) non-RCT study [Jordan *et al.* 2004].

2.7.4 Cytokines

Cytokines are systemic markers of inflammation which can be increased by damage of endothelial and vascular smooth muscle cells due to oxidative stress in SDB. Significantly higher concentration of interleukin-6 collected from expired breath condense was found in patients with SDB (AHI > 20, n = 18) in comparison with subjects with obesity (n = 10) and controls (n = 15) [Carpagnano *et al.* 2002].

2.7.5 Acute phase protein

Inflammation appears to play a major role in the pathogenesis of atherosclerosis. C-reactive protein (CRP) has been associated with progression of CAD [Teramoto *et al.* 2003b].

In the Cardiovascular Health Study (CHS), observational data from 5417 elderly (≥ 65 year-old) under longitudinal follow-up for a median of 10.2 years were analyzed [Cao *et al.* 2003]. In comparison with the 1st quartile of CRP, the adjusted hazard ratios of stroke for the 2nd, 3rd and 4th quartiles of CRP were 1.19 (95% CI = 0.92 – 1.53), 1.05 (95% CI = 0.81 – 1.37) and 1.60 (95% CI = 1.23 – 2.08) respectively. After additional adjustment for carotid intima media thickening (IMT) the hazard ratio of the 4th quartile of CRP in comparison with the 1st quartile was still significant (1.52, 95% CI = 1.16 – 1.98).

A case-control study compared patients with moderate to severe obstructive sleep apnoea/hypopnoea (AHI ≥ 20, n = 22) with controls (n = 20) [Shamsuzzaman *et al.* 2002]. Plasma CRP level was significantly higher in OSAH group (median = 0.33) than control (median = 0.09) by non-parametric test as distribution of CRP data was skewed to the right. CRP was positively and independently associated with severity of OSAH.

Another study showed plasma level of CRP and interleukin (IL)-6 was significantly higher in patients with moderate to severe OSAHS (AHI ≥ 20) than in patients with mild OSAHS (5 ≤ AHI < 20) and obese controls [Yokoe *et al.* 2003]. Treatment with CPAP for one month in the randomized controlled trial for patients with moderate to severe OSAHS significantly decreased AHI, increased lowest SaO2, decreased percentage of time with SaO2 < 90% and decreased Epworth Sleepiness Score.

2.7.6 Conclusions

Atherosclerosis is the most important pathogenesis for thrombotic brain infarction. The studies which supported increased atherosclerosis-aggravating biochemical markers and decreased atherosclerosis-alleviating markers in patients with SDB were based on either observational or case-control design. The clinical trials of CPAP were non-randomized although the results showed CPAP can decrease cell adhesion molecules, homocysteine and CRP. It will be interesting to perform further carotid duplex ultrasonography study which takes severity and duration of exposure to vascular risk factors into account.

2.8 Thrombosis and hypercoagulability

The role of SDB in the pathogenesis of thrombosis and hypercoagulability are discussed in the following sections. Main findings in patients with SDB were:

- Increased in vivo and in vitro platelet activation and aggregation and decreased after CPAP treatment
- Increased whole blood viscosity
- Increased fibrinogen level and decreased after CPAP treatment
- Hypercoagulability state by increased Willebrand factor antigen

2.8.1 Platelet activity

A few "in vitro" studies of platelet activity have been published. Platelet activation, measured by monoclonal antibodies to P-selectin, and aggregation, measured by proportion of platelets larger than resting platelets through light scattered method, were compared in six patients with SDB (AHI = 87.2 ± 23.2) and five controls who had no or mild SDB [Bokinsky *et al.* 1995]. Patients with SDB were given CPAP for one night. Percentage of activated and aggregated platelets was significantly higher in the baseline study night than in the CPAP night and controls. A similar study also found P-selectin expression before polysomnography, epinephrine level after PSG and blood pressure before and after PSG was significantly correlated with AHI in 64 patients from normal to severe SDB [Eisensehr *et al.* 1998]. Platelet aggregation to epinephrine, collagen, arachidonic acid and adenosine diphosphate was also studied "in vitro" [Sanner *et al.* 2000]. Platelet aggregation in response to epinephrine was significantly higher in patients with SDB (n = 17) than in controls (n = 15) and was significantly lowered by CPAP therapy.

As "in vitro" studies could be influenced because platelet activity might be activated through blood drawn from a catheter, an "in vivo" assessment was performed [Geiser *et al.* 2002]. The results showed patients with SDB (n = 12) had an increased percentage of platelets positive for the activation-dependent epitopes

CD63 and CD62P during sleep in comparison with controls (n = 6). The amount of CD63- and CD62P-positive platelets in patients with SDB was significantly higher at 4 a.m. (during sleep) compared to 7 a.m. (after sleep) in the morning.

2.8.2 Whole blood viscosity

Variation of whole blood viscosity (WBV) was strongly influenced by haematocrit (Hct). WBV-Hct normalized ratio was calculated in 12 patients with SDB and 8 controls [Nobili *et al.* 2000]. The results showed significantly higher ratios in the morning than in the evening only in patients with SDB.

Another similar study did not show any difference of WBV but significantly higher plasma viscosity and fibrinogen level in the morning in 13 patients with SDB in comparison with 8 controls [Reinhart *et al.* 2002].

2.8.3 Fibrinogen

Fibrinogen is a protein synthesized by the liver. Fibrinogen is broken down by thrombin to form fibrin which helps with formation of blood clot. Fibrinogen and factor VII clotting activity are independent predictors for cardiovascular mortality including recurrent ischaemic stroke [Rothwell *et al.* 2004].

Overnight polysomnography was performed and blood was drawn for fibrinogen level in a stroke rehabilitation ward about 1 month following stroke [Wessendorf *et al.* 2000]. Final analysis was performed on 113 patients after excluding those with evidence of underlying inflammatory diseases or central sleep apnoea. Plasma fibrinogen level was positively correlated with increased AHI and negatively correlated with oxygen saturation. Stepwise multiple regression analysis showed average oxygen saturation and gender were independently associated with fibrinogen level.

Fibrinolytic activity was assessed by the level of tissue plasminogen activator (tPA) and plasminogen activation inhibitor (PAI-1) in 13 patients with SDB (mean AHI = 32) and 10 male controls [Rangemark *et al.* 1995]. Eleven of 13 apnoeic

patients were also hypertensive. The results showed significantly increased PAI-1 in patients with SDB after adjustment of age, BMI and diastolic blood pressure as hypertension is a confounder for elevated PAI-1.

In a small-sampled (n = 11) and non-randomized controlled trial, fibrinogen and whole blood viscosity significantly decreased after CPAP treatment [Chin *et al.* 1996]. A further study by the same research group with similar design (n = 15) showed factor VIIc level significantly decreased after 6 months of CPAP treatment [Chin *et al.* 1998].

2.8.4 Coagulopathy

Three markers of hypercoagulability (1) thrombin/antithrombin III complex; (2) fibrin D-dimer and (3) Willebrand factor antigen [von Kanel *et al.* 2001] were studied in normotensive non-apnoeic (n = 19), normotensive apnoeic (n = 38), hypertensive non-apnoeic (n = 11) and hypertensive apnoeic (n = 19) patients. There was a significant main effect for hypertension but no significant main effect for apnoea or interaction of hypertension and apnoea on either thrombin/antithrombin III complex or fibrin D-dimer. There was no significant main effect for both hypertension and apnoea but a significant interaction of hypertension and apnoea on Willebrand factor antigen.

2.8.5 Conclusions

Thrombosis and hypercoagulability are two direct causes of ischaemic stroke but their association with SDB is still not clear. The sample size of the studies for platelet function was small. The studies about whole blood viscosity had inconsistent findings. The results of cross-sectional studies for the link between SDB and fibrinogen and fibrinolytic activity showed oxygen saturation but not AHI was significantly associated with plasma fibrinogen level after adjusting for confounding factors. No significant influence of SDB alone on coagulating factors was found. The CPAP trials for platelet activity, blood viscosity and fibrinogen level were not RCT.

2.9 Cerebrovascular reactivity and cerebral blood flow in SDB

SDB not only has influence on physiological and biological markers of cardiovascular diseases described above but also has direct central haemodynamic effect.

2.9.1 Cerebrovascular reactivity

A case control study recruited eight consecutive men with SDB (mean oxygen desaturation index, ODI = 65.6 ± 25.5) and eight controls (mean ODI = 5 ± 3.1) matched for the age and presence of hypertension and smoking for cerebrovascular reactivity to hypercapnia, which was calculated by breathing holding index (BHI) by means of Transcranial Dopper (TCD) [Placidi *et al.* 1998]. A significantly lower BHI to hypercapnia was found in normocapnic SDB patients in comparison with controls in the morning following nocturnal sleep. Decreased morning cerebrovacular reactivity to hypercapnia could contribute to most strokes happening in the morning [Qureshi *et al.* 1999].

2.9.2 Cerebral flood flow

The cerebral blood flow (CBF) in normal NREM sleep remains constant and there is increased CBF in REM sleep especially in the visual cortex which is thought to be associated with the dreaming state. The influence of SDB on cerebral blood flow was variable. Studies were biased as there was no direct measure of CBF but measure of cerebral blood flow velocity (CBFV) by Transcranial Doppler (TCD).

A study showed increased CBFV during apnoeic episodes [Klingelhofer *et al.* 1992]. Further study performed by the same group showed patients with SDB had lower CBFV in NREM sleep through stage II to IV but higher CBFV in REM sleep [Hajak *et al.* 1996]. This means that patients with SDB might have fast and profound nocturnal CBF fluctuation. It is interpreted by increased partial pressure of end-tidal carbon dioxide (ETCO2) and sensitivity of CO2 or PH receptors in the brain.

However, the fall of CBFV upon termination of the apnoea was so abrupt that arousals and neuronal activation were the most likely explanation.

On the contrary, decreased CBFV was also reported in patients with SDB during awake and all sleep stages in association with apnoeic or hypopnoeic episodes [Fischer *et al.* 1992]. Another study supported decreased CBFV especially during prolonged apnoeic episodes. It showed changes of CBFV were associated with changes of mean arterial pressure in the same direction so arterial blood pressure could be a major factor for CBF [Balfors and Franklin 1994]. CBFV dropped below baseline level after termination of apnoea episodes before coming back to normal and this drop could contribute to the pathogenesis of cerebral infarction.

There was a direct relationship between individual apnoeas and reduction of middle cerebral artery (MCA) CBFV in association with longer events and the more severe desaturation of obstructive sleep apnoeas or hypopnoeas instead of central ones [Netzer *et al.* 1998]. Intracranial pressure (ICP) is increased during sleep especially in sleep apnoea which is associated with increased arterial pressure and central venous pressure near the end of sleep apnoea [Jennum and Borgesen 1989]. Increased ICP further decreased cerebral perfusion and reduced CBF. All these could predispose to cerebral infarction.

2.9.3 The haemodynamic aspect of CPAP treatment

Studies dealing with the effect of CPAP on cardiac output and cerebral blood flow also led to variable results. I draw figure 2.1 (P. 88) to illustrate the haemodaynamic interaction between CPAP, SDB and cerebrovascular system based on literature review.

The haemodynamic effect of CPAP on the heart depends on cardiac function. A normal heart is "preload" sensitive but a failing heart becomes "afterload" sensitive. This can explain the reason why CPAP might reduce cardiac output on the normal heart but can be used to treat congestive heart failure (CHF). CPAP improves cardiac output through enhancing contractility in patients with CHF [Genovese *et al.* 1995].

CPAP is also effective in improving cardiac output in patients with concomitant CHF and SDB through abolition of SDB, associated sympathetic hyperactivity and systemic hypertension [Kaneko *et al.* 2003a;Mansfield *et al.* 2004]. On the contrary, the haemodynamic effect of CPAP on the normal heart is either neutral or negative. A study using Doppler echocardiography for normal subjects and sleep apnoea patients found there was no negative effect with increased CPAP pressure (0-15 cm H2O) on heart rate, pulmonary arterial pressure, ventricular size and cardiac index [Leech and Ascah 1991]. The other study using oesophageal catheter to detect intrathoracic pressure and an arterial line to detect SaO2, transmural pulmonary pressure and transmural atrial pressure found both CPAP and bilevel positive airway pressure decreased cardiac index [Becker *et al.* 1995].

CPAP can normalize cerebrovascular reactivity in patients with SDB [Diomedi *et al.* 1998] but only a few studies have been published about the effect of CPAP on CBF. One study revealed CBFV was decreased rather than increased with incremental levels of CPAP pressure in normal adults [Scala *et al.* 2003]. The authors found study subjects had concomitant hypocapnia so they proposed that hyperventilation induced by anxiety when they were wearing CPAP might be the major cause of decreased CBF. From the other point of view, CPAP increases intrathoracic pressure and decreases venous return to heart. This may result in increased intracranial pressure (IICP) and decreased CBF according to the formula:

Cerebral perfusion pressure (CPP) = Mean arterial pressure (MAP) – Intracranial pressure (ICP).

A normal cerebrovascular system has autoregulation by means of vasodilatation in response to decreased CBF and vasoconstriction in response to increased CBF. The study conducted by Scala et al. reminds us that even though autoregulation is intact, decreased CBF may still happen when autoregulation cannot respond to rapid haemodynamic change. This is even more important when we apply CPAP to stroke patients who have had a damaged brain and impaired autoregulation.

Although TCD measures cerebral blood flow velocity (CBFV), TCD is only a surrogate measure of cerebral blood flow (CBF). In summary, CPAP can improve quality and quantity of blood supply to the brain through normalizing SaO2 and improving cerebrovascular reactivity. But, CPAP might decrease CBF through decreasing systemic blood pressure and cardiac output. The net effect of CPAP on CBF also depends on function and response rate of autoregulation in the brain.

2.9.4 Conclusions

All clinical studies about SDB and CBF were indirect as the true measurement was CBFV measured by Transcranial Doppler (TCD). Some studies showed decreased CBFV during apnoeic or hypopnoeic episodes which might predispose ischaemic stroke but other studies, on the contrary, showed increased CBFV which might have protective effect. The studies about the effect of CPAP treatment on CBFV also varied. Although CPAP can normalize cerebrovascular reactivity in patients with SDB one study showed CPAP might be harmful for patients with stroke as it decreased CBFV in normal volunteers.

2.10 Sleep-disordered breathing after Stroke

One major problem with interpretation that SDB causes a stroke is trying to disentangle the effect of the stroke itself on the development of SDB. Two models may help with clarifying this issue. One is to deal with pre-stroke snoring as this may reflect pre-stroke obstructive sleep apnoea and hypopnoea. This will be reviewed in chapter 2.10.1. Another is to use TIA population as there is no neurological sequela in this group of patients. This will be reviewed in chapter 2.10.2.

2.10.1 Snoring as a risk factor for stroke

A few large-scaled cross-sectional case-control studies have reported the association between snoring and stroke. The odds ratio for stroke in patients with snoring was mildly but significantly increased. It ranged from 2.1 (177 patients with cerebral infarction and 177 controls) [Palomaki 1991], 2.2 (300 patients with vascular diseases including stroke and 330 controls) [Smirne *et al.* 1993], 3.2 (326 patients with stroke and 345 controls) [Spriggs *et al.* 1992] to 3.4 (133 patients with cerebral infarction and 133 controls) [Neau *et al.* 1995]. They were still biased in the following points:

- They recruited patients with previous stroke.
- They used questionable control group including (1) controls from patients with non-vascular disease; (2) patients from the other hospitals; (3) not an age- and sex-matched control.
- Recall bias
- Incomplete control for confounding factors

A matched case-control study was subsequently performed by the research group in the University of Newcastle [Davies *et al.* 2003]. Patients with first-ever stroke and community control subjects matched individually for age, gender and source (general practitioner) were recruited. A structured questionnaire was used to identify snoring, daytime sleepiness and stroke risk factors. The results showed that there was no significant difference of reported snoring between stroke patients and control

subjects with an odds ratio of 1.44 (96% = 0.88-2.41, p = 0.15). However, daytime sleepiness was significantly associated with stroke which might reflect the relationship between SDB and stroke.

A prospective cohort study showed a higher stroke incidence in snorers (28 out of 302 snorers) than in non-snorers (21 out of 396 non-snorers) during the 6-year follow-up period [Jennum *et al.* 1994]. The odds ratio was 1.82 (95% CI = 1.09-3.64, $p < 0.05$). After adjusting for confounding factors by a Cox regression model, snoring was no longer an independent risk factor for stroke with a relative risk of 1.26 (95% CI = 0.70-2.29, p = 0.42).

The above two studies with better methodology than previous publications tell us that simple snoring may not be an independent risk factor for stroke.

2.10.2 Prevalence of SDB after stroke

In the past decade, more attention has been paid to the link between SDB and hypertension since cross-sectional parts of large population-based cohort studies have been published. Sleep Heart Health Study (SHHS) with large sample size (n > 1000) found that increased apnoea/hypopnoea index (AHI) and percentage of time with oxyhaemoglobin saturation (SaO2) < 90% were associated with increased risk of hypertension after adjusting for confounding factors [Nieto *et al.* 2000]. Although they also found that the association between SDB and stroke was stronger than SDB and coronary heart disease (CAD), the relative odds ratio of the highest quartile of AHI in predicting stroke was not high (1.58, CI 1.02-2.46) [Shahar *et al.* 2001]. The shortcoming is that they used self-reported history of stroke only.

High prevalence of SDB after stroke and transient ischaemic attack (TIA) was reported in four cross-sectional studies with or without controls. They are summarized and compared (Table 2.1, P. 85). The sample size, definitions of SDB and stroke in these studies varied. The first study with full PSG, detailed clinical stroke assessment and sufficient power (n = 128) found that the prevalence of SDB in TIA was similar to that in stroke. This led to the conclusion that SDB could be a

cause rather than a consequence of stroke [Bassetti and Aldrich 1999b]. The second study with similar methodology and power (n = 161) further supported this concept by conducting a longitudinal follow-up from the acute phase to the stable phase of stroke and showing that obstructive sleep apnoea remained little changed while central sleep apnoea became less frequent during the course of either infarction or haemorrhage [Parra *et al.* 2000;Harbison *et al.* 2002b]. The third study also showed decline of AHI during the course of stroke without further clarification of the difference between obstructive and central events [Harbison *et al.* 2002b].

There had been no strong objection to the link between SDB and cerebrovascular diseases until the fourth study, a individually matched case-control TIA study, was published with competitive methodology which showed no significant difference of AHI (21/hour) between TIA and a matched control group from the community [McArdle *et al.* 2003]. Although this was a well designed study with sufficient power (n = 86 pairs), there are still some controversial points as they acknowledged: (1) There is a recall bias because TIA is a diagnosis based on history only; (2) There is a selection bias because the TIA patients who declined could have less SDB symptoms and on the contrary, the controls who attended could have more SDB symptoms; (3) Cerebrovascular diseases comprise a spectrum of heterogeneous entities and TIA can not stand for all of them. Thus further evidence is still needed to either support or refute previous hypotheses and findings.

2.10.3 Screening of SDB in stroke

Prediction models of SDB in the general population, which have been reviewed in chapter 1 could help in the screening of SDB. Prediction models of SDB in stroke patients might be more helpful as it is more difficult to perform sleep studies for patients with acute or subacute stroke. A study applied a structural SDB questionnaire to stroke patients with a standardized score and cut-off point, which has been shown to have good sensitivity and specificity (> 80%) to predict SDB in non-stroke subjects based on the diagnosis of PSG [Bassetti and Aldrich1999b]. It concluded that the diagnostic accuracy of questionnaire-based predictive models in

stroke was low. It is still convenient for first-line physicians if a similar prediction model can be used as a screening rather than a diagnostic tool for SDB in stroke, before making the decision to refer patients for overnight sleep study. This can avoid unnecessary burden, suffering and extra cost.

2.10.4 SDB and onset time of stroke

Studies using 6-hour time bins have found that most strokes were first noticed in the morning between 6 am and noon [Elliott 1998]. The time of onset of stroke in patients with SDB seems to be similar to that in the general stroke population [Bassetti and Aldrich 1999a]. Two mechanisms have been proposed for the onset of stroke and myocardial infarction being highest in the morning: (1) increased prothrombotic state, including blood viscosity and platelet activation, in the morning [Andrews *et al.* 1996;Koeltringer *et al.* 1990] (2) rise in blood pressure in the morning [Bursztyn 2002;Kario *et al.* 2003]. Both these mechanisms are present in the normal population but could conceivably be accentuated in those with SDB [Nobili *et al.* 2000].

There were only three published papers dealing with snoring, SDB and onset time of stroke. The first paper showed snoring was a risk factor for sleep-related brain infarction [Palomaki *et al.* 1989]. The second paper, focusing on AHI rather than snoring, showed that AHI and other sleep characteristics did not differ between patients with daytime (6 am – midnight) and nighttime (midnight – 6 am) onset of stroke [Bassetti and Aldrich1999a]. The third paper [Iranzo *et al.* 2002] revealed that AHI $\geq$ 25 was the only independent predictor for sleep-related stroke (OR = 1.02, 95% CI = 1.00-1.05). In that study [Iranzo *et al.* 2002], two thirds of sleep-related strokes happened between 6 and 9 am. The hypoxaemia associated with SDB is usually more severe in the latter half of nocturnal sleep which has a higher density of rapid eye movement (REM) sleep. The authors proposed that SDB had a direct impact on stroke onset through haemodynamic compromise. Although the morning surge of blood pressure may have an influence on stroke onset and patients with SDB

have sympathetic hyperactivity [Fletcher 2003] and haemodynamic changes [Franklin 2002;Netzer *et al.* 1998] the role of SDB in stroke onset is still not clear.

2.11 Treatment of SDB in stroke

2.11.1 The clinical value of CPAP treatment in stroke

As high prevalence of sleep-disordered breathing (SDB) in stroke was described previously, screening of SDB in stroke is more meaningful if treatment of SDB in stroke is effective. There are currently three domains of treatment for SDB in terms of nasal continuous positive airway pressure (CPAP), oral appliance and surgery. CPAP is the standard and most commonly prescribed method. I have reviewed the benefit of treating SDB with CPAP in non-stroke subjects in chapter 1 and 2. In brief, CPAP not only improves daytime sleepiness, cognitive performance, mood, and health-related quality of life but also reduces blood pressure and other cardiovascular risk factors including sympathetic activity, heart rate variability, platelet aggregation, blood viscosity, and adhesion molecules.

The efficacy, safety and feasibility of CPAP need to be reassessed before applying it to patients with concomitant SDB and stroke. The problems include whether these patients can tolerate CPAP, whether treatment of CPAP is effective and whether the benefit of CPAP outweighs the adverse effects. For instance, CPAP can prevent patients who receive gastrointestinal surgery from post-operative hypoventilation but CPAP might theoretically cause anastomotic leaks which could compromise the outcome [Huerta *et al.* 2002]. Theoretically CPAP has a haemodynamic effect on the whole body from heart, blood vessels to brain. Haemodynamic changes are one of the factors determining the outcome of stroke. Ischaemic penumbra in acute stroke and neuronal plasticity in subacute and recovery phase of stroke may be sensitive to swing in cardiac output, systemic blood pressure and cerebral blood flow (CBF). This means haemodynamic compromise (bradycardia) might play a role in the onset of stroke. The following haemodynamic effects of CPAP treatment should be considered before applying it to stroke patients:

- CPAP might improve cerebrovascular reactivity in patients with SDB on one hand but might decrease CBF in normal adults on the other.

- Although CPAP can reduce blood pressure in non-hypertensive patients with SDB it is still unclear whether CPAP also reduces blood pressure in stroke patients and whether reduction of blood pressure following CPAP treatment in the acute or subacute phase of stroke compromises CBF.

2.11.2 Comparison between previous CPAP trials for SDB in stroke

There are only four published original articles about CPAP trial for SDB in stroke (Table 2.2, P. 86). Two studies were conducted in Europe [Sandberg *et al.* 2001a;Wessendorf *et al.* 2001], one in Australia [Disler *et al.* 2002] and the other one in Asia [Hui *et al.* 2002]. Another short CPAP trial was published as "Letter to the Editor".

The Swedish group first showed in a cross-sectional study that SDB was significantly associated with depressive symptoms measured by Montgometry-Åsberg Depression Rating Scale (MADRS) in stroke [Sandberg *et al.* 2001b]. They further studied 59 patients who were randomized through lots drawn by a person not involved in the study [Sandberg *et al.* 2001a]. Thirty-one patients were randomized to CPAP starting between 7 and 28 days after stroke for 4 weeks. Twenty-eight patients were randomized to control without CPAP. Outcomes were assessed at 7 and 28 nights respectively in terms of functional capacity (Barthel Index, BI), cognition (Mini-mental State Examination, MMSE), mood (Montgometry-Åsberg Depression Rating Scale, MADRS) and delirium. They found CPAP could effectively improve depressive symptoms in stroke patients with SDB. There was no difference in functional capacity, cognition and delirium. As the prevalence of anxiety and depression is high (20-50%) following stroke and post-stroke depression is associated with stroke severity and functional impairment [Berg *et al.* 2003] this finding from the Swedish group is interesting.

The study conducted by a German group [Wessendorf *et al.* 2001] had a larger sample size (n = 105) but it was not a randomized control trial. They assigned CPAP to all patients at 51-69 days of stroke and used non-compliant patients as a control for

comparison. CPAP was applied independently in patients who could tolerate and use it at home after discharge. Assessment was performed 1 week after stroke. Only 41 unselected patients received measurement of wellbeing by a Visual Analogue Scale and only 16 unselected patients received measurement for ambulatory blood pressure (ABP). They found that those with CPAP acceptance ($n = 28$) had improved wellbeing but those without CPAP acceptance ($n = 13$) did not ($p = 0.021$). They also found those with CPAP acceptance ($n = 11$) had significant reduction in mean nocturnal arterial blood pressure but no pressure change was found in those without CPAP acceptance ($n = 5$, $p = 0.037$).

The study conducted by the Hong Kong group recruited 34 patients for a CPAP trial of 3 weeks [Hui *et al.* 2002]. This is not a randomized controlled trial either. Thirty-four patients who had AHI ≥ 10 were prescribed CPAP. However, 14 patients refused to take part in the treatment and 4 patients could not tolerate overnight CPAP titration. Only 4 of 16 patients who had successful CPAP titration proceeded to home CPAP treatment. They did not perform outcome measurement following CPAP treatment.

The study conducted by the Australian group was presented as a brief report because they recruited 38 patients for an overnight sleep study but only recruited 5 patients for CPAP trial without randomization [Disler *et al.* 2002]. There was no end of treatment phase and all 5 patients were happy to use CPAP at home. They did not measure outcome either.

In another British study published as "Letter to the Editor" showed none of 15 stroke patients used CPAP [Harbison *et al.* 2002a]. It is unclear why compliance has varied so much between studies but it is likely to reflect differences in patient selection, environment in which treatment is given, the CPAP system used and the amount and type of support and training given.

The above studies had the following methodology limitations:

- There was a wide time span of recruiting patients from a few weeks to a few months after stroke. Some patients might have reached the plateau of recovery before they were enrolled in the studies.
- There was only one randomized controlled trial. The others were either non-randomized controlled or non-controlled trials.
- Only two studies conducted an outcome assessment but even in these, the spectrum of measurement was incomplete.

2.11.3 Practical problems of CPAP compliance in stroke

The major problem of CPAP treatment in non-stroke subjects is compliance. Stroke patients are rarely referred for the diagnosis of SDB due to sleepiness or other major SDB-related symptoms. Patients with SDB but without excessive daytime sleepiness (EDS) have poor compliance to CPAP and the treatment is less effective [Barbe *et al.* 2001].

The CPAP compliance in German and Sweden groups was good. Seventy-four (70.5%) of 105 patients in the German group continued CPAP treatment at home [Wessendorf *et al.* 2001] although compliance was not reported in detail. Sixteen (51.6%) of 31 patients in Sweden group used CPAP for more than 4 hours per night with a mean of 4.1 ± 3.6 (0-10.9) hours [Sandberg *et al.* 2001a]. The CPAP compliance in the Hong Kong group was poor [Hui *et al.* 2002]. Only 4 (11.8%) of 34 patients proceeded to home CPAP treatment without other detailed information. A British group from Newcastle wrote "a letter to the editor" to doubt previous results with good CPAP compliance. They had 15 stroke patients who had SDB for CPAP trials but none of them accepted CPAP treatment [Harbison *et al.* 2002a]. There was no report of CPAP compliance for 5 patients in the Australian group [Disler *et al.* 2002].

As described in chapter 1, auto-titrating CPAP (auto-CPAP) can save time from in-lab CPAP titration and maintain a minimal necessary pressure [Ficker *et al.* 1998;Ficker *et al.* 2000]. It may be more suitable for stroke patients to prevent them from extra traffic between hospitals and increase tolerability to CPAP pressure. There

are two major problems need to be clarified: (1) the value of unattended auto-CPAP when applied to CPAP naïve patients without in-lab titration [Littner *et al.* 2002]; (2) whether central sleep apnoea and Cheyne-Stokes respiration which are more common in stroke will interfere with pressure determination by auto-CPAP.

2.12 Sleep-disordered breathing and the outcome of stroke

2.12.1 Sleep-disordered breathing acting on the brain

I have reviewed in chapter 1 that the major manifestations of sleep-disordered breathing (SDB) are, in brief: (1) cognitive deficits in terms of vigilance (excessive daytime sleepiness, difficulty in maintaining wakefulness), attention, memory and executive functions; (2) psychosocial maladjustment in terms of mood and health-related quality of life.

Understanding the prognostic factors of stroke can let us, on one hand, avoid unnecessary treatment for those who may have a good outcome independent of treatment and, on the other hand, deal with those treatable factors more precisely. Many factors might affect functional outcome of stroke and sleep-disordered breathing (SDB) is one of them through the following two mechanisms:

- SDB indirectly affects the outcome of stroke through causing or enhancing other prognostic factors such as mood, cognition and motivation for rehabilitation
- SDB directly affects the outcome of stroke through compromising the recovery of the damaged central nervous system

The underlying causes of major clinical manifestations of SDB are still controversial. Most studies support the following two mechanisms and these are also common in stroke:

- Sleep fragmentation
- Nocturnal hypoxaemia.

Sleep fragmentation and nocturnal hypoxaemia are also common in stroke. It is not easy to deal with sleep fragmentation and nocturnal hypoxaemia separately in clinical studies of SDB. SDB causes frequent arousals which results in sleep fragmentation, disruption of sleep architecture and sleep loss [Douglas and Martin 1996]. The major difference in sleep architecture between patients with SDB and

normal control is that patients with SDB have less slow wave sleep (stage III and IV) and REM sleep. This kind of change is also similar in stroke. A study showed that patients with stroke had decreased sleep efficiency, total sleep time, rapid eye movement (REM) sleep and slow wave sleep [Muller *et al.* 2002].

Hypoxaemia is one of major physiological changes in SDB. Patients with stroke also have higher risk of developing hypoxaemia due to impaired central regulation of breathing, weakness of respiratory musculature and respiratory complications. I will review the objectives in the following two sections.

Recent evidence has shown that SDB is directly associated with "neuronal loss". Neuronal loss is a major consequence of stroke especially infarction. A study using magnetic resonance spectroscopy (MRS) showed that N-acetyl aspartate (NAA) decreased in the grey and white matter of patients with SDB due to cell death. The other two studies using magnetic resonance imaging (MRI) also showed decreased volume of grey matter in the multiple areas of brain especially hippocampus [Macey *et al.* 2002;Morrell *et al.* 2003]. Seven-eight previously independent patients with acute stroke were recruited in another study. CT scans of brain were performed within 72 hours of admission and evaluated independently by two neuroradiologists blind to the sleep study results with good agreement [Harbison *et al.* 2003]. The presence or absence of pre-stroke cerebrovascular diseases was determined using validated Age-Related White Matter Change (ARWMC) Scale. The result showed SDB was worse in subjects with pre-stroke cerebrovascular disease than in those without (mean AHI = 35 ± 21 vs. 23 ± 10, $p < 0.01$). Multiple regression analysis was performed and the only factor independently associated with AHI was presence of pre-stroke cerebrovascular disease. There are two implications from these pioneering studies of brain morphology when we take treatment of SDB in stroke and impact of SDB on the outcome of stroke into account:

- Pre-stroke neuronal loss might exist in patients with SDB so they might have worse neurological status at admission and lower chance of recovery.
- CPAP treatment might not be completely successful in stroke as there has been some permanent damage in the brain.

2.12.2 The association of SDB with other prognostic factors in stroke

Sleep-disordered breathing was reported to be associated with other prognostic factors of stroke:

- Age and severity of stroke

Age and severity of stroke are two most important factors determining the functional outcome. A prospective study with a large sample size (1079 patients for generating the predictive model and 1307 patients for external validation) showed that old age and initial NIH Stroke Scale (NIHSS) measured within 6 hours of stroke were associated with both incomplete functional recovery (Barthel Index < 95) and mortality [Weimar *et al.* 2004]. A recently published study from the Department of Clinical Neuroscience in Edinburgh University tried to simplify the predictive model for the outcome of stroke into six variables. Most of them are related to initial severity [Counsell *et al.* 2004]. SDB is common in the elderly. Age might be a confounder of SDB for the outcome of stroke. Thus controlling for initial severity of stroke and age should be considered first when we deal with the impact of SDB on the outcome of stroke.

- Gender

A European multi-centre study involving 7 countries and recruiting 2239 male and 2260 female patients showed that female sex was a significant predictor for disability and handicap after controlling for baseline variables [Di Carlo *et al.* 2003]. SDB is more common in middle-aged men than women but women after menopause have increased prevalence of SDB. If two groups of stroke patients, one with SDB and the other without, were compared for the outcome the group with SDB might be male predominant and the better outcome might be confounded by the effect of gender difference.

- Excessive daytime sleepiness (EDS)

There is no direct evidence that people with SDB have more severe strokes than people without it. Study conducted by Newcastle University in the UK found pre-stroke EDS was correlated with Barthel score at week 2 after stroke [Harbison *et al.* 2002b]. Pre-stroke EDS is not equal to SDB but might reflect a group of symptomatic SDB (SDB with EDS). This implies that pre-stroke EDS might be associated with initial severity of stroke or early neurological deterioration after stroke as the latter has been published [Iranzo *et al.* 2002].

Sleep fragmentation independently causes EDS in patients with SDB [Bennett *et al.* 1998] but seems not significantly associated with EDS in stroke [Vock *et al.* 2002]. This means EDS in stroke either share different underlying mechanism as EDS in SDB or has a broader spectrum of causes. There is no further study dealing with EDS and outcome of stroke.

- Cognition and depression

Cognitive impairment and depression are interrelated. Both of them are associated with functional outcome of stroke. A prospective cohort study following up 286 stroke patients aged 55-85 years found worsening of Mini-mental State Examination (MMSE) and Beck Depression Inventory (BDI) at three months after stroke were independent predictors for dependent living at 15 months [Pohjasvaara *et al.* 2002b]. The same research group also found that executive dysfunction was most significant cognitive impairment related to post-stroke depression [Pohjasvaara *et al.* 2002a].

The function of human sleep is still not very clear but basically slow wave sleep is reported to be associated with neuronal restoration and rapid eye movement (REM) sleep, associated with memory consolidation. Decreased slow wave sleep and REM sleep can also result in cognitive deficits [Verstraeten *et al.* 1996]. SDB has been associated with neuropsychological deficits in the domains of vigilance, attention, memory and executive function. Previous studies showed that impaired vigilance in patients with SDB is mostly explained by sleep fragmentation resulting from frequent arousals [Colt *et al.* 1991]. Executive dysfunction in frontal lobe-related tests is mostly explained by nocturnal hypoxaemia [Naegele *et al.* 1995]. Memory

impairment in SDB might also be due to frontal and subcortical mechanism [Salorio *et al.* 2002] which are similar to neuropsychological deficits of vascular dementia due to stroke [Kertesz and Clydesdale 1994]. From the above points of view SDB and stroke may share common cognitive deficits.

There are two possibilities regarding cognitive deficits in patients with both SDB and stroke: (1) the cognitive deficits resulting from SDB exacerbate the existing cognitive deficits in stroke; (2) the cognitive deficits resulted from SDB are intermixed and masked by the existing cognitive deficits in stroke. If this latter point is predominant, the impact of SDB or the treatment effect of SDB on the cognitive outcome of stroke might be less prominent.

Psychosocial maladjustment in stroke usually depends on cognitive deficits in which impaired vigilance and attention play a more important role than other neuropsychological deficits. CPAP can reverse both EDS and psychosocial maladjustment but the effect of CPAP on other neuropsychological deficits is only partial [Naegele *et al.* 1998].

Many studies pointed out that post-stroke depression is associated with increased morbidity. Stroke patients with negative thoughts and fatalism are also associated with increased mortality [Dennis *et al.* 2000].

- Other cardiovascular risk and prognostic factors

Blood pressure, atrial fibrillation and hyperglycaemia are three of the proposed prognostic factors for the outcome of stroke in which SDB might play a role. Control of blood pressure has been discussed in chapter 5. Extremely high or relatively low blood pressure is harmful in acute and subacute stroke. SDB might be associated with abnormal swings of blood pressure and haemodynamic change in these stages. SDB might predispose to recurrence of atrial fibrillation which not only potentiates haemodynamic compromise but also increases the possibility of recurrence of stroke. A study found that recurrence of atrial fibrillation was much higher (82%) in patients with non-treated or mal-treated SDB in contrast to 42% of CPAP-treated patients and 53% of control [Kanagala *et al.* 2003]. The association of SDB and diabetes is

largely explained by obesity as reported in Sleep Heart Health Study [Resnick *et al.* 2003]. The other study which used enzyme immunoassay to measure insulin and calculate insulin resistance found, after adjusting for BMI in a regression model, that AHI was still independently associated with insulin resistance [Ip *et al.* 2002]. If so, SDB might worsen hyperglycaemia in stroke and result in poor outcome.

2.12.3 The hypothesised model of SDB on the outcome of stroke

According to the above reviews, I propose a hypothesis of the impact of SDB on the outcome of stroke (Figure 2.2, P. 89).

SDB can cause nocturnal hypoxaemia which compromises neuronal function and results in poor emotional, cognitive and functional outcome. SDB might be associated with haemodynamic swing due to change of blood pressure or induction of atrial fibrillation. SDB might also be associated with hyperglycaemia due to increased insulin resistance. All these factors deteriorate ischaemic penumbra or neuronal plasticity in patients with acute or subacute infarction in the brain, resulting in further neuronal death and permanent brain damage.

SDB causes sleep fragmentation. It decreases vigilance, increases EDS and results in poor emotional and cognitive outcomes. SDB not only reduces rapid eye movement (REM) sleep which results in impaired memory consolidation and cognitive function but also reduces non-rapid eye movement (NREM) sleep which cause neuronal dysfunction, neuronal death and permanent brain damage.

Poor emotional and cognitive outcomes might result in poor motivation in attending rehabilitation programmes in stroke which further compromises functional outcome. All above three outcomes are associated with poor health-related quality of life in stroke.

2.12.4 Comparison between previous studies for SDB and the outcome of stroke

There are only seven published original articles about SDB and the functional outcome of stroke. Four studies were conducted in Europe, two in North America and one in Israel. The comparison is shown (Table 2.3, P. 87).

The first paper published by the American group applied the Barthel Index (BI) which is one of the most commonly used scales for functional outcome [Good *et al.* 1996]. They conducted oximetry for 47 stroke patients and had extra full polysomnography for 19 of them. They found that the desaturation index (DI) which was obtained by oximetry and defined as number of desaturation < 4% per hour underestimated AHI which was obtained by polysomnography although DI might be closer to AHI than other oximetric variables. The analysis still depended on oximetric variables including desaturation index (DI), mean SaO2 and percentage of time with SaO2 < 90%. The results showed oximetric variables were significantly correlated with lower BI score at discharge, 3 and 12 months after stroke but the correlation of oximetric variables and BI were more prominent in mean SaO2 and time at SaO2 < 90% than DI. Mortality at one year (n = 5) was also correlated with mean SaO2 and percentage of time with SaO2 < 90%. They did not adjust for baseline data. There was no direct correlation between functional outcome and AHI.

The second paper published by the British group at Newcastle University mainly focused on a longitudinal change of AHI between 2 weeks and 6-9 weeks [Harbison *et al.* 2002b]. The device they used for limited sleep studies consisted of only two physiological channels, oximetry and nasal cannula. They also performed BI and Scandinavian Stroke Scale at these two time points. They found there was no difference in mortality or neurological recovery between patients in whom SDB improved or deteriorated. The change in AHI did not correlate with change of neurological deficits or functional capacity. They didn't compare outcome between two groups according to a cut-off point of AHI.

The third paper published by the Spanish group recruited 50 patients who had had their first-ever stroke. They conducted polysomnography on the first night after stroke onset. They found SDB (dichomatised by AHI ≥ 10), AHI and oxyhemoglobin desaturation (percentage of time with SaO2 < 90%) were independently associated with early neurological worsening after adjusting for initial severity of stroke. During longitudinal follow-up there was no significant difference of BI and Scandinavian Stroke Scale between groups with AHI < 10 and ≥ 10 at 1, 3 and 6 months after stroke.

The fourth paper published by the Israel group replaced BI by a more detailed Functional Independence Measure (FIM) [Cherkassky *et al.* 2003]. They conducted oximetry for the diagnosis of SDB. The total sample size was only 30. In univariate analysis, there was a trend that patients with AHI > 10 defined by number of fall of SaO2 ≥ 4% per hour (usually taken as DI) had lower FIM scores and FIM gain on discharge but power might be too low to show statistical significance. In multivariate analysis by controlling confounders at baseline especially severity of stroke they found that RDI was an independent predictor for FIM gain (adjusted R-square = 0.209, p = 0.025). The negative coefficient means that the higher the RDI the smaller the functional improvement. This finding was not strong because the total model could only explain 20.9% of the total variance. They also found that patients in more severe group (FIM < 70) had the worst outcome. The sample size might be too small to show significance as well (p = 0.085).

The fifth paper published by Canadian group also used the FIM [Kaneko *et al.* 2003b]. They conducted polysomnography (PSG) for 60 stroke patients. After adjusting for Canadian Stroke Scale and MMSE at baseline using multiple linear regression, they showed obstructive AHI was an independent predictor for FIM score at discharge from rehabilitation ward (p = 0.030). The term "at discharge" in their study was vague in definition. After adjusting for CSS, they also found that obstructive AHI was an independent predictor for total length of hospitalization (p = 0.043) in chronic rehabilitation units. The latter is an unique finding, which, if confirmed, could have a major influence on the total cost of stroke in-hospital care

and enable the treatment of SDB in stroke to be cost-effective by decreasing the total length of patient hospitalization.

The sixth paper published by Spanish group focused on mortality of the same cohort [Parra *et al.* 2004] about four years after they published the paper regarding the longitudinal changes of the frequency of sleep apnoea and hypopnoea in 161 patients following stroke or TIA [Parra *et al.* 2000]. A limited sleep study was conducted in all cases and the entire cohort was followed by a structured telephone interview. The mean duration of follow-up was 22.8 months (range 0.4-32 months). The wide range of follow-up time was due to patients died (13.7%) during this period. In the univariate analysis age, AHI and Cheyne-Stokes respiration (CRS) were associated with mortality. In multi-variate analysis by Cox's proportional hazard model age (hazard ratio = 1.14, 95% CI = 1.06-1.21, p = 0.000), AHI (obstructive predominantly, hazard ratio = 1.05, 95% CI = 1.01-1.08, p = 0.004), middle cerebral artery (MCA, hazard ratio = 2.86, 95% CI = 1.04-7.84, p = 0.04) stroke and concomitant coronary artery disease (CAD, hazard ratio = 3.25, 95% CI = 1.05-10.03, p = 0.04) were independent predictors of mortality after adjusting for other confounders.

The seventh paper published by a British group recruited 120 unselected stroke patients admitted to hospital in the UK who might be representative of hospitalized stroke patients in the UK [Turkington *et al.* 2004]. They had PSG recordings for 24 hours soon after admission and this might reflect the true RDI in patients with acute stroke because most stroke patients during this stage are bed-ridden and may fall asleep for most of the time. Follow-up for 6 months was obtained in all but 6 patients. The regression analysis after adjusting for confounders showed both 24-hour and light-out RDI, which were predominantly obstructive, were significant predictors for mortality. The minimal oxygen saturation was an independent predictor for disability (Barthel Index). This did not directly link SDB to poor functional outcome because desaturation during acute stroke can be caused by many factors other than SDB, for example, aspiration pneumonia.

2.13 Discussion

There were inconsistent findings regarding the link between SDB and cardiovascular risk factors. Only hypertension was independently associated with SDB based on several well-designed large-scaled prospective case-control and cohort studies. Several randomized controlled trials also showed that reduction of blood pressure by CPAP was minimal but clinically significant. Hypertension is one of the major risks of stroke. Thus CPAP may have a role in the secondary prevention of stroke.

A high prevalence of SDB in stroke and poor outcome of stroke in patients with SDB have been reported in cross-sectional studies. These raise the question whether treatment of the SDB might improve outcomes. However, stroke patients may have physical difficulty coping with CPAP. CPAP may further decrease cerebral blood flow velocity. The role of CPAP for treatment of SDB in stroke needs further research to support.

There have been few trials of CPAP for SDB in stroke, and only one involved random allocation to CPAP or control. CPAP had no effect on recovery from stroke but there were fewer depressive symptoms amongst those treated with CPAP. Some other non-randomised studies have also been published. However, CPAP use was poor. Based on these studies some centres are now using CPAP to treat SDB after stroke.

Therefore, we performed a further randomized controlled trial in stroke patients with SDB to clarify whether CPAP is beneficial. Particularly, we hypothesised firstly that nasal CPAP might improve sleepiness, fatigue, cognitive function and mood in stroke patients with SDB and making them more compliant with rehabilitation. Secondly, we hypothesised that nasal CPAP may stabilize circadian blood pressure in the recovery phase of stroke; and thus CPAP would result in better functional outcome.

Table 2.1 Previous studies for the prevalence of SDB after cerebrovascular diseases (CVD)

	Bassetti et al 1999	Parra et al 2001	Harbison et al 2002	McArdle et al 2003
Sample size	128	161	68	86
Type of CVD	TIA (n = 53), infarction (n = 75)	TIA (n = 39), infarction (n = 112), haemorrhage (n = 10)	Infarction (n = 66), haemorrhage (n = 2)	TIA
First ever stroke	61/75	100%	80%	-
Stroke severity	SSS = 38 (2-58)	CSS = 7.9 ± 2.2	SSS = 26 ± 16	-
Control group	+ (n = 25)	-	-	+ (n = 86)
Diagnosis of SDB	Polysomnography	Limited sleep study	Limited sleep study	Polysomnography
Time of study (after stroke)	9 days (1-71 days)		10 days	-
Mean age	59 ± 15 (19-80)	72 ± 9	73	65 ± 11
Male: Female	71:57	82:79		
AHI > or ≥ 5 (control)				12% (13%)†
AHI > or ≥ 10 (control)	62.5% (12.5%)	72%	94%	-
AHI > or ≥ 20	31%	-	66%	-
AHI > or ≥ 30	12.5%	28%	46%	-

SSS: Scandinavian Stroke Scale; CSS: Canadian Stroke Scale; †: SDB associated with EDS

Table 2.2 Previous CPAP trials for SDB in stroke

	Wessendorf et al 2001	Sandberg et al 2001	Disler et al 2002	Hui el al 2002
Sample size	105	59	5	34
Randomization	–	+	–	–
Control	± (Noncompliant)	+ (No CPAP)	–	–
Mean age	61	77, 78	65 †	64
Male: Female	3:1	1:1	N/A	1:1
Diagnosis of SDB	Polysomnography	Limited sleep study	Limited sleep study	Polysomnography
Severity of SDB	AHI = 38	$(A+H)\cdot h^{-1} = 28$ †	$(A+H)\cdot h^{-1} = 15$	AHI = 23
Severity of stroke	BI = 15/20	BI = 8/20	FIM Motor = 53/91	BI = 14/20
Timing of treatment ‡	51-69 days	14-28 days	7-35 days	< 7 days
Duration of treatment	N/A§	4 weeks	N/A§	3 months
Timing of follow-up	10 days	7 and 28 days	–	N/A
Dimension of measurement	WB, ABP #	FC, COG, WB	–	–

† Median; ‡ If not described, it is estimated according to timing of sleep study; § During admission and after discharge

For 41 and 16 patients respectively; FC: functional capacity, COG: cognition, WB: wellbeing, ABP: ambulatory blood pressure

Table 2.3 Comparison of previous studies about SDB and the outcome of stroke

	Good 1995	Harbison 2002	Iranzo 2002	Cherkassay 2003	Kaneko 2003	Parra 2004	Turkington 2004
Sample size	47	43 †	50	30	60	161	120
Mean age	69 (median)	73	66/67*	57/65*	63/68*	72	79
Sleep study	PSG (n = 19), Oximetry	Limited sleep study	PSG	Oximetry	PSG	Limited sleep study	PSG
Time of Dx	1-7 d	8-14 d	12 ± 5 h	57 ± 53 d	45 ± 3 d	48-72 h	24 h
AHI/DI	36 §	30	28	37% (DI ≥ 10)	4/27*	21	30
AHI/DI cut-off	10	N/A	10	10	10	N/A	10
Stroke severity	BI = 6 #	BI = 7	SSS = 40/36*	FIM = 70/67*	BI = 6 ± 3 #	BI = 15/14§	BI = 3
Follow-up	3, 12 mo	2, 6-9 wk	3 d, discharge, 1,3,6 mo	Discharge	Discharge	0.4-32 mo	6 mo
Outcomes in SDB	Lower BI on 3,12 mo, mortality on 12 mo	Lower BI on 2, 6-9 wk ‡	Deterioration of SSS on 3 d	Lower FIM on discharge	Lower FIM on discharge, longer hospitalizatio n	Higher mortality	Higher mortality, lower BI with desaturation

† N = 68 for sleep study; ‡ Median; * divided by the cut-off point of AHI/ODI; § divided by alive or dead; # Original 100 points BI is converted into 20 points BI for easy comparison; ‡ associated with pre-stroke sleepiness; PSG: polysomnography; AHI: apnoea hypopnoea index; DI: desaturation index; BI: Barthel Index; SSS: Scandinavian Stroke Scale; FIM: Functional Independence Measure

Figure 2.1 The influence of SDB and CPAP on haemodynamics and cerebral blood flow

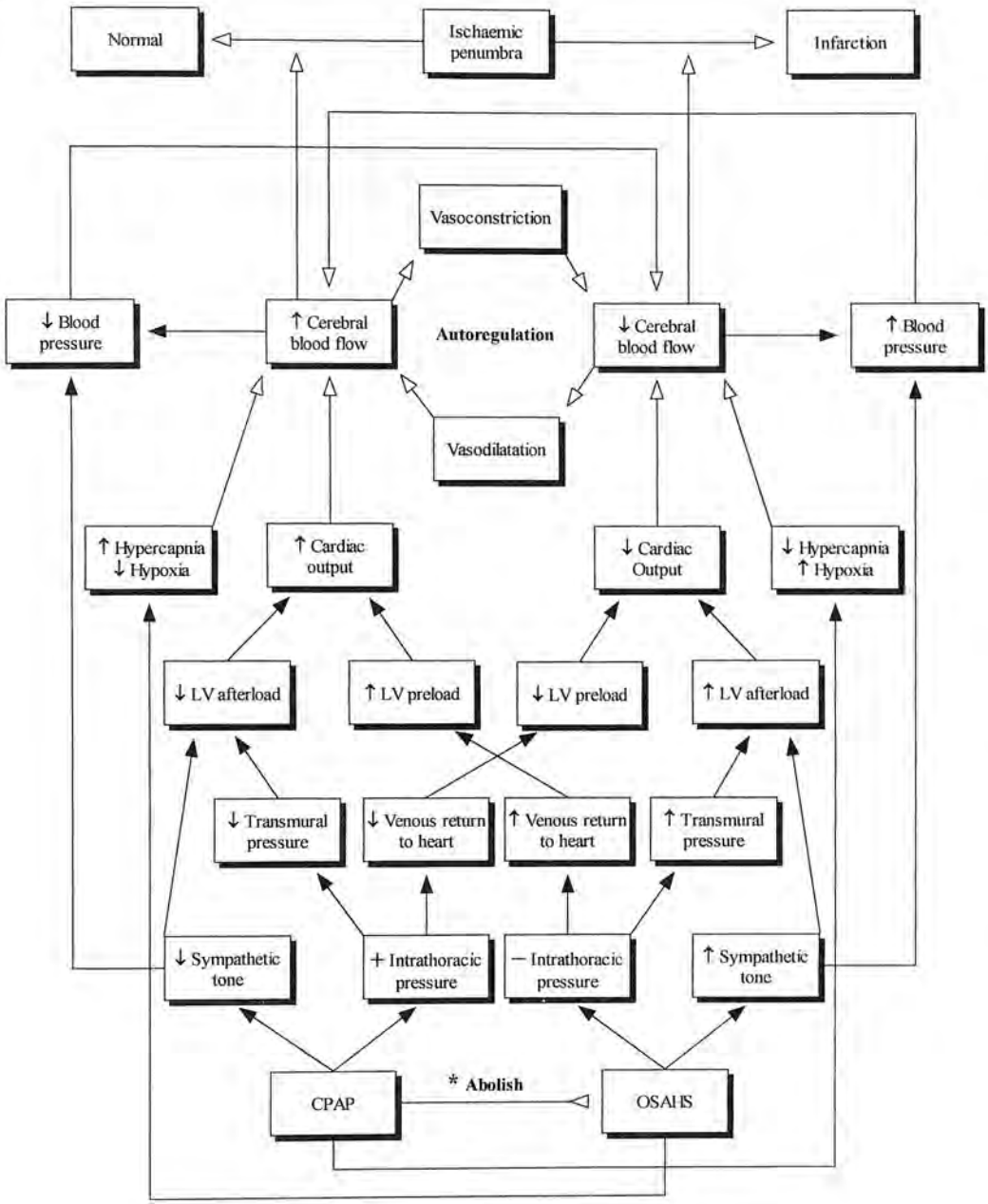
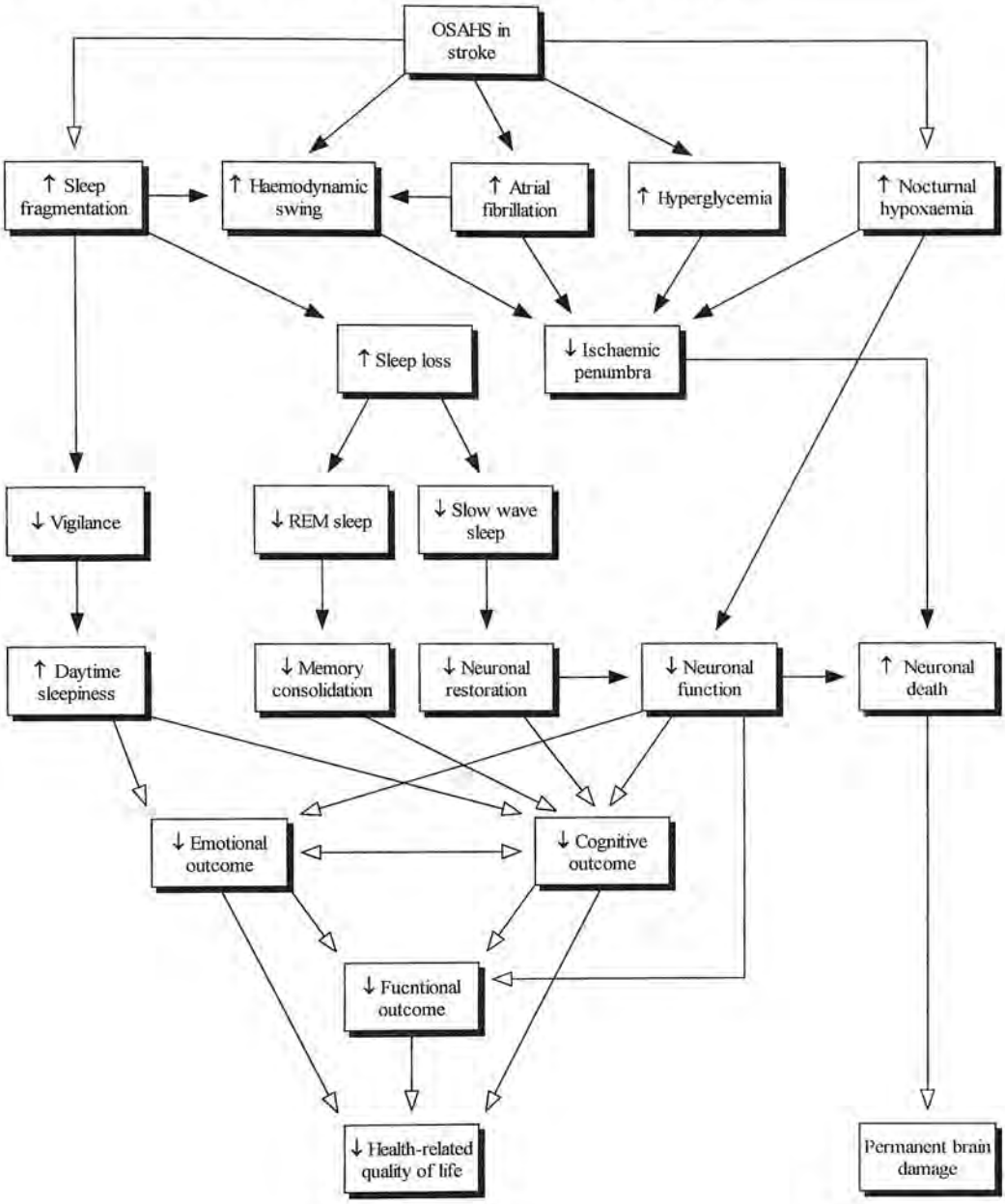


Figure 2.2 The impact of SDB on the outcome of stroke



Chapter 3 General Methodology of Measurement, Recruitment, Randomization and Data Analysis

3.1 Introduction

This three-stage study of sleep-disordered breathing (SDB) after stroke was conducted with the participation of mild to moderately affected stroke sufferers. I hypothesised that: (1) SDB is related to stroke outcome and (2) treatment of SDB in stroke patients with CPAP would improve functional outcome. The study included observational and intervention phases and a longitudinal follow-up conducted serially within a single patient cohort. I recruited consecutive stroke patients from March 2001 until June 2003 in four NHS teaching hospitals of Edinburgh University: Western General Hospital, Royal Victoria Hospital, Royal Infirmary of Edinburgh and Astley Ainsley Hospital. I visited the wards and screened all eligible stroke patients, performed all sleep studies and scoring and all baseline and outcome assessment. The flow diagram is shown in Figure 3.1 (P. 113).

The first, observational screening phase involved a limited, non-invasive sleep study in sub-acute stroke (14-19 days after stroke) for consenting, suitable patients. This means patients had gone beyond the acute phase of stroke (first two weeks) and were relatively clinically stable for overnight sleep studies and nasal continuous positive airway pressure (CPAP) titration. Baseline assessments were performed on the morning following the sleep study. The second, therapeutic parallel-limb randomized controlled trial (RCT) phase involved the subgroup of patients demonstrating moderate to severe obstructive sleep apnoea and hypopnoea (OSAH) on screening, who then were allocated to either 8 weeks of an auto-titration CPAP, AutoSet T® (ResMed Ltd., SanDiego USA, Figure 3.2, P. 114) or conservative treatment for SDB on day 21-25 following stroke. The detail of allocation and intervention will be described in the chapter 5.3.2. The patients without SDB also received outcome assessment at 3 months. The third, longitudinal follow-up involved all recruited patients who received outcome assessment at 6 months after stroke. If available, patients also received 12 months and 18 months follow-up until the last recruited patient had had his 6 months follow-up on December 2003.

3.2 Eligibility criteria

The criteria for inclusion and exclusion were set up based on the randomized controlled trial of nasal CPAP in order to recruit a group of stroke patients who had normal functional status or mild functional disability prior to the stroke, mild to moderate neurological deficits and less complications following stroke so were thought to be compliant with CPAP treatment and available for longitudinal outcome assessment.

The inclusion criteria for overnight sleep study were:

- Male and female patients aged between 21-90;
- Stroke 14-19 days previously;
- Pre-stroke Modified Rankin Score (MRS) ≤ 2;
- NIH Stroke Score (NIHSS) ≥ 4.

The exclusion criteria for overnight sleep study were:

- Severe or unstable medical conditions including dementia, severe dysphasia or confusion that would result in the patient not understanding or tolerating the diagnostic study or CPAP treatment;
- Unusual stroke including stroke caused by collagen vascular diseases, drug addiction or brain tumours;
- Either insufficient hand function to put on mask and take it off, or do not have caregiver present overnight to do this for them.

The following patients were particularly excluded: (1) severe bulbar or pseudo bulbar palsy which could cause SDB following stroke [Askenasy and Goldhammer 1988]; (2) severe conscious disturbance, dysphasia or cognitive impairment which could result in inaccurate responses to questionnaire and some assessment scales; (3) severe medical illnesses, for example, severe congestive heart failure, COPD or epilepsy in which SDB is co-morbid even without stroke.

The inclusion criteria for RCT after sleep study were:

- $(A+H)\cdot h^{-1} \geq 30$
- < 30 central apnoeas or Cheyne-Stokes respiration

The cut-off NIHSS score for recruitment was changed from NIHSS ≥ 6 to ≥ 4. This change in NIHSS criterion was made before any patients were recruited into the randomized study – that is after the first 2 patients (chapter 5.4.1) were assessed but not randomized or treated. The reason for the change was that it became apparent that recruitment would be too slow if the original criteria were followed.

3.3 Sample size calculation

The Barthel Index (BI) and the Nottingham Extended ADL Index (EADL) dealing with functional capacity were chosen as primary outcome measures based on a priori hypothesis. The ambulatory blood pressure (ABP), Mini Mental State Examination (MMSE), Addenbrooke's Cognitive Examination (ACE), Hospital Anxiety and Depression Scale (HADS), EuroQol and SF-36 were chosen as secondary outcome measures.

A priori sample size was determined for randomised controlled trial (RCT) in this study based on the following formula:

$$\text{N in each group} = \frac{2\,\sigma^2\,(z_{\alpha/2} + z_{\beta})^2}{\Delta^2}$$

where σ = the common standard deviation of each group,

Δ = mean difference,

Δ/σ = standardized mean difference (SMD), which is the effect size (mean difference divided by standard deviation) generally recommended in clinical trials and other studies assessing treatment effects on outcomes.

α = significance level, and β = 1- Power,

Z = standard normal distribution,

$Z\alpha/2 = 1.96$ ($\alpha = 0.05$),

$Z\beta = 0.84$ ($\beta = 0.20$).

Thus 40 CPAP and 40 control patients would provide 80% power at 5% significance level to show 0.57 point SMD in the EADL, using data from the RCT of outpatient occupational therapy (OT) for stroke [Walker *et al.* 1999]. Allowing for 20% dropouts suggested an initial recruitment target of 100 to the RCT with 50 CPAP and 50 control patients (Figure 3.1, P. 113).

A preliminary analysis would be undertaken after 80 subjects were recruited, and if definitive results had been obtained recruitment would cease. Alternatively, sample

size requirements based on the observed prevalence of SDB and treatment effects will be reassessed.

3.4 Sleep study

3.4.1 Portable limited sleep study

I used a pocket-sized portable recording system (Embletta PDS®, Medcare Flaga Ltd., Iceland) in my study incorporating the following sensors (Figure 3.3, P. 115):

- Nasal pressure transducer: a disposable nasal cannula connected to a pressure transducer to record the square root of pressure as an index of flow;
- Oral thermistor: measuring mouth leakage;
- Respiratory efforts sensors: a piezo crystal transducer in a stretch Velcro strap to record thoracic and abdominal respiratory movement;
- Pulse oximeter: recording oxygen saturation and pulse rate;
- Body position sensor: recording supine, prone, left side, right side and upright positions.

The Embletta PDS® is a device for limited sleep study which records only cardiorespiratory signals without concomitant recording of EEG and EMG. It was chosen in my study as this is our standard diagnostic approach [Dingli *et al.* 2003;Whittle *et al.* 1997] and also complied with the clinical guidelines proposed by American Academy of Sleep Medicine and American Thoracic Society which have been reviewed in chapter 1.5.2.

3.4.2 Validity and reliability in sleep studies

Validity of a portable limited sleep study is estimated according to the comparison of sleep variables between the device to be tested and a gold standard device, polysomnography (PSG). Two portable limited sleep study devices are used in the sleep centre of Edinburgh University, EdenTrace® and Embletta® with validation based on synchronous studies. One study compared unattended EdenTrace® recording at home with conventional PSG in the sleep centre in 23 patients with SDB [Whittle *et al.* 1997]. The overall fail rate was 13%. The mean difference (PSG - EdenTrace®) in $(A+H)\cdot h^{-1}$ in bed was $8 \pm 12 \cdot h^{-1}$ with a significant

correlation between the results of the two studies ($r = 0.8$, $p < 0.001$). There was a bias to lower score on home studies at higher $(A+H)\cdot h^{-1}$ value. Another study compared unattended Embletta® recording at home with conventional PSG in the sleep centre in 50 patients with SDB. The overall fail rate was 18% but decreased to 12% if only latter two-thirds of the study was counted which showed learning effect. The mean difference (PSG - Embletta®) in $(A+H)\cdot h^{-1}$ in bed was $2 \pm 5\cdot h^{-1}$ ($p = 0.02$) with a significant correlation between the results of the two studies ($rho = 0.98$, $p < 0.001$) [Dingli *et al.* 2003]. The home studies tended to have lower score. The mean difference increased to $8 \pm 16\cdot h^{-1}$ if $(A+H)\cdot h^{-1}$ of Embletta was compared with AHI of PSG ($AHI\cdot h^{-1}$ in sleep) but returned to $2 \pm 5\cdot h^{-1}$ if those with $> 40\cdot h^{-1}$ in bed on both devices were excluded. This means the difference between two methods was greater in those with severe SDB.

Reliability in sleep studies is estimated according to the following three viewpoints that the instrument can yield the same scores when: (1) administered in different times (test-retest reliability); (2) scored in different times (intra-rater reliability); (3) scored by different persons who are experienced in the same field (inter-rater reliability). A study conducted in the sleep centre of Edinburgh University showed a high intra-rater reliability for scoring apnoea ($r = 0.99$, mean percentage difference of apnoea number = 8%) [Whyte *et al.* 1992]. A similar finding was shown for scoring hypopnoea even based on thorocoabdominal signals alone ($r = 0.98$, mean percentage difference of hypopnoea number = 11%). The reliability test in this thesis was simply to check my ability to interpret sleep studies which will be presented and discussed in chapter 4.

3.5 Baseline and outcome measurement

3.5.1 The severity of stroke

The severity of stroke was measured by the National Institute of Health Stroke Scale (NIHSS) shown in appendix A. The NIHSS is a 15-item stroke scale [Brott *et al.* 1989]. It was designed to measure the severity for all types of stroke according to 11 domains of neurological deficits:

- Consciousness and orientation
- Gaze
- Visual field
- Facial paresis
- Motor function of arm
- Motor function of leg
- Limb ataxia
- Sensory
- Best language
- Dysarthria
- Extinction and inattention

The higher scores indicate worse neurological status. NIHSS do not require advanced experience to complete but NIHSS requires more detailed neurological examination than the Canadian Stroke Scale. NIHSS is more appropriately used in prospective than retrospective assessment although NIHSS still can be abstracted from case notes with high degree of validity and reliability [Kasner *et al.* 1999]. NIHSS at baseline of stroke strongly predicts outcome - in the TOAST Trial of Org 10172 (a low molecular weight heparinoid, danaparoid) in Acute Stroke Treatment NIHSS ≤ 6 was significantly associated with good outcome of stroke and NIHSS ≥ 16, on the contrary, associated with poor outcome [Adams, Jr. *et al.* 1999].

NIHSS tends to be used to assess the severity of neurological deficits. In this study, the a cut-off point of NIHSS ≥ 4 was used as an inclusion criterion at baseline

(14-19 days after stroke) and also used as a secondary outcome measure 3 months following stroke.

3.5.2 Functional capacity

The Rankin Scale, Barthel Index (BI) and Nottingham Extended ADL Index (EADL) have been widely accepted as measures of functional outcome following stroke. Modified Rankin Scale (MRS) is used to measure handicap following stroke. Instead, BI and EADL are used to measure disability.

3.5.2.1 Modified Rankin Scale

The Modified Rankin Scale (MRS) is shown in appendix B. The Rankin Scale was developed in 1957 [Rankin 1957] and later modified [Bonita and Beaglehole 1988]. The MRS is a Likert scale with seven levels (0-6):

- No symptom at all (0)
- No significant disability despite symptoms (1)
- Slight disability (2)
- Moderate disability (3)
- Moderate severe disability (4)
- Severe disability (5)
- Dead (6)

The MRS, along with the Barthel Index (BI) and the Functional Independence Measure, are three common measures for the activities of daily living (ADL). The three measures are highly correlated but MRS a more simple scale so is less sensitive in stroke patients in lower and higher ends of disability [Kwon *et al.* 2004]. The NIHSS after stroke and MRS prior to stroke were used in this study as two of the inclusion criteria. The purpose was to include a group of patients who were independent prior to stroke and had mild to moderate stroke only.

In this study, the MRS was used at baseline to screen for pre-stroke functional status and also as a secondary outcome measure for functional status along with "Status of Independence" scale at 3, 6, 12 and 18 months following stroke.

3.5.2.2 Barthel Index

The Barthel Index (BI) is shown in appendix C. The BI was developed in 1965 [MAHONEY and BARTHEL 1965]. There are 10 domains of measurement for the activities of daily living:

- Feeding
- Bathing
- Grooming
- Dressing
- Bowels
- Bladder
- Toilet use
- Transfer (bed to chair, and back)
- Mobility (one level surfaces)
- Stairs

There are two scoring rules. The maximum score is 100 if 5-point increment is used but, is 20, if 1-point increment is used. The BI is the most widely used scale for assessing activities of daily living but the cut-off points used to classify patients with good outcome in previous stroke trials varied and were arbitrarily defined [Sulter *et al.* 1999]. Most patients are independent for essential self-care with a score of $\geq$ 60/100 and are independent with minimal assistance with a score of $\geq$ 85/100. Both Barthel Index and motor subscale of Functional Independence Measure show high internal consistency, concurrent validity and responsiveness to be used in stroke [Hsueh *et al.* 2002]. This means they have similar psychometric characteristics.

In this study, the BI was used to assess basic functional capacity at baseline and as a primary outcome measure at 3 months and 6 months following stroke.

3.5.2.3 Nottingham's Extended ADL Scale

The Nottingham Extended Activities of Daily Living Scale (EADL) is shown in appendix D. The EADL which was developed more recently than MRS and BI in 1993 [Gladman *et al.* 1993]. It consists of 22 items of question in four domains:

- Mobility (6 items)
- Kitchen (5 items)
- Domestic (5 items)
- Leisure abilities (6 items)

Total score can be obtained by summation of four subscores.

The term "functional capacity" has a multi-dimensional nature. The BI designed for basic activities of daily living usually has a ceiling effect in stroke patients with favourable outcome in activities of daily living. The EADL is especially designed to assess extended activities of daily living for stroke patients who live in their own home. On the other hand, it may have less test-retest reliability both in the total score and individual items than basic ADL scale such as the BI [Green *et al.* 2001] and the effect size before and after the treatment may be small [Harwood and Ebrahim 2000].

In this study, the EADL was used as a primary outcome measure for extended functional capacity at 3 and 6 months following stroke.

3.5.3 Sleep questionnaire and daytime sleepiness

3.5.3.1 The sleep and stroke questionnaire

The sleep and stroke questionnaire is shown in appendix E. It was developed based on the sleep questionnaire used in the sleep centre of Edinburgh University. The sleep and stroke questionnaire consists of two domains of question:

- Time and level of consciousness (sleep or wakefulness) at stroke onset.

- Major symptoms of SDB: including excessive daytime sleepiness, frequency and severity of snoring, witnessed apnoea, choking or suffocating episode, awakening unrefreshed, nocturia and morning headache.

In this study, the sleep and stroke questionnaire was applied to patients at baseline for general information about sleep-disordered breathing prior to stroke and association between sleep and stroke onset.

3.5.3.2 Stanford Sleepiness Scale

The Stanford Sleepiness Scale (SSS) is shown in appendix F. The SSS consists of seven statement regarding seven levels of current sleepiness [Hoddes *et al.* 1973]. A principal components analysis showed SSS is not a uni-dimensional scale but contains two components identified as activation and sleepiness [MacLean *et al.* 1992].

A study recruiting 10 healthy subjects with valid driver licenses for a computer-based Driving Simulation Task. The results showed the most significant driving parameters (crashes, excess speed, mean reaction time and lane position variability) correlated highly ($p < 0.01$) with objective sleepiness measured by the multiple sleep latency test (MSLT). Lower but significant correlations ($p < 0.05$) were found between the same parameter and subjective sleepiness measured by SSS although the correlation between SSS and MSLT was not reported [Pizza *et al.* 2004]. There was no strong association between objective sleepiness measured by Maintenance of Wakefulness Test (MWT) and subjective sleepiness measure by SSS. Patients with moderate sleep apnoea/ hypopnoea have in one study been reported to have higher SSS scores than patients with severe sleep apnoea/ hypopnoea [Sauter *et al.* 2000].

In this study, the SSS was used to measure excessive daytime sleepiness at baseline and as a secondary outcome measure at 3 months following stroke.

3.5.3.3 Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is shown in appendix G. The ESS [Johns 1991] has been used widely to assess subjective daytime sleepiness especially in patients with the obstructive sleep apnoea/hypopnoea syndrome (SDB). It consists of eight questions for sleep propensity in different daily situations, scored from 0 (no chance of dozing), 1 (slight chance of dozing), 2 (moderate chance of dozing) to 3 (high chance of dozing) for each question:

- Sitting and reading
- Watching TV
- Sitting inactive in a public place
- As a passenger in a car for one hour without break
- Lying down to rest in the afternoon
- Sitting and talking to someone
- Sitting quietly after a lunch without alcohol
- In a car, when stopped for a few minutes in a traffic

The results of factor analysis showed the SSS, the Profile of Mood Scale (POMS) and sleepiness-related Visual Analogue Scale (VAS) loaded onto one factor at a very similar and high rate whereas modified ESS alone loaded highly onto the other factor [Pilcher *et al.* 2003]. This may indicate that ESS measures a different aspect of subjective sleepiness from that measured by SSS. The ESS showed a moderate correlation with mean sleep latency measured by MSLT (rho = -0.37, p = 0.0042) [Chervin *et al.* 1997]. A high ESS score ($\geq$ 16) was significantly associated with a low mean sleep latency in MSLT ($\leq$ 8).

In this study, the ESS was not used as an outcome measure but for information about pre-stroke sleepiness.

3.5.4 Cognitive function

3.5.4.1 Addenbrooke's Cognitive Examination

The Addenbrooke's Cognitive Examination (ACE) is shown in appendix H. The limitation of MMSE is insensitivity to the early stage of dementia. There is only one question related to memory (free recall of three objects), one question related with visuospatial function (copy of a crossed pentagon) and no question related to executive function. This limitation might result in the ceiling effect when patients who have SDB or stroke without dementia are assessed as impairment of both memory and executive function are the major neuropsychological findings. This problem can be solved by applying a more comprehensive neuropsychological battery but this is time-consuming and not well tolerated by stroke patients.

The ACE was originally developed to increase the sensitivity to differentiate fronto-temporal dementia from Alzheimer's disease [Mathuranath *et al.* 2000]. It incorporates the MMSE, expands memory, language, visuo-spatial components and adds tests of verbal fluency which belong to parts of executive function. Total score of ACE is 100 including 30 points for MMSE. The ACE had a higher sensitivity (82% vs. 52%) and predictive value than the MMSE with equal specificity (96%) for the diagnosis of dementia. It consists of six domains of questions:

- Orientation (10)
- Attention (8)
- Memory (35)
- Verbal fluency (14)
- Language including naming (28)
- Visuospatial (5)

In this study, the ACE was used as a secondary outcome measure for cognitive function at baseline and 3 months following stroke.

3.5.4.2 Mini-Mental State Examination

The Mini Mental State Examination (MMSE) is currently one of the most popular instruments for screening cognitive impairment [Folstein *et al.* 1975]. The total score of MMSE is 30. Scores ranged 0-23 indicate impaired cognition. There are five domains in the MMSE:

- Orientation (10)
- Registration (3)
- Attention and calculation (5)
- Recall (3)
- Language (naming, repetition, comprehension, reading, writing, drawing) (9)

The median of MMSE score in the normal U.S. population was 25 in subjects aged 80 or older, including 29 in subjects who had undertaken education for ≥ 9 years, 26 in subjects with education 5-8 years and 22 in subjects with education 0-4 years [Crum *et al.* 1993]. All tests in the MMSE are included in the ACE so the MMSE can be extracted from completed ACE scores.

Mean score of MMSE was 22.1 in acute and sub-acute stroke (median 7.9 days following stroke) and 48.7 % of the patients had cognitive decline defined as MMSE ≤ 24 [Adunsky *et al.* 2002]. The MMSE was significantly correlated with Clock Drawing Test (CDT) which was used to evaluate attention, praxis, visuospatial and executive functions. A significant correlation was also noted between both MMSE and CDT to parameters of motor outcome assessed by motor score of Functional Independence Measure (FIM).

In this study, the MMSE was not used alone but the score of MMSE was subtracted from the ACE for measuring the cognitive function at baseline and the cognitive outcome at 3 months following stroke.

3.5.5 Mood and health-related quality of life

3.5.5.1 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is shown in appendix I. The HADS was developed in 1983 [Zigmond and Snaith 1983].

The correlations between HADS and physical measures (Barthel Index and Modified Rankin Scale) at 6-month following stroke were weak but still significant [Dennis, O'Rourke, Lewis, Sharpe, and Warlow2000]. Depression subscale in HADS had higher association with BI (rho = -0.4) and MRS (rho = 0.5) than anxiety subscale did (rho = -0.2 with BI, rho = 0.3 with MRS).

About 23% of stroke patients at a long-term (5 years) follow-up had scores suggesting depression and 18 (19%) had scores suggesting anxiety [Wilkinson *et al.* 1997]. The proportion of depression was significantly higher in those who were disabled (BI = 0-19/20) than in those who were independent (BI = 20/20).

In this study, the HADS was used to assess mood status at baseline and as a secondary outcome measure at 3 months following stroke.

3.5.5.2 EuroQol

The EuroQol is shown in appendix J. The EuroQol is a generic measure of health status developed by EuroQol group in 1990 [1990]. It is a simplified questionnaire including EQ-5D which consists of Visual Analogue Scale (VAS) rated from 0 to 100 and five single questions in five dimensions:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

There was a significantly higher response rate in EuroQol group than in SF-36 group in the International Stroke Trial [Dorman *et al.* 1997]. The absolute difference of "response without missing data" was 11% and odds ratio was 1.64 ($p < 0.0001$). The reproducibility of EuroQol was generally good (un-weighted kappa = 0.63 – 0.80) and similar to those for SF-36 (intra-class correlation coefficient = 0. 67 – 0.80 except mental health and role emotional) in stroke patients [Dorman *et al.* 1998].

In this study, the EuroQol was used as a secondary outcome measure for general health status at 3 months following stroke.

3.5.5.3 SF-36

The Medical Outcomes Study short form 36 health survey (SF-36) is shown in appendix K. The SF-36 is the most widely used scale in assessing health-related quality of life [McHorney *et al.* 1993;Ware, Jr. and Sherbourne 1992]. There are more than 2000 articles regarding the validity of eight subscales of SF-36 with physical summary score and mental summary score generated from them. The SF-36 consists of:

- Physical function (10 items)
- Role limitations–physical (4 items)
- Bodily pain (2 items)
- General health (5 items)
- Vitality (4 items)
- Social functioning (2 items)
- Role limitations–emotional (3 items)
- Mental health (5 items)

SF-36 obtained by post from old-aged stroke patients had good response rates (83%) but variable completion rates (66 - 96%) especially for role limitation-physical and role-limitation emotional subscales [O'Mahony *et al.* 1998]. Interview administration might be more appropriate than self-completing the questionnaire in stroke wards or rehabilitation units as many patients may have some mental, visual or physical disability [Anderson *et al.* 1996].

SF-36 might also have limitations in a number of subscales in stroke patients [Hobart *et al.* 2002]. Subscale for role limitation-physical had a notable floor effect. In contrast, subscales for role limitation-emotional and mental health had ceiling effects. Assumptions for generating 2 SF-36 summary measures were not satisfied. Principle components analysis revealed two factors of SF-36 which supported two summary scores but these two components can only explain less than 60% of the total reliable variance in all SF-36. Thus all subscales instead of two summary scores only were used.

In this study, the SF-36 was used as a secondary outcome measure for health-related quality of life at 3 and 6 months following stroke.

3.5.6 Ambulatory blood pressure

Conventional use of the sphygmomanometer has some problems including: (1) terminal digit preference; (2) inter-observer variation and (3) improper technique. A single measurement cannot reflect the circadian rhythm of 24-hour blood pressure. Especially for ageing people, some physiological changes include: (1) increased blood pressure variability; (2) arterial rigidity; (3) more pronounced diurnal variation; (4) baroreceptor insensitivity can make an isolated measurement inaccurate. There is also the "white-coat effect", an increased blood pressure only in the medical care environment, which can result in inaccuracy of in-office blood pressure measurement.

The ambulatory blood pressure (ABP) is not only a convenient device for detecting 24-hour circadian rhythm of blood pressure but also more objective than casual blood measurement to represent the true "blood pressure burden". There are two patterns of common circadian rhythm of blood pressure depending on whether afternoon dipping is slight or marked: (1) If afternoon dipping is slight, a 24-hour period of circadian rhythm is noted with a peak in the late afternoon and a nadir in-between the descending and ascending limbs of overnight dipping [Clement *et al.* 2003]; (2) If afternoon dipping is as marked as overnight dipping, a 12-hour period of circadian rhythm is noted [Stergiou *et al.* 2002].

In this study the circadian blood pressure was used as a secondary outcome measure by a compact and light-weighted portable Spacelabs 90207 ABP Monitor® (SpaceLabs Medical Ltd., Redmond, WA, USA, Figure 3.4, P. 116). The BP monitor was programmed to measure every 30 minutes for 24 hours, starting between 2-3 PM. We defined pressures between 6:00 AM and 9:59 PM as occurring during the daytime and between 10:00 PM and 5:59 AM as nighttime, corresponding to the schedule of the stroke wards.

3.6 Data analysis

The Nottingham Extended ADL Index (EADL) was chosen as the primary outcome measure. Secondary outcome measures included: Subscales of EADL, NIH Stroke Scale (NIHSS), Barthel Index (BI), Stanford Sleepiness Scale (SSS), Addenbrooke's Cognitive Examination (ACE) and Mini-Mental State Examination (MMSE), Hospital Anxiety and Depression Scale (HADS), MOS Short Form 36 Health Survey (SF-36) and ambulatory blood pressure. Data was collected from sleep studies, from information stored nightly in the AutoSet T and from hospital and home visits. Analysis was performed following two major principles:

- Intention-to-treat analysis

All patients recruited in the RCT study were followed-up at eight weeks regardless of compliance with treatment. This permitted a conservative estimate of the effectiveness of treatment in this group of patients. Where patients withdrew sub-group analysis was done to ensure that there were no differences between patients who participated and those who withdrew (i.e. homogeneity of randomization preserved).

- Hypothesis-driven data analysis

Hypothesis-driven data analysis was conducted for primary and secondary outcomes to determine: (1) the differences between the CPAP and the conservative treatment groups after 8 weeks of treatment; (2) the differences between the apnoeic and non-apnoeic groups at the end of 3 months and 6 months after stroke.

- Post-hoc data analysis

Post-hoc exploratory data analysis was conducted for: (1) the difference between the CPAP and the conservative treatment groups and between the apnoeic and non-apnoeic groups in certain subgroups divided by NIHSS, MMSE and HADS; (2) correlations of the sleep data and the outcome variables and advanced analysis of the ABP data to support the underlying mechanisms for hypothesis. Post-hoc analysis is biased in both multiple statistical comparisons and data dredging so it is inherently

sub-optimal. The results should be interpreted conservatively and are only used for hypothesis generation for subsequent studies in the future.

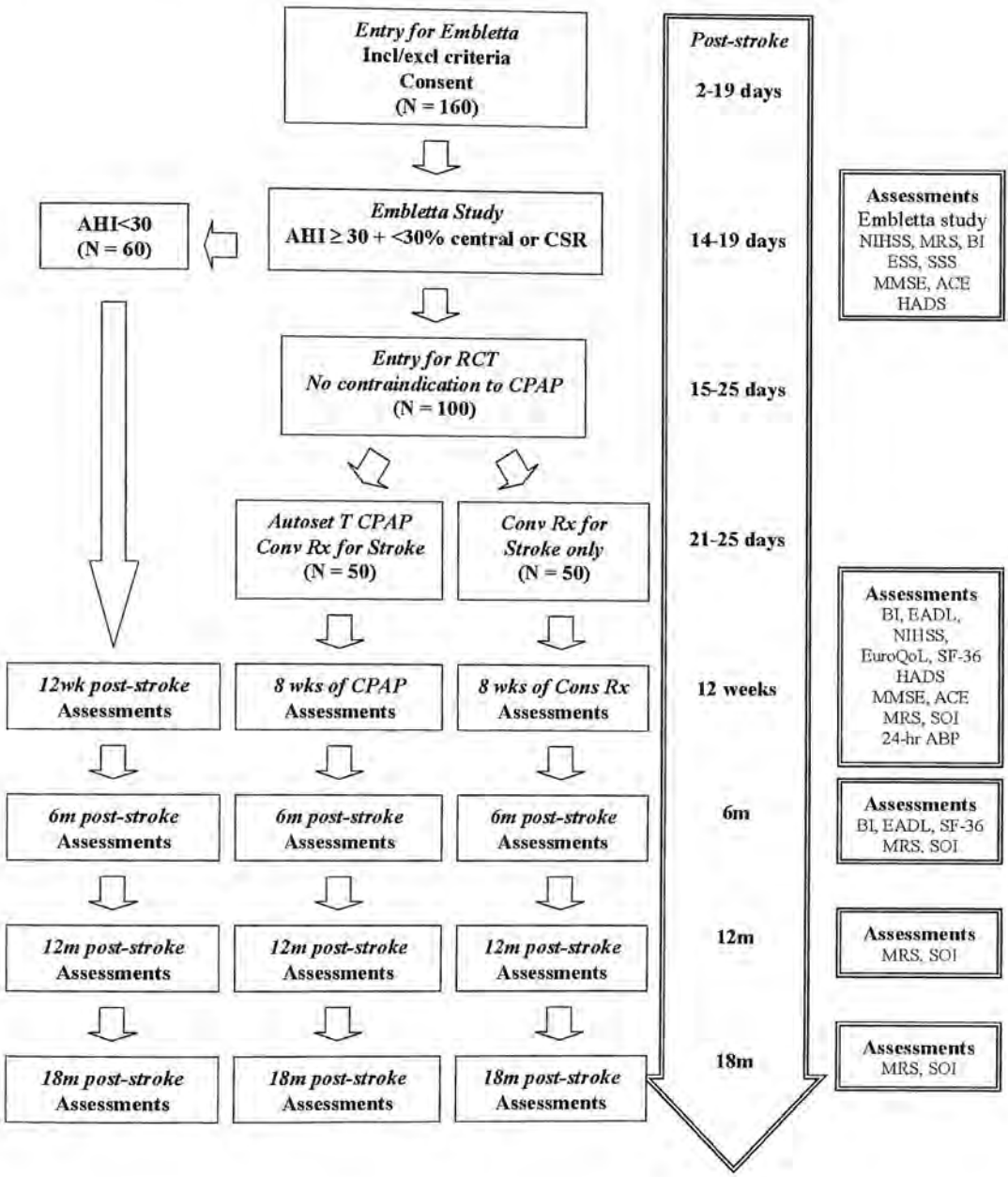
3.7 Ethics and informed consents

Ethics approval has been obtained from the Lothian Research Ethics Committee (Reference MREC/2000/4/44). Trust management approval has been given by Research & Developmental Office on behalf of the Trust Chief Executive and Medical Director (Reference R&D/99/17/08). Written informed consents were obtained from all participants.

In the first instance we had considered a two-stage consent process i.e. consent for the prevalence study, and then consent for the RCT. We finally decided against this after the two patients had been recruited. The novel and most important part of this study was RCT. As the facilities to perform sleep studies were limited we determined that recruiting those who were not willing to attend CPAP trial might delay the time course of the study and decrease the sample size of the RCT. Thus we focused on the RCT component of the study.

Patients with severe dysphasia (receptive dysphasia, severe expressive dysphasia and global aphasia) were excluded. Patients with mild to moderate dysphasia (mild to moderate expressive dysphasia) still could fill in the sleep questionnaire including onset time of stroke and scales and respond to face-to-face interviews.

Figure 3.1 Patient flow diagram



NIHSS: National of Health Stroke Scale, MRS: Modified Rankin Scale, BI: Barthel ADL Index, ESS: Epworth Sleepiness Scale, SSS: Stanford Sleepiness Scale, MMSE: Mini Mental State Examination, ACE: Addenbrooke's Cognitive Examination, HADS: Hospital Anxiety and Depression Scale, EADL: Nottingham Extended ADL Index, ABP: Ambulatory Blood pressure, SOI: State of Independence

Figure 3.2 AutoSet T®: reproduced from ResMed company (www.resmed.com)

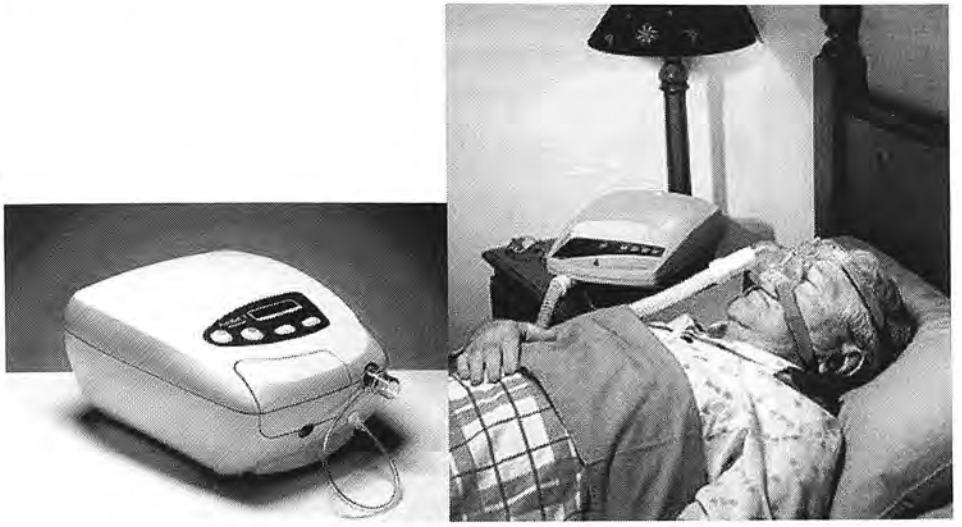


Figure 3.3 Embletta® PDS recording system: reproduced from Medcare company (www.medcare.com)

Figure 3.4 ABP Monitor®: reproduced from SpaceLabs company (http://www.spacelabs.com) and R.L.Dolby company (http://www.dolby-ltd.co.uk)

Chapter 4 A Cross-Sectional Study of Obstructive Sleep Apnoea/Hypopnoea in Patients with Stroke

associated with cognitive impairment (Addenbrooke's Cognitive Examination total score ≤ 80, p = 0.002).

Conclusions: We supported high prevalence of SDB and related symptoms in stroke and emphasized the role of SDB in stroke onset and cognitive function.

Key words: Sleep-disordered breathing; stroke; prevalence; snoring; excessive daytime sleepiness; stroke onset; sleep-related stroke

4.2 The aims of the study

Scientific background of this randomized controlled trial (RCT) has been reviewed in chapter 2.10. According to previous reviews, we had five aims in this cross-sectional study:

- To established the feasibility or not of applying overnight sleep studies to stroke patients in the UK.
- To find out the prevalence of SDB based on hospital-based stroke patients in Edinburgh city in the UK.
- To clarify the predictive value of pulse oximetry and major sleep symptoms for moderate to severe SDB.
- To clarify the relationship between SDB, stroke onset and sleep-related stroke.
- To assess the influence of AHI and oximetric variables on functional capacity, cognitive function, anxiety and depression in the subacute stage of stroke.

4.3 Methods

4.3.1 Patient recruitment

All participants were contacted in the first 2 weeks following their most recent stroke at either acute stroke units or stroke rehabilitation wards in four university hospitals in Edinburgh city. Five stroke specialists made the diagnosis of stroke according to history, neurological examination and neuroimaging (CT or MRI scan) findings. The criteria for inclusion and exclusion have been described in chapter 3. Both ischaemic and hemorrhagic strokes were included. Ischaemic stroke was classified according to the Oxford Community Stroke Project (OCSP), i.e. total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI) and lacunar infarct (LACI) [Bamford *et al.* 1991].

4.3.2 Sleep studies

On day 14-19 after stroke, recruited patients underwent sleep study using a portable device (Embletta PDS, Medcare Flaga, Reykjavik, Iceland) incorporating: (1) nasal pressure; (2) oral thermistor; (3) thoraco-abdominal movement; (4) finger pulse oximetry; (5) body position. The detail of the device has been described in chapter 3.4.1. The validity and reliability of the Embletta machine has been demonstrated [Dingli *et al.* 2003].

The portable device was programmed to record from 9 pm to 6 am. Each patient was visited about one hour before recording began. It took about 15-20 minutes to set up all the sensors so he or she had at least half an hour to get used to them. Any problem during this period was checked and corrected. After I had started recording, I stayed for a further two hours to make sure that Embletta was working properly. During that time I also took information from the casenotes. Before leaving I left the container of the device with simple instructions pasted outside and detailed instructions inside. Night staff in the ward helped to keep an eye on the sensors especially when patients went to the toilet. The sensors were removed either when

patients woke up without further sleep or after 6 am in the morning. The device was packed up and brought back to the Department of Sleep Medicine for analysis.

Raw data were downloaded onto computer with a sleep analysis programme. Manual scoring was performed because automatic scoring is not reliable according to previous clinical experience. As Embletta does not record sleep, the onset of sleep was taken as the onset of rhythmic stable breathing. The end of the study was taken as the patient's or caregiver's report of final awakening time or continuous movement artefacts without coming back to regularity of breathing pattern. The interval between the onset and the end of the study was calculated as "hours in bed".

Apnoeas and hypopnoeas were scored using standard criteria based on the report of an American Academy of Sleep Medicine Task Force [1999]. Apnoea was defined as the absence of nasal airflow for at least 10 seconds. It was classified as obstructive type if there was concomitant thoracic or abdominal respiratory effort, as central type if there was no associated respiratory effort and, as mixed type if there was a central pattern followed by an obstructive pattern. Hypopnoea was defined as a 50% or greater reduction in the amplitude of either nasal pressure or thoraco-abdominal movement for at least 10 seconds [Gould *et al.* 1988]. The total number of apnoea and hypopnoea per hour in bed after "sleep onset" was reported as $(A+H)\cdot h^{-1}$. Oxygen desaturation was scored if there was a $\geq 4\%$ decrease of pulse oximetry preceded by either apnoea or hypopnoea. Total number of oxygen desaturations per hour in bed after "sleep onset" was reported as oxygen desaturation index (ODI).

4.3.3 Reliability tests

After study was finished, I repeated blind scoring for 31 patients to test intra-rater reliability who were randomly chosen by an experienced polysomnographer (MV) in the department who was not involved in the first scoring. She also scored 7 of 31 patients' sleep data herself to test inter-rater reliability. The mean interval between the first and second scoring was 15 months, ranging from 3 months to 32 months. Intraclass correlation (ICC) was used to measure intra-rater and inter-rater reliability.

Bland-Altman plot is a statistical method to compare two methods of clinical measurement [Bland and Altman 1986]. The differences between the two measurements are plotted against the averages of the two measurements. In this study I applied Bland-Altman plot to compare the 2nd scoring of $(A+H)\cdot h^{-1}$ to the 1st one performed by me and also, to compare the 2nd scoring of $(A+H)\cdot h^{-1}$ performed by me to the scoring of $(A+H)\cdot h^{-1}$ performed by MV.

4.3.4 Sleep questionnaire

On the morning following the overnight sleep study, a sleep questionnaire with a 4-choice response for each question was given to all patients. There were four domains of questions in the sleep questionnaires: (1) Time and conscious state (asleep or awake) of stroke onset; (2) Nocturnal SDB-related symptoms, namely: duration, frequency and intensity of snoring, choking episodes, witnessed apnoea and nocturia. (3) Daytime SDB-related symptoms in terms of awakening unrefreshed, excessive daytime sleepiness (EDS), morning headaches and road traffic accidents; (4) Basic information about the sleep study in terms of the subjective sleep/wake time and quality of sleep, measured by a 5-level Likert scale.

The Stanford Sleepiness Scale (SSS), which is a 7-level Likert scale, was applied for current sleepiness following stroke. The Epworth Sleepiness Scale (ESS) was applied for pre-stroke sleepiness if patients were clear and cooperative enough to fill in the questions.

4.3.5 Onset time of stroke

Every patient was asked about the time of stroke onset defined by the time they last recalled being unaffected (the last-seen-well principle). The information given by patients was checked with routine records in the casenotes at admission. If there was a discrepancy, it was further clarified with partners or caregivers. These data were analyzed according to the following 3 steps:

- Circadian distribution of relative risk of stroke onset was calculated and expressed for each 4-hour interval throughout a day (24 hours). The method

of calculating relative risk has been previously used [Elliott1998]. It is assumed that all events of stroke would be evenly distributed over the 6 intervals, i.e. 11 patients in each interval for total 66 patients. Thus the relative risk for each interval is calculated by the ratio of the observed number of strokes to the expected number of strokes.

- Stroke onset times were further grouped by 1 hour blocks for patients with $(A+H)\cdot h^{-1} < 15$, $15 \leq (A+H)\cdot h^{-1} < 30$ and $(A+H)\cdot h^{-1} > 30$. As the sample size in the three groups of patients were not equal, the number of strokes in each 1-hour block was transferred into odds, defined as number of strokes occurring in that hour divided by number of non-events (i.e. the number of strokes in that group occurring in the remaining 23 hrs) for further comparison between groups. The raw data were smoothed by using a running average of two consecutive 1-hour blocks before putting them into a polynomial regression model for curve fitting and plotting as previously used [Hill and Newcommon 2003].
- Two arbitrary time intervals were defined as "sleeping time" (00:00 to 7:59, 8 hours) and "waking time" (8:00 to 23:59, 16 hours) according to our previous definition [Engleman *et al.* 1996b]. It is also assumed that if all events of stroke were evenly distributed, 1/3 of events would occur in "sleeping time" and 2/3 in "waking time". The relative risk for each interval was calculated using a similar method to that described above and was compared between groups with SDB ($(A+H)\cdot h^{-1} < 15$) and without SDB ($(A+H)\cdot h^{-1} \geq 15$) by Chi-square test.
- The frequency of sleep-related stroke, defined as stroke noticed on awakenings, and wake-related stroke was compared between four groups of patients, i.e. $(A+H)\cdot h^{-1} < 15$, $15 \leq (A+H)\cdot h^{-1} < 30$, $30 \leq (A+H)\cdot h^{-1} < 45$ and $(A+H)\cdot h^{-1} > 45$ by Chi-square test.
- Logistic regression was used to predict sleep-related stroke by demographic variables and variables obtained in sleep study in total patients and in patients SDB ($(A+H)\cdot h^{-1} < 15$) and without SDB ($(A+H)\cdot h^{-1} \geq 15$).

4.3.6 Baseline assessment and other data collection

Baseline assessment was performed on the morning following the overnight sleep study at the same time as the sleep questionnaire. The Barthel index (BI) based on self-report was used to assess functional capacity in terms of independence of mobility and self-care. Psychological distress was assessed by the Hospital Anxiety and Depression Scale (HADS) including 7 questions for anxiety and 7 for depression. The Addenbrooke's Cognitive Examination (ACE) developed by Cambridge University [Mathuranath *et al.* 2000] was chosen to assess cognitive function including six domains of questions in terms of orientation, attention, memory, verbal fluency, language and visuospatial ability. A Mini Mental State Examination (MMSE) score can be obtained directly from ACE. The total score is 100 including 30 for MMSE. Total assessment time is about 30 minutes. Detailed information about the scales has been presented in chapter 3.

Demographic information and baseline data which were collected either from the casenotes or by patient interviews include: (1) date of birth, gender and duration of education; (2) body weight and body height for calculation of body mass index (BMI) as weight/(height) ^{2}; (3) date of stroke, date of admission and discharge; (4) blood pressure, body temperature and SaO2 at admission (5) past medical history of cardiovascular risk factors, smoking and alcohol consumption; (6) previous and current medications.

Results of laboratory tests which were collected from the casenotes were: (1) haematocrit, haemoglobin, platelet count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); (2) plasma glucose and total cholesterol; (3) chest X-ray, ECG and echocardiography; (4) neuroimaging study (CT or MRI) and carotid duplex ultrasonography. Evidence of atrial fibrillation (AF) and left ventricular hypertrophy (LVH) was obtained by the findings of either electrocardiography (ECG) or echocardiography.

4.3.7 Statistical methods

The mean number of sleep apnoea and hypopnoea per hour in bed was expressed as $(A+H)\cdot h^{-1}$ in the text of the article but for the purpose of convenience, as AHI in tables and figures. All continuous data were presented as a median and an interquartile range (IQR) and categorical data were presented as a number (n) or percentage (%). Non-parametric tests were conducted including the Mann-Whitney U test and the Chi-square Test (Fisher's test in case there were less than 5 patients in a category) for between-group comparisons. The p value < 0.05 was taken as significant.

Binary logistic regression was conducted to control confounding factors or to adjust for interactions. All predictors with $p < 0.1$ in univariate regression analysis were entered into the final model. Odds ratio and confidence interval (CI) for each predictor were expressed. The predictors with $p < 0.05$ in final model were taken as significant. Statistical analysis was done by the statistical software, SPSS version 11.0 (SPSS Inc. USA).

4.4 Results

4.4.1 Recruitment of cases

I screened 658 patients believed to have had a stroke from March 2001 to June 2003 by myself. The recruitment pattern is shown (Figure 4.1, P. 162). Only 96 (15%) of 658 patients were eligible. Informed consent was not given by 25 (26%) of these. The reasons for refusal were: (1) 7 were not happy with extra research; (2) 4 were not happy with overnight sleep monitoring; (3) 4 were not concerned if they had SDB; (4) 4 had had a similar study before so were not keen to repeat; (5) 3 were not happy with nasal CPAP treatment even though they might be randomized to no treatment; (6) 2 patients' consultants didn't think they would tolerate an overnight study; (7) 1 patient's family declined. In total 71 patients were successfully recruited for overnight sleep study.

4.4.2 Sleep studies

The sleep study was performed in an acute stroke unit for 25 patients, in rehabilitation ward for 42 patients and at home for 4 patients. Eight patients had inadequate recording in the first night, defined as less than five hours of satisfactory quality of tracings. Of those eight, one had nocturnal confusion, one had severe diarrhoea, one had severe coughing and chest discomfort, and one could not sleep with monitors until midnight and so took them off. The other four patients did not have clear reasons. Three of these eight patients agreed to have repeated sleep studies on the next night, which were all successful. Five patients refused to repeat the study. They were further excluded. This resulted in 66 valid patients. Only one patient was happy to have three consecutive sleep studies in the 1st, 3rd and 12th week after stroke. His $(A+H)\cdot h^{-1}$ was 22.4, 21.5 and 21.3 respectively. There was slight decrease of $(A+H)\cdot h^{-1}$ from 1 week to 3 months after stroke in this patient. Only the sleep study in the 3rd week was put into analysis.

The results of sleep study were shown in Table 4.1 (P. 148). Half of patients had $(A+H)\cdot h^{-1} \geq 30$, 60 % had $(A+H)\cdot h^{-1} \geq 20$, 70 % had $(A+H)\cdot h^{-1} \geq 15$ and 85 % had $(A+H)\cdot h^{-1} \geq 10$. The distribution of $(A+H)\cdot h^{-1}$ was positively skewed but the difference between median (30.5/hr) and mean (30.9/hr) was minimal. All patients with SDB had predominantly obstructive SDB. Patients were divided into two groups based on cut-off score of $(A+H)\cdot h^{-1} \geq$ or < 30 for further comparison. The cut-off score of $(A+H)\cdot h^{-1} \geq 30$ was chosen to discriminate severe SDB from mild ($5 \leq (A+H)\cdot h^{-1} < 15$) and moderate ($15 \leq (A+H)\cdot h^{-1} < 30$) SDB according to the definition described in chapter 1.4.

Hypopnoea was more common than apnoea. The proportion of central sleep apnoea was low but higher in patients with $(A+H)\cdot h^{-1} \geq 30$ than < 30. The median of the central apnoea index (CAI) was only 0.4 (IQR 0.0-1.1). Nine patients had a few episodes of Cheyne-Stokes respiration (CSR) but none of them fulfilled the proposed criteria of diagnosis [Bassetti *et al.* 1997]. Among them, 8 patients belonged to $(A+H)\cdot h^{-1} \geq 30$. Only 1 patient had $(A+H)\cdot h^{-1} < 30$. The median $(A+H)\cdot h^{-1}$ of those who had CSR (56.8, n = 9) was significantly higher (p = 0.002) than those without CSR (23.1, n = 57).

There were significant correlations between $(A+H)\cdot h^{-1}$, oximetric variables and heart rate variables (Table 4.2, P. 149). Heart rate variability (HRV) was defined as the standard deviation of overnight pulse rate data recorded by pulse oximetry The higher the $(A+H)\cdot h^{-1}$ or the more severe desaturation was, the higher the heart rate variability was. In contrast, the higher the $(A+H)\cdot h^{-1}$ or the more severe the desaturation was, the lower the lowest heart rate was.

4.4.3 Reliability tests

The sleep study had high intra-rater reliability (Intraclass Correlation Coefficient, ICC = 0.983, $p < 0.001$, Figure 4.2a, P. 163) and inter-rater reliability (ICC = 0.977, $p < 0.001$, Figure 4.2c, P. 164). The Bland-Altman plot of 31 patients for the comparison between the 1st and 2nd scoring of $(A+H)\cdot h^{-1}$ performed by me showed that the $(A+H)\cdot h^{-1}$ of the first scoring was slightly higher than the second scoring

(mean difference = 0.4, SD = 6.3, Figure 4.2b, P. 163). The Bland-Altman plot of seven patients for the comparison between the scoring of $(A+H)\cdot h^{-1}$ performed by me and by an experienced research nurse showed that there was no clear difference of scoring in four patients with $(A+H)\cdot h^{-1} < 20$ but I scored slightly higher $(A+H)\cdot h^{-1}$ in three patients with $(A+H)\cdot h^{-1} > 25$ (mean difference = 1.7, SD = 3.1, Figure 4.2d, P. 164).

4.4.4 Demographic characteristics and baseline assessments

The demographic characteristics for 66 patients undergoing initial sleep study analysis were shown in Table 4.3 (P. 150). All patients had normal SaO2 on air (> 90%) on admission and all were apyretic on admission and during the sleep study. The mean age was 72 (SD = 11) median age was 74 (IQR = 65-81). There were 45 men and 21 women. There was no significant difference in age between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30. The $(A+H)\cdot h^{-1}$ increased with age from 40s to 70s but dropped down in 80s (Kruskal-Wallis test, $p < 0.001$, Figure 4.3, P. 165). There was no gender difference between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30. Although those who had $(A+H)\cdot h^{-1} \geq 30$ also had slightly higher BMI and BMI was positively correlated with $(A+H)\cdot h^{-1}$ (Spearman rho = 0.308, p = 0.012, Figure 4.4, P. 166) patients with SDB were not obese (BMI < 30). Sixty percent of patients had a history of hypertension. There was no significant difference in history of hypertension and other cardiovascular risk factors between the two groups but patients with $(A+H)\cdot h^{-1} \geq 30$ seemed to have higher proportion of diabetes, atrial fibrillation (AF) and left ventricular hypertrophy (LVH).

Stroke was classified into different subtypes by me according to Oxford Community Stroke Project (OCSP) [Bamford *et al.* 1991]. Most of the patients (n = 41) had PACI, 13 patients had TACI, 3 had POCI and 4 had LACI. The other 5 patients had primary ICH. The group with $(A+H)\cdot h^{-1} \geq 30$ consisted of more patients with TACI and POCI and the group with $(A+H)\cdot h^{-1} < 30$ consisted of more patients with PACI and LACI. Six of nine patients who had CSR belonged to PACI, one belonged to TACI, one belonged to ICH and one belonged to POCI.

The baseline assessments were shown in Table 4.4 (P. 151). All patients were functionally independent prior to their most recent stroke (MRS ≤ 2). Pre-stroke MRS was "0" in 56, "1" in 7 and "2" in 3 patients. Median NIHSS score was 6. There was no significant difference in NIHSS, MMSE, ACE, BI, HADS between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 despite patients with $(A+H)\cdot h^{-1} \geq 30$ had relatively lower scores in ACE. There was no significant difference of $(A+H)\cdot h^{-1}$ between patients with and without dysarthria and, between patients with and without dysphasia.

Although the stroke patients studied were inevitably a highly selected group they were similar with "typical" stroke patients admitted to the Western General Hospital in Edinburgh. A study was performed during the same period (31 October 2001 – 31 October 2003) in the same stroke unit (Western General Hospital) with the same device of recording (Embletta) to investigate the relationship between hypoxaemia and stroke [Rowat *et al.* 2005]. They had entry criteria to recruit any patient who had a suspected first or recurrent ischaemic or haemorrhagic stroke, was admitted within working hours on weekdays and could be approached within 24 hours after stroke onset. Although they had a broad spectrum of entry criteria in contrast to my strict ones there was still no clear difference in demographic characteristics and baseline assessment between our data. In their study, 29% of stroke patients had Total Anterior Circulation Stroke (TACS) and 40% had Partial Anterior Circulation Stroke (PACS). The median age was 81 (IQR = 74-86) with 50% of male patients in hypoxic group and the median age was 77 (IQR = 74-84) with 44% of male patients in non-hypoxic group. The median NIHSS score on day 1 was 6 (IQR = 4-15) and on day 7 was 4 (IQR = 1-11) in hypoxic group. The median NIHSS score on day 1 was 6 (IQR = 3-15) and on day 7 was 4 (IQR = 1-14) in non-hypoxic group.

As this study (Edinburgh Stroke and Sleep Apnea Study, ESSAS) belonged to Edinburgh Stroke Study (ESS), the baseline data of patients who refused to sign informed consent could still be used to investigate selection bias. As non-consenting patients did not receive any extra assessment only demographic data and type of stroke were available. The demographic characteristics and baseline assessments of

25 non-consenting patients and 5 patients who had inadequate sleep studies were not significantly different from the finally recruited patients. The median age of these 30 patients was 73. There were 20 male and 10 female. Pre-stroke Modified Rankin Scales were "0" in 28 and "1" in 2 patients. Median NIHSS was 6. Four patients had TACI, 20 had PACI, 3 had POCI, 1 had LACI and 2 had ICH.

4.4.5 Laboratory data at baseline

The laboratory data at baseline were shown in Table 4.5 (P. 152). There was no difference in the laboratory data between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30. Patients with a history of hypertension also had significantly higher systolic blood pressure ($p = 0.021$) and relatively higher diastolic blood pressure on admission than non-hypertensive ones. The patients with $(A+H)\cdot h^{-1} \geq 30$ had relatively but not significantly higher ESR level. One patient in the $(A+H)\cdot h^{-1} \geq 30$ group had a stroke within a few days of abdominal surgery and his ESR increased to 105 and CRP to 300. The statistical significance did not change whether or not the outliers were included. Twenty-eight patients had had results of carotid duplex ultrasonography following their most recent stroke. There was no difference of significant stenosis ($\geq$ 60%) of the internal carotid artery (ICA) on either the left or the right side between the groups ($p = 0.461$).

4.4.6 The association between SDB-related symptoms and $(A+H)\cdot h^{-1}$ in stroke

Self-reported snoring and EDS were two predominant symptoms which distinguished apnoeic and non-apnoeic stroke patients (Table 4.6, P. 153). There was a significantly higher proportion of snoring (80%, answer of "yes") in patients with $(A+H)\cdot h^{-1} \geq 30$ (Chi-square $p = 0.001$). If we take frequency into consideration, the difference of habitual snoring (answer of "often" or "almost everyday") between $(A+H)\cdot h^{-1} \geq 30$ and < 30 was smaller and not significant ($p = 0.071$). Among 33 stroke patients with $(A+H)\cdot h^{-1} \geq 30$, only 6 patients (18.2%) denied a history of

snoring and 5 patients (15.2%) didn't know whether they snored or not. Five out of 6 patients who answered "don't know" for snoring had $(A+H)\cdot h^{-1} \geq 30$.

There was a significantly higher proportion of EDS (66.6%, answer of "yes") in patients with $(A+H)\cdot h^{-1} \geq 30$ as well (Chi-square $p = 0.007$, Table 4.6, P. 153). If we take frequency into consideration again, the difference of moderate to severe EDS (answer of "always" or "4-6 times per week") between $(A+H)\cdot h^{-1} \geq 30$ and < 30 was also smaller but still significant ($p = 0.039$). Median pre-stroke ESS in 24 patients with $(A+H)\cdot h^{-1} \geq 30$ was only 6 although it was significantly higher than patients with $(A+H)\cdot h^{-1} < 30$ (ESS = 4, Mann-Whitney U test, $p = 0.03$). Only 29.2% of patients with $(A+H)\cdot h^{-1} \geq 30$ had ESS ≥ 10. The SSS results at baseline were not different between groups. There was a weak correlation between $(A+H)\cdot h^{-1}$ and ESS (Spearman's rho = 0.289, $p = 0.047$, Figure 4.5a, P. 167). Patient with $(A+H)\cdot h^{-1} \geq 30$ had a wider spectrum of ESS and SSS than patients with $(A+H)\cdot h^{-1} < 30$ (Figure 4.5b, P. 167). There was no significant correlation either between $(A+H)\cdot h^{-1}$ and SSS ($p = 0.896$, Figure 4.5c, P. 168) or between ESS and SSS ($p = 0.055$, Figure 4.5d, P. 168).

Almost all (97%) patients with $(A+H)\cdot h^{-1} \geq 30$, in contrast to 3/4 (75.8%) of patients with $(A+H)\cdot h^{-1} < 30$, had at least 1 of 5 major SDB-related symptoms in terms of snoring, EDS, choking episodes, witnessed apnoea and awakening unrefreshed ($p < 0.05$, Table 4.6, P. 153). About 90% of patients with $(A+H)\cdot h^{-1} \geq 30$, in contrast to less than 50% of patients with $(A+H)\cdot h^{-1} < 30$, had at least 2 of 5 major symptoms (Chi-square, $p < 0.001$). More than half (57.6%) of patients with $(A+H)\cdot h^{-1} \geq 30$, in contrast to less than 1/4 (24.2%) of patients with $(A+H)\cdot h^{-1} < 30$, had at least 3 of 5 major symptoms ($p < 0.01$).

The sensitivity and specificity of all major SDB-related symptoms were not high (< 90%, Table 4.7, P. 154). Snoring, EDS and choking episodes were 3 major symptoms with a relatively higher positive likelihood ratio (LR+ ≥ 2). The likelihood ratio of other single variables was low (LR+ < 2).

After controlling for confounding factors in a logistic regression model, only age (65-79), BMI (≥ 25) and snoring remained independent predictors for moderate to

severe SDB, $(A+H)\cdot h^{-1} \geq 30$ (Table 4.8, P. 155). EDS and choking episodes were no longer significant. I propose a simple clinical pathway of decision making to be used in the future for moderate to severe SDB in stroke based on the results of logistic regression with age, BMI, snoring and forced entry of EDS as predictors. A flow chart of decision making for sleep study in a stroke based on the best-fitted model was drawn (Figure 4.6, P. 169). Three predictors in the final regression model, age, BMI and reported snoring and one not in the model, self-reported EDS, were used to draw the flow chart. EDS was still used to increase the predictive value of the model because it is a common symptom and there was a significant difference of EDS between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 in my study. The purpose of the flow chart was to predict the probability of having moderate to severe SDB, i.e. $(A+H)\cdot h^{-1} \geq 30$, in stroke. As the prevalence of SDB with $(A+H)\cdot h^{-1} \geq 30$ in my study was 50% the probability of $\geq 50\%$ is used as a cut-off point to consider whether stroke patients can be referred for a sleep study.

4.4.7 The role of pulse oximetry in the diagnosis of SDB in stroke

Oximetric variables in terms of oxygen desaturation index (ODI), percentage of time with SaO2 < 90% and mean SaO2 obtained from pulse oximetry were used to calculate the Receiver Characteristics Curve (ROC) for predicting moderate to severe SDB (AHI $\geq$ 30) according to sensitivity and specificity at different cut-off points. The results showed that ODI had low sensitivity (69.7%) but high specificity (90.9%) at the cut-off point of 11.8/h (Figure 4.7, P. 170 and Table 4.9, P. 156). The area under the ROC curve was 0.87 (95% CI = 0.77-0.94), which means it had only fair predictive accuracy (> 0.80). ODI was slightly but not significantly better than the percentage of time with SaO2 < 90% in predicting moderate to severe SDB. The predictive value of mean oxygen saturation was significantly lower than ODI and the percentage of time with SaO2 < 90.

4.4.8 Sleep-related stroke and onset time of stroke

The distribution of stroke onset in 66 patients showed a peak of relative risk located in the 4-hour interval between 8 am and noon (Figure 4.8a, P. 171). Three curves were drawn for the odds of stroke onset in patients with $(A+H)\cdot h^{-1} < 15$, $15 \leq (A+H)\cdot h^{-1} < 30$ and $(A+H)\cdot h^{-1} > 30$ based on the best fitted polynomial regression model. Morning peak of stroke onset was evident in all three groups. The circadian pattern of odds of stroke onset was similar in patients with $15 \leq (A+H)\cdot h^{-1} < 30$ and > 30 but different from that in patients with $(A+H)\cdot h^{-1} < 15$ (Figure 4.8b, P. 171). Patients with $(A+H)\cdot h^{-1} \geq 15$ appeared to have the peak of stroke onset located in the 4-hour interval between 8 am to noon (9:30 am) and patients with $(A+H)\cdot h^{-1} < 15$ appeared to have the peak of stroke onset located in the 4-hour interval between 4 am to 8 am (7:30 am). There was about 2 hours of difference of peak time between these two groups. Because the raw data entered into the regression model were smoothed by moving average of number of events in two consecutive 1-hour block of time and the number of events was relatively low, the difference of 2 hours is approximately equal to 2 hours of error bar, so this difference might not be significant.

Patients with $(A+H)\cdot h^{-1} \geq 15$ had higher odds of stroke onset from midnight to noon but patients with $(A+H)\cdot h^{-1} < 15$ had higher odds of stroke onset from noon to midnight (Figure 4.8b, P. 171). I further compared two groups for waking time and sleeping time (see chapter 4.3.5) which also approximate the schedule in the stroke wards. Patients with SDB $[(A+H)\cdot h^{-1} \geq 15]$ had more strokes presenting in "waking time" ($p = 0.006$, Figure 4.8c, P. 172) than in "sleeping time". A similar finding was seen in patients with atrial fibrillation (AF, $p = 0.029$).

Twenty-four (36.4%) of 66 patients had sleep-related stroke. Nine of 24 patients had stroke onset between midnight and 5:59 am. Eleven of 24 had stroke onset happened between 6:00 and 9:00 am. One of 24 had a stroke during an afternoon nap and three of 24 during evening naps. There was no significant difference of $(A+H)\cdot h^{-1}$ between patients with (median = 23.5/h, IQR = 12.7-42.5) and without (median = 32.5/h, IQR = 17.2-48.0) sleep-related stroke (Mann-Whitney U test, $p = 0.497$,

Table 4.10, P. 157). There was no significant difference of age, type of stroke, severity of stroke, pre-stroke and post-stroke sleepiness between patients with and without sleep-related stroke. There was also no significant difference in the frequency of sleep-related or wake-related stroke in 4 groups of patients from lower to higher $(A+H)\cdot h^{-1}$ (Chi-square test, p = 0.523, Figure 4.8d, P. 172).

In the logistic regression model of prediction, neither $(A+H)\cdot h^{-1}$ nor oximetric variables were independent predictors for sleep-related stroke either in the total patient group or in the subgroup of patients with $(A+H)\cdot h^{-1} \geq 30$. In the subgroup with $(A+H)\cdot h^{-1} < 30$, the interaction of lowest SaO2 and lowest heart rate (HR) was the only independent predictor for sleep-related stroke (p = 0.023, Table 4.11, P. 158). The formula generated from the logistic regression model was:

Log (odds) = -0.002 * (lowest SaO2) * (lowest HR) + 4.103.

Where odds = p/1-p ("p" is the probability of sleep-related stroke),

Coefficient for (lowest SaO2) * (lowest HR) = -0.002,

Constant (also called the "intercept") = 4.103,

A surface plot derived from the logistic regression model according to table 4.11 (P. 158) was drawn to demonstrate this relationship (Figure 4.8e, P. 173). The z-axis represented odds of sleep-related stroke. The x- and y-axis represented lowest heart rate and lowest SaO2 respectively. The plot showed the lower the lowest SaO2 and the lower the lowest heart rate the higher the odds of sleep-related stroke in the group with $(A+H)\cdot h^{-1} < 30$.

4.4.9 The relationship between variables in sleep study and baseline assessment in stroke

Lowest SaO2 and variables related with heart rate were significantly correlated with cognitive functions measured by MMSE and ACE at baseline (Table 4.12, P. 159). Post-hoc multivariate analysis with logistic regression after adjusting for

dysphasia showed that dysphasia ($p = 0.001$) and the interaction of lowest SaO2 and lowest heart rate ($p = 0.002$) were two independent predictors for lower cognitive score (ACE ≤ 80) at baseline (Table 4.13, P. 160).

There was no significant gender difference in age, BMI, $(A+H)\cdot h^{-1}$ and oximetric variables. Female patients had slightly but significantly lower haemoglobin ($p = 0.01$), haematocrit ($p = 0.001$), platelet count ($p = 0.017$) and score of MMSE ($p = 0.048$, Table 4.14, P. 161).

4.5 Discussion

4.5.1 Prevalence of SDB in stroke

The reasons why only 15% of screened stroke patients were eligible in this study were:

- I had strict entry criteria which were designed for randomized controlled trial (RCT) of nasal continuous positive airway pressure (CPAP).
- Patients had to agree to both overnight sleep study and CPAP treatment before being recruited into the observational part of the study.

This might increase the rate of compliance to CPAP treatment but, on the other hand, could result in bias of reporting prevalence of SDB. The prevalence study in my research was designed to determine the frequency of SDB in patients 14-19 days after definite stroke who might be able to cope with CPAP therapy. This might be not the same as the prevalence of SDB in all patients after stroke. It is a relevant and theoretically important question and has to be seen in the specific clinical context. By excluding patients with severe incapacity from stroke the prevalence observed in this study might be lower than in the whole stroke population whereas by excluding patients with mild stroke (NIHSS < 4) the opposite effect might have occurred. The baseline data of stroke patients in my study were similar with those in another study performed in the same stroke unit with broadened entry criteria which have been presented in chapter 4.4.4. This reflects that my stroke patients might be similar with typical in-hospital stroke patients, at least in Edinburgh. Thus the difference of prevalence of SDB between my study and general stroke population might not be big.

Our study supports the high prevalence of SDB in acute stroke noted by others [Bassetti and Aldrich1999b]. We found that 50% of stroke patients had $(A+H)\cdot h^{-1} \geq 30$ and 60% had $(A+H)\cdot h^{-1} \geq 20$. We also found that SDB increased in patients aged from age 40s to 70s but dropped in patients aged in the 80s although a previous study showed there was no significant change of AHI over time unless it was associated with increased BMI [Ancoli-Israel *et al.* 2001]. The difference between their study

and mine is that I did a cross-sectional study and conducted an analysis for four different age groups of stroke patients but they did a longitudinal follow-up for a group of non-stroke elderly patients with SDB. SDB may not change over time in the elderly but the proportion of patients with SDB could be higher in older age. The reason why $(A+H)\cdot h^{-1}$ decreased in the age group of 80s could be: (1) those who had SDB died before their 80s due to cardiovascular diseases or other mortality [Ancoli-Israel, Kripke, Klauber, Fell, Stepnowsky, Estline, Khazeni, and Chinn1996]; (2) very old stroke patients were too ill to participate the study.

High prevalence of SDB in stroke means that SDB is related to stroke. This could be because (1) SDB is a cause of stroke; (2) SDB is a consequence of stroke; (3) some risk factors are confounders between SDB and stroke. Like many other previous publications, we face the following problems in the cross-sectional prevalence study:

- There is selection bias in recruiting stroke patients.
- There is no control.

It is more difficult to conduct a community-based study to clarify the relationship between SDB and stroke. Recruitment in this study was hospital-based without a standardized sampling method. Admitted stroke patients could have had more complicated medical illness prior to stroke which may include SDB so the prevalence of SDB could be higher than that obtained from community-based studies.

Prospective cohort studies and individually matched case-control studies are better epidemiological designs in determining the prevalence of an illness. To apply these two methods to study the relationship between SDB and stroke is not only time consuming but also difficult in collecting suitable controls. Some large population-based prospective studies are on their way although results of cross-sectional parts had been published. Only one individually matched case-control study has been published but that dealt with TIA which is much more stable than stroke.

4.5.2 Diagnosis and screening of SDB in stroke

The apnoeas and hypopnoeas detected after stroke were mainly obstructive in my study. Predominant central sleep apnoea and Cheyne-Stokes respiration were reported in a study recruiting 32 patients with ischemic stroke [Nachtmann *et al.* 1995] and another study recruiting 161 patients with first-ever stroke, either ischemic or haemorrhagic, or TIA [Parra *et al.* 2000]. Their sleep studies were conducted in the acute phase of stroke. For example, all stroke patients of Parra et al. were admitted within 48 hours of onset of stroke and limited sleep studies were performed during the first 48-72 hours after admission. Sleep-disordered breathing was also obstructive predominantly in the study conducted by Bassetti et al. recruiting 128 patients [Bassetti and Aldrich1999b]. In their study polysomnography was recorded 9 days (1-71 days) after stroke which was similar to our study in both methodology and result.

The failure rate of overnight Embletta recording was only 7% in our study. If we count three repeated, the failure rate was 11.3% for the first recording. We had a lower failure rate than the previous study in non-stroke subjects conducted in our sleep centre (18%) [Whittle *et al.* 1997]. The reasons could be:

- I excluded most of the severe or complicated stroke patients so patients recruited were more stable and could tolerate overnight sleep study better.
- The Embletta study was partially attended. I stayed with patients in the first two hours of recording to check whether all monitors were in position properly.
- Most of the recordings were performed in the ward. Nurses on the ward could, though not constantly, keep an eye on the patients.

Three problems are faced in a time-consuming overnight sleep study in stroke: (1) it is an extra burden for patients especially when they are unstable and have many other critical diagnostic and treatment procedures waiting to be done; (2) patients could have unstable vital signs, fluctuating consciousness, risk of mortality, cognitive impairment and emotional distress especially in the acute and subacute phase; (3) it is

expensive especially for in-lab sleep studies which need extra space, attendant and transfers between stroke unit and sleep laboratory and this can increase the total cost of stroke care. According to these practical problems we need to sort out how to make the diagnosis of SDB in stroke more feasible.

The devices used in stroke patients in previous publications ranged from pulse oximetry [Cherkassky *et al.* 2003;Good *et al.* 1996], portable limited sleep study [Harbison *et al.* 2002b;Parra *et al.* 2000] to full portable or in-lab PSG [Bassetti and Aldrich1999b;Kaneko *et al.* 2003b].

Pulse oximetry which is one of the most available devices in stroke unit, has been used as not only an initial screening [Epstein and Dorlac 1998] but also, when combined with sleep-related history [Bennett and Kinnear 1999] or heart rate variability [Raymond *et al.* 2003], as a direct diagnosis of SDB to reduce clinical loading of PSG. A repetitive and profound desaturation is highly specific for SDB [Douglas, Thomas, and Jan1992] but this kind of pattern can happen in central sleep apnoea and Cheyne-Stokes respiration which are common in acute stroke [Nachtmann *et al.* 1995;Parra *et al.* 2000]. According to my study, oxygen desaturation index (ODI) had high specificity (90%) but relatively lower sensitivity. About 30% of patients with moderate to severe SDB could be missed by oximetry alone so pulse oximetry is better to be used as a screening instead of diagnostic tool for SDB in stroke.

I chose a portable limited sleep study instead of pulse oximetry alone because of the following reasons:

- It is no more inconvenient than overnight pulse oximetry.
- It is recommended as a higher level of diagnostic tool for SDB by the American Academy of Sleep Medicine.
- It has been proved to be valid in comparison with the gold standard of PSG in diagnosis of SDB [Dingli *et al.* 2003].
- It can save time and money [Douglas 2003].

There are several kinds of commercial portable devices for limited sleep study, which are rated level 3 or level 4 by APSS. The device we used (Embletta) belongs to level 3 and it actually contains full cardiopulmonary signals and sensor for body position. For unstable stroke patients, more cardiorespiratory sensors can ensure a higher success rate because if one of them comes off or fails during the recording one can still make the diagnosis with the remaining sensors. Oximetry alone is rated level 4. If the single signal comes off during an unattended sleep study the procedure is completely failed and no diagnosis can be made at all. This situation is common in stroke studies than ordinary studies performed in sleep centres. In our study only 3 of 8 patients who had an inadequate sleep study in the first night were happy to repeat the recording.

A limited sleep study using the Embletta device is different from conventional polysomnography. Embletta does not include electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG) so might be better tolerated by stroke patients. On the contrary, without EEG, EOG and EMG we can not score sleep stages and arousals so could overestimate AHI. Thus we use $(A+H)\cdot h^{-1}$ instead of AHI to express the total amount of apnoea and hypopnoea events in bed instead of during sleep and set up a higher cut-off criteria ($(A+H)\cdot h^{-1} \geq 30$ and < 30) for further randomization and comparison of outcome between groups which will be discussed in chapter 5.

4.5.3 Characteristics of SDB in stroke

Our stroke patients with SDB were older (74 year-old) but had lower BMI (26 kg/m^2) than those referred to a sleep centre (47 year-old, 30 kg/m^2) [Engleman *et al.* 1998]. There are two possibilities to explain these findings:

- SDB and stroke are more common in older age. Those who have symptomatic SDB since younger age could have either been treated or died of other cardiovascular diseases before they had a stroke.

- There is increased frequency of SDB in women after menopause. Women usually have lower BMI than men so could "dilute" the mean BMI in the elderly.

Frequency of self-reported habitual snoring was variable in stroke ranging from 32 to 56 % in all patients and 28 to 100% in patients with SDB [Bassetti and Aldrich1999b;Cherkassky *et al.* 2003;Harbison *et al.* 2002b;Iranzo *et al.* 2002]. In our study, we found self-reported snoring was significantly higher in patients with $(A+H)\cdot h^{-1} \geq 30$ than $(A+H)\cdot h^{-1} < 30$ but difference of habitual snoring between groups was less prominent.

A similar phenomenon happens in self-reported EDS. In my study I found that patients with $(A+H)\cdot h^{-1} \geq 30$ had significantly higher proportion of self-reported EDS prior to stroke than those with $(A+H)\cdot h^{-1} < 30$ although logistic regression did not show EDS was an independent predictor for $(A+H)\cdot h^{-1} \geq 30$. We did not apply ESS to all patients to assess pre-stroke sleepiness because we found patients in acute phase of stroke were sometimes not able to make proper judgment for all situations mentioned in ESS especially for some questions which were difficult to answer, for instance, dozing off in front of traffic lights and in meetings or a theatre. We found that SSS for post-stroke sleepiness was not sensitive enough to tell any difference between groups. Although ESS can make a difference the ESS score in stroke patients with SDB is low and it is for pre-stroke sleepiness only. Stroke patients with SDB are less sleepy than those seen in sleep centres probably because patients referred to sleep centre are usually symptomatic and coming from the community. This is rather different from stroke patients who usually don't know they have any problems related to SDB until they receive a screening test in the ward. Lowering the cut-off score of ESS in combination with taking self-reported symptom of EDS into account can make a more accurate diagnosis in the elderly with stroke.

It is common for patients with acute or subacute stroke to have a certain degree of disturbance of consciousness resulting from their brain lesion which may not equal to the sleepiness measured by ESS. A new sleepiness scale for stroke which can distinguish between true sleepiness and consciousness disturbance might be helpful.

Previous studies depending on self-reported sleep symptoms without applying scales of sleepiness to the elderly also showed clear association between EDS and falls [Brassington *et al.* 2000], increased rate of myocardial infarction in women [Newman *et al.* 2000] and poor functional outcome [Gooneratne *et al.* 2003]. A few stroke studies [Bassetti *et al.* 1996;Iranzo *et al.* 2002] had similar findings to mine that ESS was not high in stroke patients who had SDB. Only one study emphasized pre-stroke ESS as it was associated with poor outcome of stroke [Harbison *et al.* 2002b].

About 4% of men and 2% of women in general population have SDB with EDS [Young *et al.* 1993]. Whether treating patients with SDB and without EDS is effective, is still controversial [Barbe *et al.* 2001]. Elderly patients with symptomatic SDB could be neglected because their SDB-related symptoms are usually vague and they might have many other medical problems which shift the attention of their partners, family, caregivers and even first-line physicians who could care more about other medical problems than SDB-related symptoms.

4.5.4 A propose clinical pathway for SDB in stroke

A practical problem we face is that whether we can perform a simple bedside screening test for SDB in stroke units or stroke rehabilitation wards. I propose a clinical pathway with four predictors, age, BMI, reported snoring and EDS. The flow chart is more convenient than pulse oximetry for screening SDB and is easily used by first-line physicians who have little experience in SDB. The model allows prediction for moderate to severe SDB, i.e. $(A+H)\cdot h^{-1} \geq 30$, in stroke patients. It can avoid too many unnecessary overnight sleep studies in case some first-line physicians tend to refer stroke patients with snoring to sleep centre. Two problems are faced before using this model:

- The proposed clinical pathway needs model validation. The prediction model was generated in this study and should be validated by applying it to another group of stroke patients in the future.

- The proposed clinical pathway assumes that a sleep study is worthwhile in stroke but this depends on whether stroke patients benefit from CPAP treatment or not. The results of randomized controlled trial (RCT) which will be presented in chapter 5 do not convince that this is the case.

4.5.5 SDB and stroke onset

The time onset of stroke in my study using 4 hr blocks for analysis has a peak in the morning hours, that is to say, between 8 am to noon confirming earlier observations [Elliott1998]. However, there was no evidence that patients with SDB had an excess of sleep related strokes.

I found in my study that there was no significant difference in sleep-related stroke between patients with higher and lower $(A+H)\cdot h^{-1}$. Furthermore, patients with SDB, defined as $(A+H)\cdot h^{-1} \geq 15$, had more strokes happening in the waking time (8:00 am to 11:59 pm) rather than in the sleeping time (0:00 am to 7:59 am). These finding, which showed that patients with SDB ($(A+H)\cdot h^{-1} \geq 15$)) might be associated with daytime stroke, is in contrast to previous finding which showed that patients with SDB (AHI $\geq$ 25) were independently associated with sleep-related stroke [Iranzo *et al.* 2002]. However timing of stroke onset is not an exact science and may be influenced by cultural factors such as normal waking time. In addition the number of patient in my study is relatively low.

Most of the sleep-related strokes (66%) in the study performed by Iranzo *et al.* happened between 7:01 - 9:00 am. As there was a higher percentage of REM sleep during this period which might aggravate pre-existing SDB they proposed that repetitive episodes of desaturation caused by SDB might provoke ischaemic stroke. Unfortunately they did not find that oxygen desaturation played a significant role. On the contrary, we could not find a strong association between SDB and sleep-related stroke. In further sub-group analysis although it was sub-optimal and biased in post-hoc analysis, I found the interaction between oxygen desaturation (lowest SaO2) and bradycardia (lowest heart rate) was significantly associated with sleep-related stroke, but, this was only found in patients with less severe SDB ($(A+H)\cdot h^{-1} < 30$). The

significance perhaps reflects the large number of comparisons based on post-hoc analysis. Bradycardia has been recognized in SDB [Brown *et al.* 1996;Zwillich *et al.* 1982] and may be explained by increased vagal tone associated with hypoxia [Hanly *et al.* 1989]. Bradycardia is more common than hypotension in patients with SDB [Guilleminault *et al.* 2001]. Bradycardia and hypoxaemia could impair cerebral circulation especially in patients who have impaired cerebrovascular autoregulation [Livera *et al.* 1991]. Although oxyhaemoglobin desaturation alone was not found to play a significant role in sleep-related stroke in previous study [Iranzo *et al.* 2002] our study showed interaction between hypoxia and bradycardia is more important.

Iranzo *et al.* thought that stroke in patients who first noticed neurological deficits immediately following awakening between 6:00 am to 7:59 am could be overestimated as stroke happened in the daytime rather than during sleep. I did not face this problem as I defined the daytime period from 8:00 am to 11:59 am for analysis of stroke onset. Actually almost half of sleep-related stroke in our study happened between 6 and 9 am.

My results also support the previous finding that patients with atrial fibrillation also have more strokes appearing in the daytime [Lip *et al.* 2001]. SDB was reported to have an influence on recurrence of AF [Kanagala *et al.* 2003]. Whether or not the interaction of SDB and AF plays a role in daytime onset of stroke needs further clarification. The underlying mechanisms for excessive stroke onset in the morning could be enhanced by the existence of SDB through the following complications:

- Swings of blood pressure [Akashiba *et al.* 1999;Guilleminault *et al.* 2001]and heart rate [Sato *et al.* 1997].
- Increased blood viscosity [Nobili *et al.* 2000], platelet aggregation [Sanner *et al.* 2000] and fibrinogen [Wessendorf *et al.* 2000].
- Aggravation of AF or paroxysmal AF [Kanagala *et al.* 2003].

4.5.6 Influence of bradycardia and hypoxaemia on baseline cognitive function in stroke

In ischaemic stroke, any further haemodynamic compromise in terms of hypoxia, bradycardia or hypotension could turn vulnerable areas called ischaemic penumbra into permanent infarction in acute stage and compromise neuronal plasticity to prevent damaged areas from recovery in subacute stage. We found cognitive functions at baseline (14-19 days after stroke) were correlated with lowest oxygen saturation, lowest heart rate and heart rate variability. Logistic regression was performed to control strong confounders of cognitive deficits, i.e. dysphasia and depression. In the final model interaction of lowest oxygen saturation and lowest heart rate remained independently associated with cognitive impairment. Hypoxia and bradycardia are highly associated with severity of SDB as mentioned in a previous section. Thus we think SDB has an influence on the cognitive function of stroke patients in the subacute stage through haemodynamic compromise as well.

4.6 Conclusions

In this cross-sectional study we have the following conclusions:

- Overnight limited sleep study can be applied to a group of highly selective (about 15%) stroke patients with low failure rate.
- The prevalence of SDB in hospital-based stroke patients is high in Edinburgh, UK.
- The characteristics of stroke patients with SDB are similar to those of non-stroke patients with SDB but the former are older, less obese and less sleepy.
- The predictive value of pulse oximetry alone for SDB in stroke is not high as 1/3 (31.3%) of stroke patients with moderate to severe SDB can be missed.
- Combination of age, BMI, snoring and EDS based on logistic regression model may be useful as a simple screening tool at bedside in stroke unit.
- Patients with $(A+H)\cdot h^{-1} \geq 15$ had more strokes happening between 8:00 am to 11:59 pm than between 0:00 am to 7:59 am. A similar finding was seen in patients with atrial fibrillation.
- Interaction of lowest oxygen saturation and lowest heart rate in a regression model was independently associated with sleep-related stroke in patients with $(A+H)\cdot h^{-1} < 30$ and cognitive impairment (ACE score < 81) in all recruited patients.

Table 4.1 Findings of overnight sleep study (n=66)

	Total	AHI < 30	AHI ≥ 30
Apnoea Hypopnoea Index, n/hr	30.5 (14.5-45.5)	14.5 (8.0-21.8)	44.8 (36.5-55.3)
Obstructive Apnoea Index, n/hr	3.1 (0.5-11.8)	0.7 (0.2-2.3)	11.7 (7.1-20.2)
Mixed Apnoea Index, n/hr	0.0 (0.0-0.2)	0.0 (0.0-0.0)	0.2 (0.0-1.2)
Central Apnoea Index, n/hr	0.4 (0.0-1.1)	0.2 (0.0-0.5)	0.5 (0.2-1.6)
Hypopnoea Index, n/hr	20.5 (12.3-32.1)	12.4 (6.6-16.7)	32.0 (23.5-39.1)
Desaturation Index, n/hr	7.8 (3.7-21.0)	4.8 (2.2-7.3)	20.5 (8.7-34.9)
Mean SaO2, %	94.0 (92.8-95.4)	94.7 (93.4-95.7)	93.3 (92.0-94.6)
Lowest SaO2, %	83.0 (79.8-86.0)	86.0 (82.5-88.0)	81.0 (73.5-85.0)
Mean DESAT, %	5.1 (4.8-5.7)	4.9 (4.5-5.5)	5.2 (4.8-5.9)
% Time SaO2 < 90%	1.2 (0.2-7.8)	0.3 (0.1-1.3)	3.9 (1.1-16.5)
Mean A/H duration, sec †	18.5 (16.0-21.1)	17.9 (15.4-20.4)	18.8 (17.0-21.8)
Mean Heart Rate	63.7 (55.8-70.3)	60.1 (55.1-67.6)	64.3 (59.4-73.0)
CSR, n (%)	9 (13.6%)	1 (3.0%)	8 (24.2%)
AHI ≥ 30, n (%)	33 (50%)		
AHI ≥ 20, n (%)	42 (63.6%)		
AHI ≥ 15, n (%)	48 (72.7%)		
AHI ≥ 10, n (%)	57 (86.4%)		

† A/H: apnoea or hypopnoea

Table 4.2 Correlation between heart rate variables and other sleep variables (n = 66) ¶

	Mean HR	HRV †	Min HR
Apnoea Hypopnoea Index	r = 0.147	r = 0.353	r = -0.372
	p = 0.240	p = 0.004**	p = 0.002**
Desaturation Index	r = 0.246	r = 0.428	r = -0.307
	p = 0.046	p < 0.001***	p = 0.012*
Mean SaO2	r = -0.238	r = -0.342	r = 0.249
	p = 0.054	p = 0.005**	p = 0.043*
% Time SaO2 < 90%	r = 0.216	r = 0.553	r = -0.467
	p = 0.081	p < 0.001***	p < 0.001***
Lowest SaO2	r = -0.182	r = -0.516	r = 0.407
	p = 0.143	p < 0.001***	p = 0.001**

¶ Spearman's rank correlation

† HRV: heart rate variability, defined as standard deviation of overnight pulse rate data recorded by pulse oximetry

* p < 0.05, ** p < 0.01, *** p < 0.001

Table 4.3 Demographic characteristics, past medical history and classification of stroke in patients with AHI ≥ 30 (n = 33) and AHI < 30 (n = 33)

	Total	AHI < 30	AHI ≥ 30	p Value¶
Age	74 (65-81)	74 (59-82)	74 (72-79)	0.149
Male/Female, N	45/21	22/11	23/10	0.792
Body mass index, kg/m^2	25.3 ± 4.9	24.3 ± 4.0	26.3 ± 5.5	0.087
Hypertension, %	60.6	60.6	60.6	1.000
Diabetes mellitus, %	9.1	6.1	12.1	0.392
Hypercholesterolemia, %	43.9	48.5	39.4	0.457
Previous stroke or TIA, %	25.8	24.2	27.3	0.778
First ever stroke, %	90.9	90.9	90.9	1.000
Coronary artery disease, %	24.2	27.3	21.2	0.566
Atrial fibrillation, %	19.7	12.1	27.3	0.122
Left ventricular hypertrophy, %	12.3	9.7	18.5	0.423
Current smoking, %	25.8	30.3	21.2	0.398
OCSP classification				0.342
TACI, n	13	5	8	
PACI, n	41	23	18	
POCI, n	3	0	3	
LACI, n	4	2	2	
ICH, n	5	3	2	

¶ Mann-Whitney U test or Chi-square test

§ OCSP: Oxford Classification of Stroke project; TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; POCI: Posterior circulation infarct; LACI: Lacunar infarct; ICH: Intracerebral haemorrhage

Table 4.4 Baseline assessment in patients with AHI < 30 and AHI ≥ 30 ¶

	AHI < 30	AHI ≥ 30	p Value
NIH Stroke Scale (0-42)	6 (5-8)	6 (5-9)	0.974
Barthel Index (0-20)	12 (8-17)	12 (9-17)	0.918
Mini-mental Status Exam (0-30)	27 (25-29)	27 (24-29)	0.703
Addenbrooke's Cognitive Exam (0-100)	84 (71-91)	80 (64-86)	0.248
Orientation (1-10)	10 (8-10)	10 (8-10)	0.923
Attention and concentration (0-8)	8 (6-8)	7 (6-8)	0.576
Memory (0-35)	29 (26-33)	29 (20-32)	0.434
Verbal fluency (0-14)	8 (6-9)	6 (4-9)	0.213
Language (0-28)	27 (23-28)	26 (22-27)	0.228
Visual spatial (0-5)	3 (2-5)	3 (1-4)	0.326
Hospital Anxiety Depression Scale (0-42)	9 (6-14)	9 (6-15)	0.989
Anxiety (0-21)	4 (2-7)	4 (2-6)	0.808
Depression (0-21)	5 (3-8)	5 (3-9)	0.935

¶ Mann-Whitney U test

Table 4.5 Laboratory data in patients with AHI ≥ 30 (n = 33) and AHI < 30 (n = 33)

	AHI < 30	AHI ≥ 30	p Value ¶
Systolic BP on admission	153 (132-173)	150 (133-169)	0.898
Diastolic BP on admission	86 (75-94)	85 (79-92)	0.635
Haemoglobin	142 (135-155)	143 (136-153)	0.949
Haematocrit	42.1 (39.8-45.1)	42.4 (39.7-44.9)	0.923
Platelet	230 (203-279)	216 (196-241)	0.089
Plasma glucose	5.9 (5.4-6.6)	6.1 (5.8-7.4)	0.142
Total Cholesterol	5.3 (4.8-5.9)	5.1 (4.3-6.3)	0.639
Fibrinogen (N = 19/18)	3.7 (2.8-4.5)	3.7 (3.0-5.0)	0.523
ESR (n = 26/25)	10 (6-23)	20 (10-30)	0.058
CRP (n = 17/13)	6.9 (3.1-14.0)	6.9 (0.8-13.5)	0.615
Carotid stenosis, n †	6/13	4/15	0.461

¶ Mann-Whitney U test

† Stenosis of internal carotid artery > 60% on either side measured by duplex ultrasonography and compared between groups by Fisher's exact test

Table 4.6 Sleep questionnaire in patients with AHI ≥ 30 (n = 33) and AHI < 30 (n = 33)

	AHI < 30	AHI ≥ 30	p Value ¶
Sleep Questionnaire			
Snoring	37.5	78.6	0.001**
Snoring including "don't know", %	39.4	81.8	< 0.001***
Habitual snoring, % (1)	24.2	45.5	0.071
Witnessed apnoea, % (2)	19.2	25.0	0.623
Choking episode, %	9.1	24.3	0.099
Awakening unrefreshed, %	54.5	69.7	0.205
Excessive daytime sleepiness (EDS), %	33.3	66.7	0.007**
Moderate to severe EDS, % (3)	6.1	24.2	0.039*
Road traffic accident, N	1	0	0.396
Morning headache, %	21.2	18.2	0.757
Nocturnal polyuria, % (4)	18.2	24.2	0.547
Major symptoms in sleep questionnaire (5)			
≥ 1 of 5 major symptoms, %	75.8	97.0	0.012*
≥ 2 of 5 major symptoms, %	45.5	87.9	< 0.001***
≥ 3 of 5 major symptoms, %	24.2	57.6	0.006**
≥ 4 of 5 major symptoms, %	3.0	15.2	0.087
5 major symptoms, %	3.0	6.1	0.555
Epworth Sleepiness Scale (0-24) (6)	4 (2-7)	6 (3-11)	0.030*
Epworth Sleepiness Scale > 10, %	8.3	29.2	0.064
Stanford Sleepiness Scale (1-7)	2 (2-4)	3 (1-4)	0.459

(1) "often" or "almost everyday"; (2) available for N = 26,24; (3) "always" or "4-6 times per week"; (4) more than 2 times per night; (5) snoring, EDS, choking episode, witnessed apnoea, awakening unrefreshed; (6) pre-stroke sleepiness, N = 24,24

¶ Mann-Whitney U test or Chi-square test

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4.7 The predictive value of major SDB-related symptoms for moderate to severe SDB (AHI ≥ 30)

Items	Sensitivity (CI)	Specificity (CI)	LR +	LR –	PPV (%)	NPV (%)
Snoring †	81.8 (68.7-95.0)	60.6 (43.9-77.3)	2.08 (1.32-3.27)*	0.30 (0.14-0.65)	67.5 (53.0-82.0)	76.9 (60.7-93.1)
EDS	63.0 (44.7-81.2)	68.8 (52.7-84.8)	2.01 (1.12-3.63)*	0.54 (0.31-0.93)	63.0 (44.7-81.2)	68.8 (52.7-84.8)
Witnessed apnoea	25.0 (7.7-42.3)	80.8 (65.6-95.9)	1.30 (0.46-3.71)	0.93 (0.69-1.25)	54.5 (25.1-84.0)	53.8 (38.2-69.5)
Choking episode	24.2 (9.6-38.9)	90.9 (81.1-100)	2.67 (0.77-9.18)*	0.83 (0.67-1.04)	72.7 (46.4-99.0)	54.5 (41.4-67.7)
Unrefreshed	71.0 (55.0-86.9)	43.8 (26.6-60.9)	1.26 (0.86-1.84)	0.66 (0.34-1.30)	55.0 (39.6-70.4)	60.9 (40.9-80.8)
Any 1	97.0 (91.1-100)	24.2 (9.6-38.9)	1.28 (1.05-1.57)	0.12 (0.02-0.94)	56.1 (43.3-69.0)	88.9 (68.4-100)
Any 2	87.9 (76.7-99.0)	54.5 (37.6-71.5)	1.93 (1.30-2.87)	0.22 (0.08-0.59)	65.9 (51.9-79.9)	81.8 (65.7-97.9)
Any 3	51.5 (34.5-68.6)	78.8 (64.8-92.7)	2.43 (1.16-5.07)*	0.62 (0.42-0.91)	70.8 (52.6-89.0)	61.9 (47.2-76.6)
Any 4	15.2 (2.9-27.4)	97.0 (91.1-100)	5.00 (0.62-40.5)*	0.88 (0.75-1.02)	83.3 (53.5-100)	53.3 (40.7-66.0)

† including "don't know" answer; * LR+ > 2

LR+ (positive likelihood ratio) = (sensitivity) / (1 – specificity)

LR– (negative likelihood ratio) = (1 – sensitivity) / (specificity)

PPV (positive predictive value) = (true positive) / (true + false positive)

NPV (negative predictive value) = (true negative) / (true + false negative)

Table 4.8 Prediction of moderate to severe SDB by demographic data and SDB-related symptoms (n = 66) ¶

Dependent variable	Sleep-disordered breathing ($(A+H)\cdot h^{-1} \geq 30$)		
Predictors	Age (p = 0.001), BMI (p = 0.049), snoring (p = 0.001), EDS (p = 0.007), choking (p = 0.099)		
Variables	Odds Ratio	Confidence Interval	p Value
Age (65-79) †	6.160	1.230-23.273	0.007**
BMI (≥ 25) †	4.389	1.149-16.759	0.030*
Snoring ‡	9.016	2.072-39.225	0.003**
EDS	1.460	0.402-5.308	0.565
Choking	2.655	0.537-13.117	0.231
Model Chi-Square	30.143 (df = 5)		< 0.001
Correct Predictions	78.8%		
Nagelkerke-R^2	0.489		

† Age (65-79 and others) and BMI (≥ 25 and < 25) were treated as dichotomous variables to increase power of model fit.

‡ "Don't know" answer is included.

¶ Logistic regression with enter method

* $p < 0.05$, ** $p < 0.01$

Table 4.9 Pairwise comparison of oximetric variables in prediction of moderated to severe SDB (AHI ≥ 30)

	ODI †	% Time SaO2 < 90%	Mean SaO2
ODI	Area under the ROC curve 0.871 (0.765-0.940)		
% Time SaO2 < 90%	Dif ‡ = 0.091 (-0.015-0.197) p = 0.092	Area under the ROC curve 0.780 (0.661-0.872)	
Mean SaO2	Dif = 0.192 (0.057-0.328) p = 0.005**	Dif = 0.101 (0.014-0.189) p = 0.023*	Area under the ROC curve 0.678 (0.552-0.788)

† ODI = oxygen desaturation index

‡ Dif = difference between areas under the ROC curves

* $p < 0.05$, ** $p < 0.01$

Table 4.10 Comparison between patients with sleep-related stroke (N = 24) and wake-related stroke (N = 42)

	Sleep-related stroke	Wake-related stroke
Age ‡	73 ± 10	72 ± 11
Baseline NIH Stroke Scale †	6 (5-7)	6 (5-8)
Baseline Stanford Sleepiness Scale †	2 (2-3)	3 (2-4)
Pre-stroke Epworth Sleepiness Scale †	4 (2-9)	6 (3-9)
Stroke type by OCSP (N) §		
TACI	4	9
PACI	16	25
POCI	0	3
LACI	3	1
ICH	1	4
$(A+H)\cdot h^{-1}$ †	23.5 (12.7-42.5)	32.5 (17.2-48.0)
Circadian onset of stroke (N)		
00:00 – 03:59	3	2
04:00 – 07:59	13	1
08:00 – 11:59	4	21
12:00 – 15:59	1	7
16:00 – 19:59	2	6
20:00 – 23:59	1	5
Total N	24	42

‡ Mean and SD

† Median and IQR

§ TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; POCI: Posterior circulation infarct; LACI: Lacunar infarct; ICH: Intracerebral haemorrhage

¶ Mann-Whitney U test: all $p > 0.05$

Table 4.11 Prediction of sleep-related stroke by oximetric variables in patients with mild SDB (AHI < 30, n = 33) ¶

Dependent variable	Sleep-related stroke		
Predictors	Lowest SaO2 (0.030), Lowest HR (0.029)		
Variables	Coefficient	Odds Ratio	p Value
Lowest SaO2 × Lowest HR	−0.002*	0.998 (0.997-1.000)	0.023*
Model Chi-Square		7.10 (df = 1)	0.008**
Correct Prediction		78.8%	
Nagelkerke-R^2		0.262	

¶ Logistic regression with forward likelihood method

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4.12 Correlation between sleep variables and cognitive functions ¶

	AHI	ODI	Lowest SaO2	Mean HR	HRV †	Min HR
Mini-mental Status Exam	r = -0.022	r = -0.018	r = 0.280	r = -0.045	r = -0.209	r = 0.094
	p = 0.863	p = 0.886	p = 0.023*	p = 0.719	p = 0.093	p = 0.455
Addenbrooke's Cognitive Exam	r = -0.061	r = -0.041	r = 0.311	r = -0.074	r = -0.322	r = 0.331
	p = 0.230	p = 0.750	p = 0.012*	p = 0.559	p = 0.009*	p = 0.008*
Orientation	r = 0.105	r = 0.075	r = 0.268	r = 0.044	r = -0.262	r = 0.266
	p = 0.411	p = 0.557	p = 0.033*	p = 0.731	p = 0.036*	p = 0.033*
Attention and concentration	r = -0.043	r = -0.048	r = 0.149	r = -0.026	r = -0.087	r = -0.037
	p = 0.738	p = 0.704	p = 0.241	p = 0.840	p = 0.494	p = 0.771
Memory	r = -0.033	r = -0.065	r = 0.278	r = -0.104	r = -0.273	r = 0.344
	p = 0.795	p = 0.611	p = 0.026*	p = 0.414	p = 0.029*	p = 0.005**
Verbal fluency	r = -0.074	r = -0.036	r = 0.144	r = -0.113	r = -0.271	r = 0.178
	p = 0.559	p = 0.777	p = 0.257	p = 0.373	p = 0.031*	p = 0.161
Language	r = -0.053	r = 0.098	r = 0.256	r = 0.003	r = -0.223	r = 0.284
	p = 0.678	p = 0.439	p = 0.041*	p = 0.979	p = 0.076	p = 0.023*
Visual spatial	r = -0.165	r = -0.076	r = 0.263	r = -0.098	r = -0.152	r = 0.133
	p = 0.194	p = 0.551	p = 0.036*	p = 0.442	p = 0.229	p = 0.294

¶ Spearman's rank correlation; † HRV: heart rate variability, defined as standard deviation of overnight pulse rate data recorded by pulse oximetry; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4.13 Prediction of cognitive impairment at baseline by logistic regression analysis ¶

Dependent variable	Addenbrooke's Cognitive Exam total score < 81		
Predictors	Lowest SaO2 (p = 0.079), Min HR (0.017), HRV (p = 0.004), dysphasia (p = 0.013), HADS depression (p = 0.094)		
Variables	Odds Ratio	Confidence Interval	p Value
Lowest SaO2 × Min HR	1.002	1.001-1.003	0.002
Dysphasia	22.424	2.932-171.490	0.001
Model Chi-Square	21.072 (df = 2)		< 0.001
Correct Predictions	71.9%		
Nagelkerke-R^2	0.374		

¶ Logistic regression with forward likelihood method

Table 4.14 Gender differences of demographic, sleep and baseline data ¶

	Male	Female	p Value
Age	73 (62-78)	75 (73-81)	0.151
Body mass index, kg/m^2	25.1 (22.0-28.2)	22.5 (21.2-28.3)	0.315
Apnoea Hypopnoea Index, n/hr	33.5 (14.6-49.6)	28.5 (13.9-31.2)	0.540
Desaturation Index, n/hr	9.4 (3.6-22.1)	7.0 (3.1-18.4)	0.441
% Time SaO2 < 90%	1.2 (0.3-10.0)	1.2 (0.1-4.5)	0.412
Haemoglobin	146 (137-155)	135 (129-145)	0.010*
Haematocrit	42.8 (41.1-45.5)	39.3 (38.2-42.4)	0.001**
Platelet	216 (187-251)	246 (215-323)	0.017*
Plasma glucose	6.0 (5.6-7.3)	6.1 (5.6-6.6)	0.929
OCSP classification			0.388
TACI, n (%)	11 (24.4)	2 (9.5)	
PACI, n (%)	26 (57.8)	15 (71.4)	
POCI, n (%)	3 (6.7)	2 (9.5)	
LACI, n (%)	1 (2.2)	1 (4.8)	
ICH, n (%)	4 (8.9)	1 (4.8)	
Epworth Sleepiness Scale	6 (3-10)	3 (2-7)	0.188
Stanford Sleepiness Scale	3 (2-4)	2 (1-4)	0.272
NIH Stroke Scale	6 (5-8)	6 (5-7)	0.590
Barthel Index	12 (9-17)	14 (7-16)	0.403
Mini-mental Status Exam	27 (25-29)	25 (22-28)	0.048*
Addenbrooke's Cognitive Exam	84 (70-89)	75 (61-87)	0.100
Hospital Anxiety Depression Scale	8 (6-13)	9 (7-16)	0.289
Anxiety	4 (2-7)	4 (2-6)	0.903
Depression	5 (2-7)	5 (4-11)	0.097

¶ Mann-Whitney U test

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Figure 4.1 Flow chart of patient recruitment

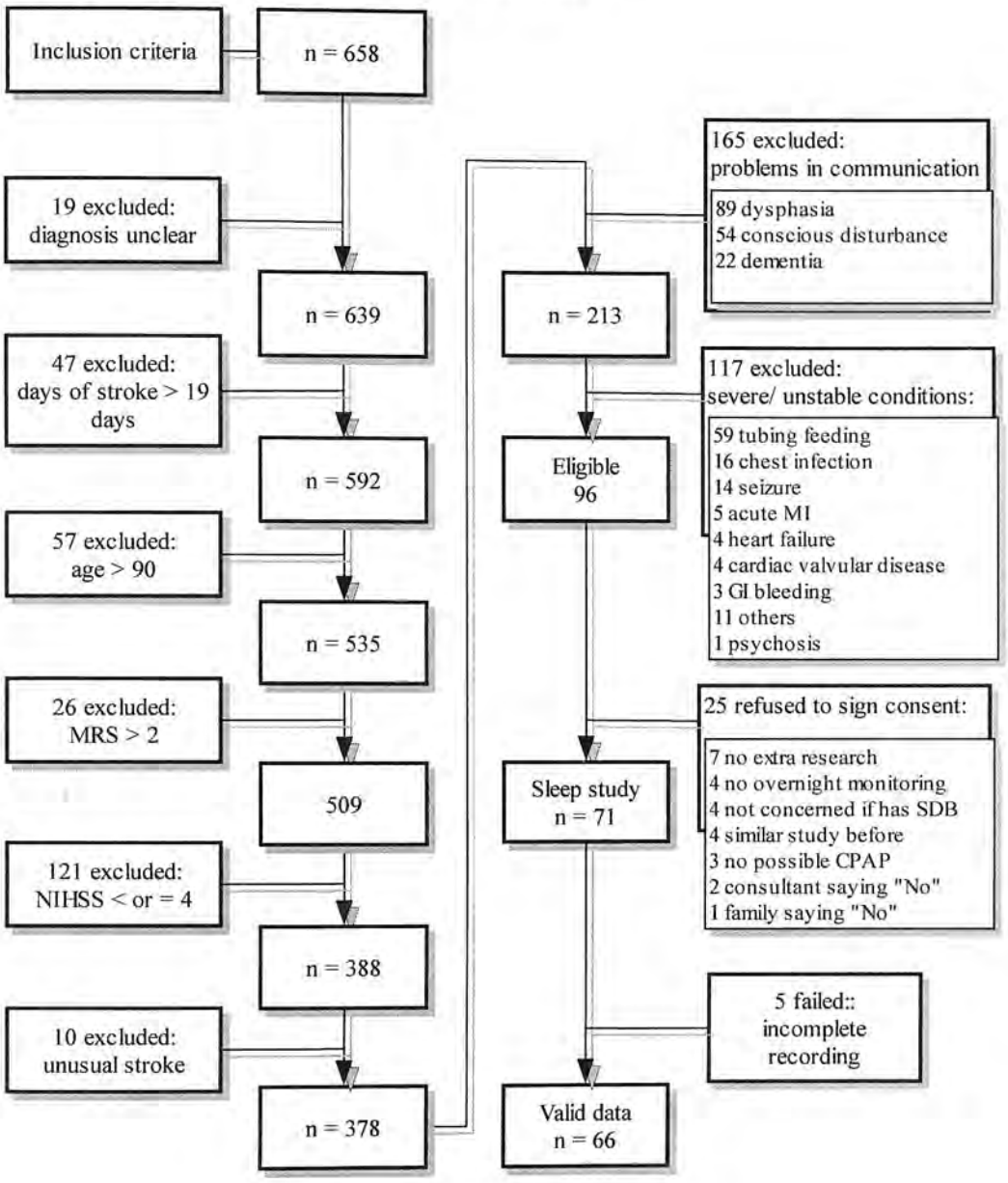
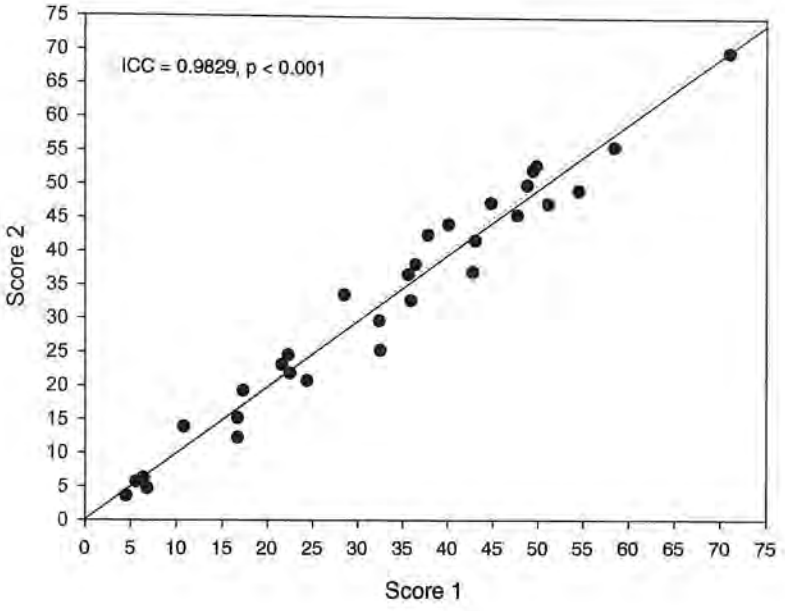
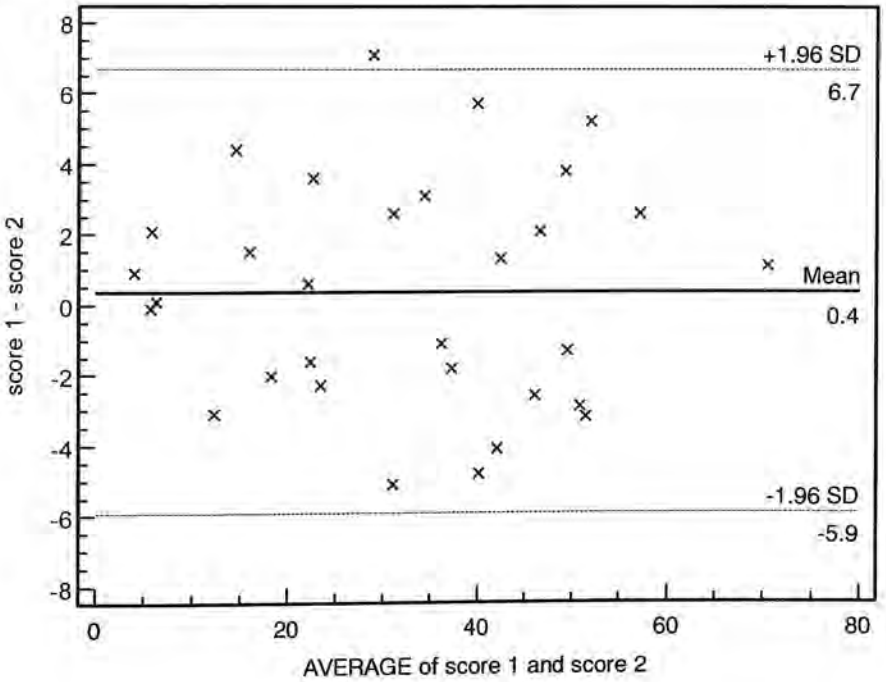


Figure 4.2 Intra-rater and inter-rater reliability of sleep study

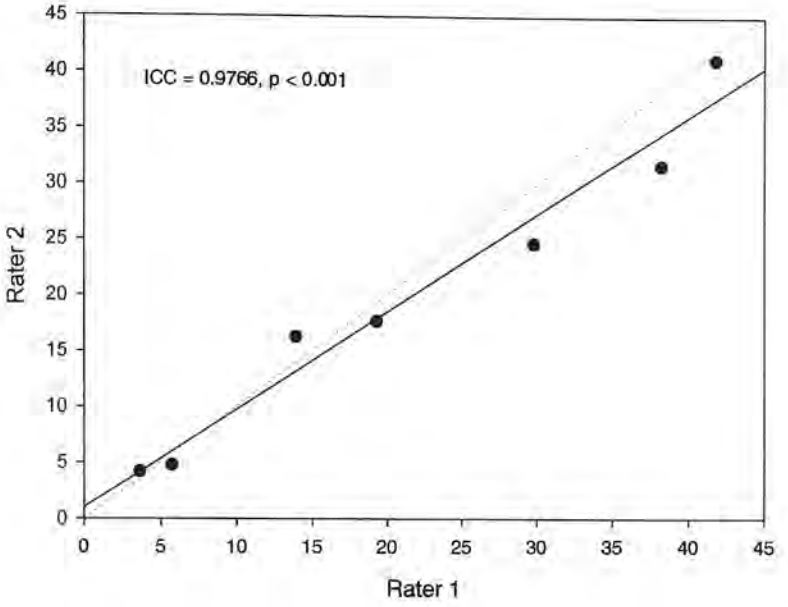
(a) Scatter plot and intraclass correlation coefficient (ICC) across 1st and 2nd scoring by me (Chung-Yao Hsu)



(b) Bland and Altman plot across 1st and 2nd scoring by me



(c) Scatter plot and intraclass correlation coefficient (ICC) across rater 1 (me) and rater 2 (MV)



(d) Bland and Altman plot across rater 1 (me) and rater 2 (MV)

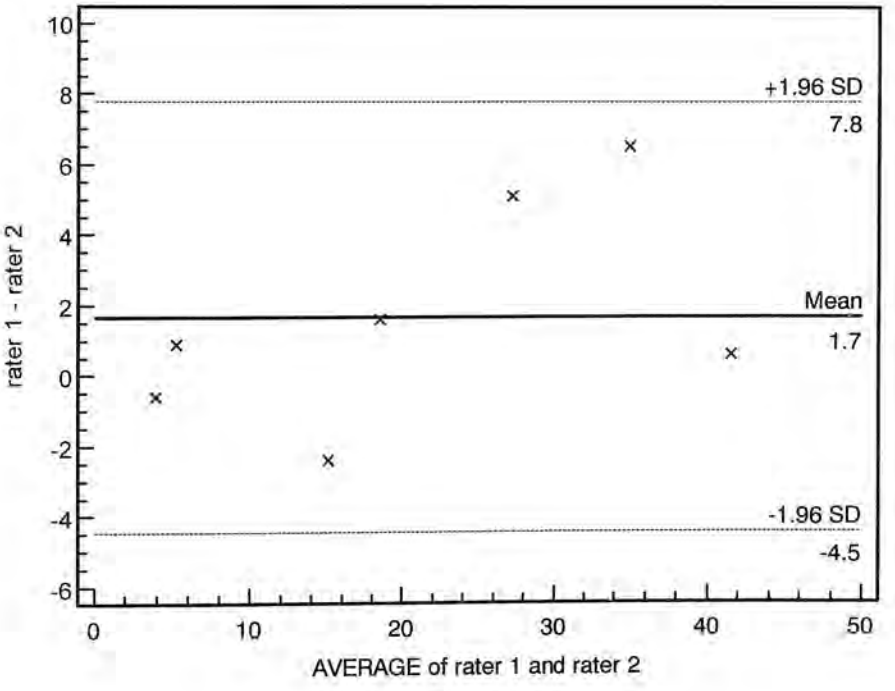


Figure 4.3 Relationship between AHI (median and IQR) and age

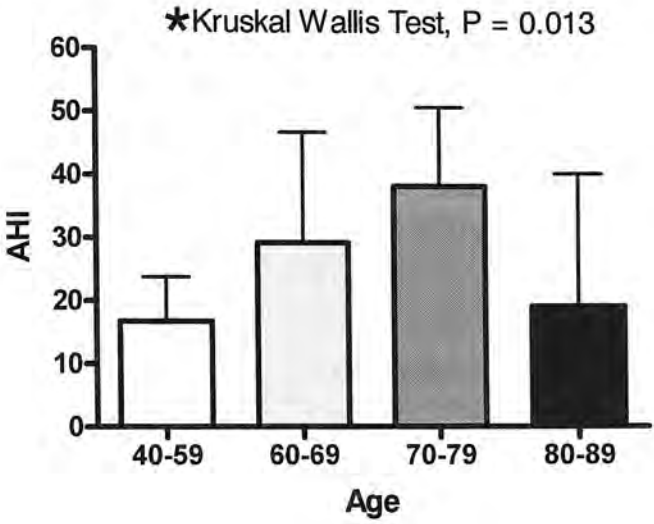


Figure 4.4 Relationship between AHI and BMI

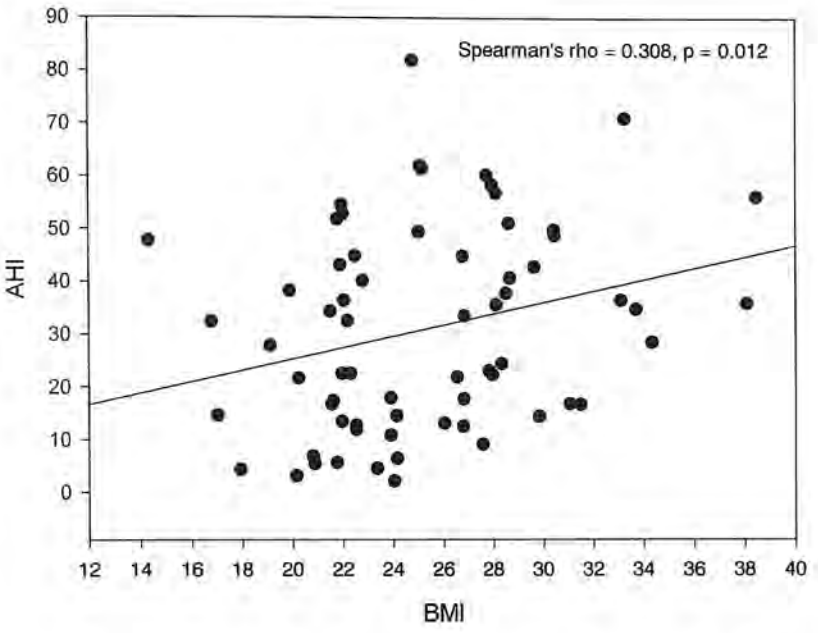
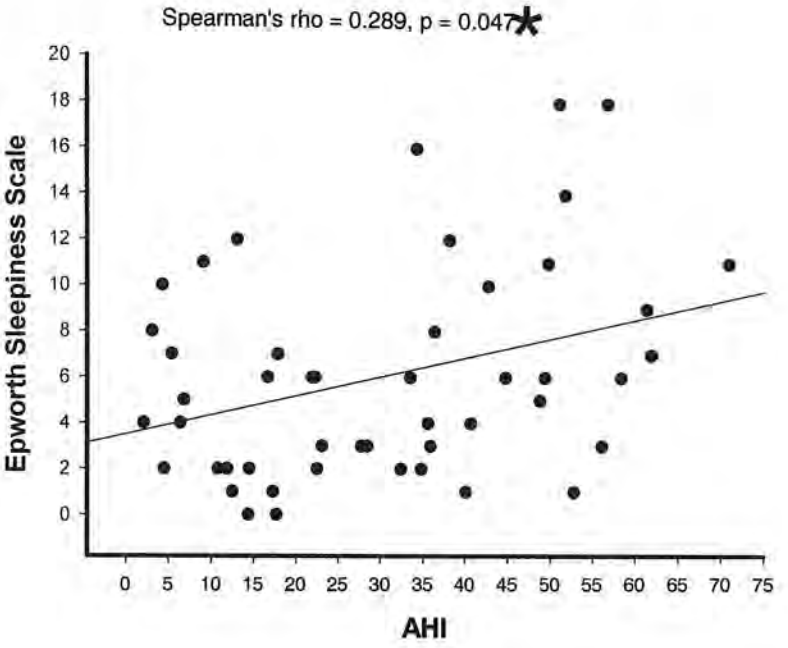
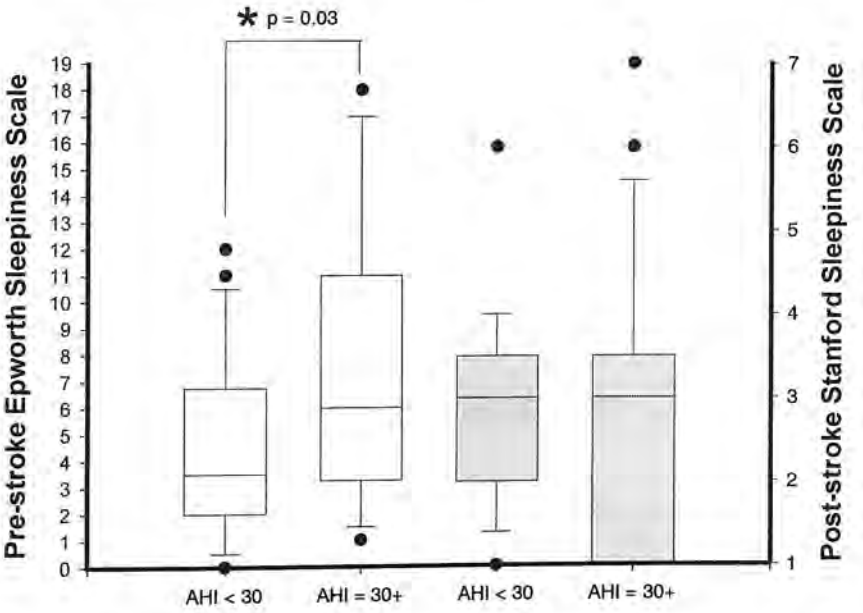


Figure 4.5 Relationship between pre-stroke Epworth Sleepiness Scale, and Stanford Sleepiness Scale at baseline and AHI

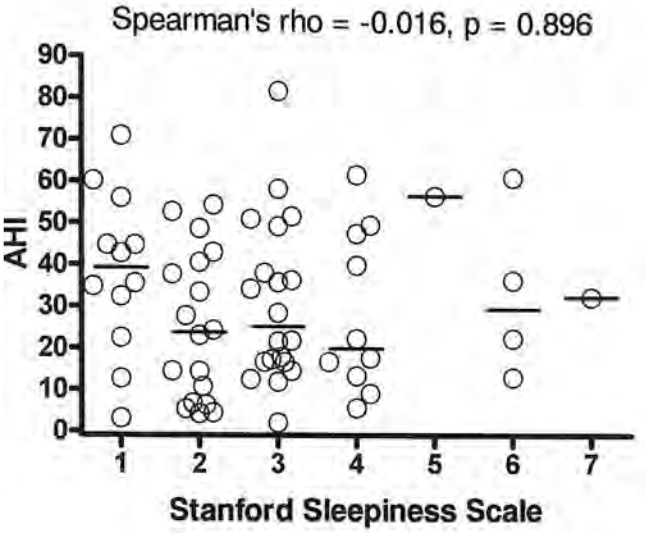
(a) Correlation between AHI and pre-stroke Epworth Sleepiness Scale



(b) Differences of distribution of Epworth Sleepiness Scale and Stanford Sleepiness Scale between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30



(c) Correlation between AHI and Stanford Sleepiness Scale at baseline



(d) Correlation of pre-stroke Epworth Sleepiness Scale and Stanford Sleepiness Scale at baseline

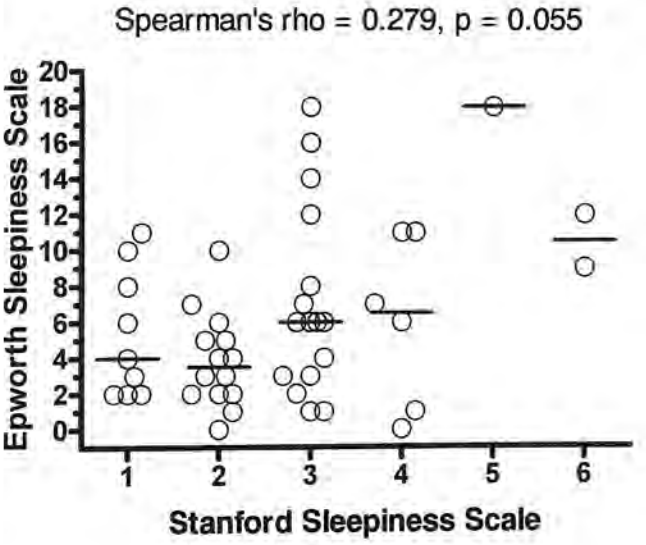
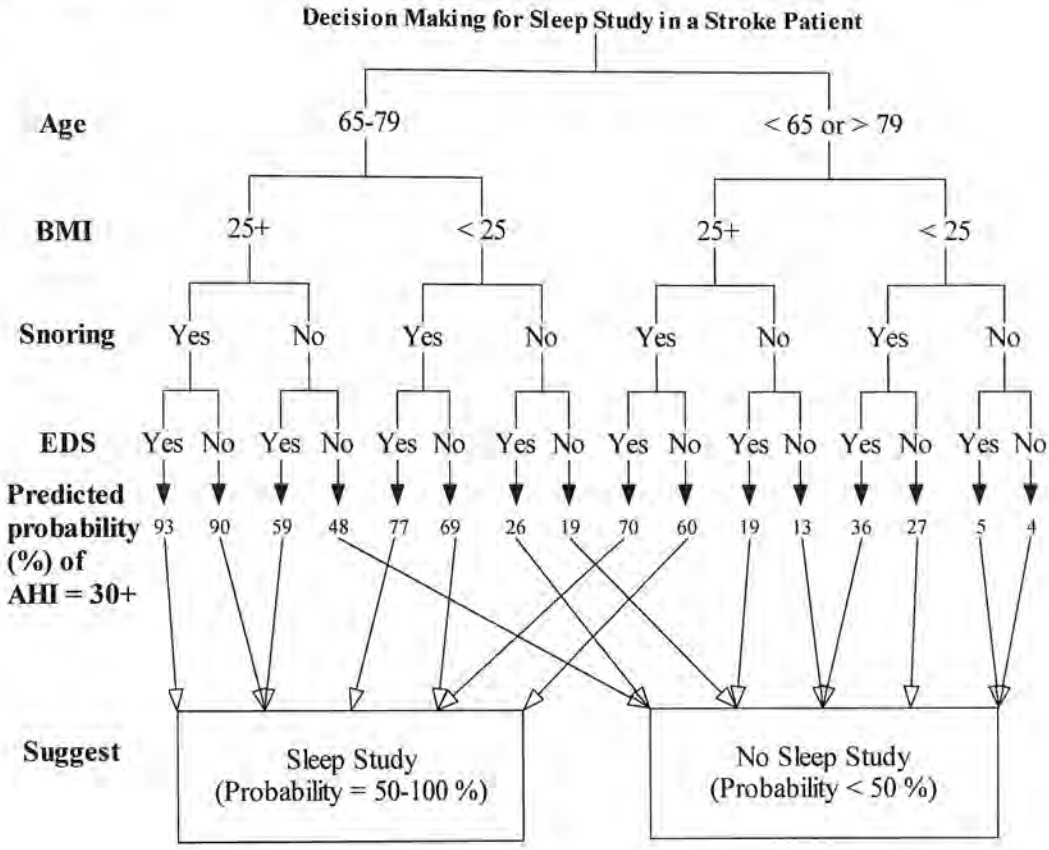


Figure 4.6 Flow chart of decision making for referring sleep study in stroke unit



BMI: body mass index; EDS: excessive daytime sleepiness

Figure 4.7 ROC curves of oximetric variables in prediction of moderate to severe SDB (AHI ≥ 30)

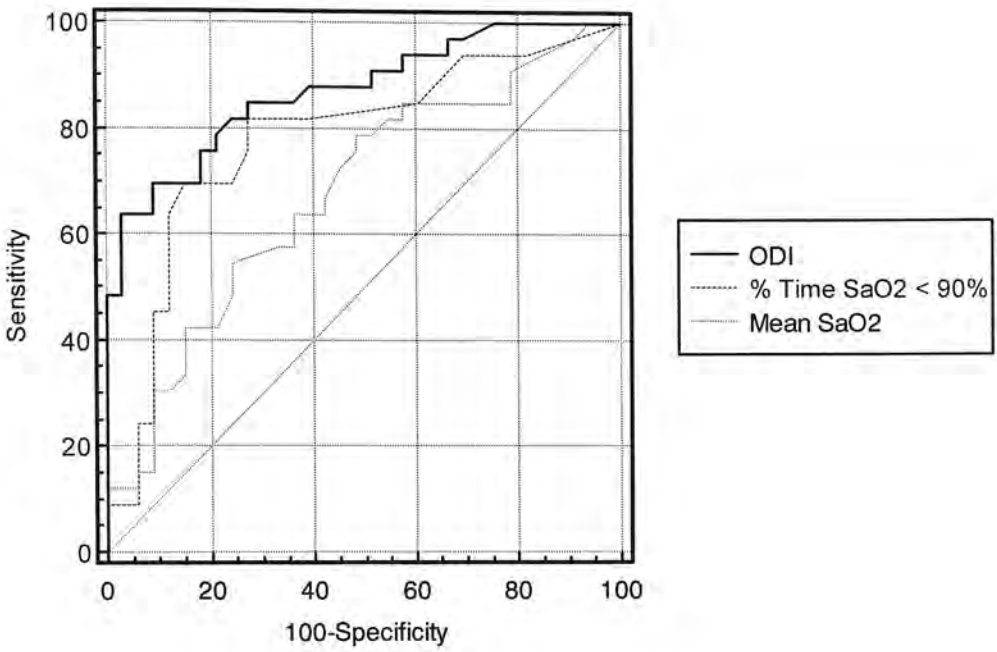
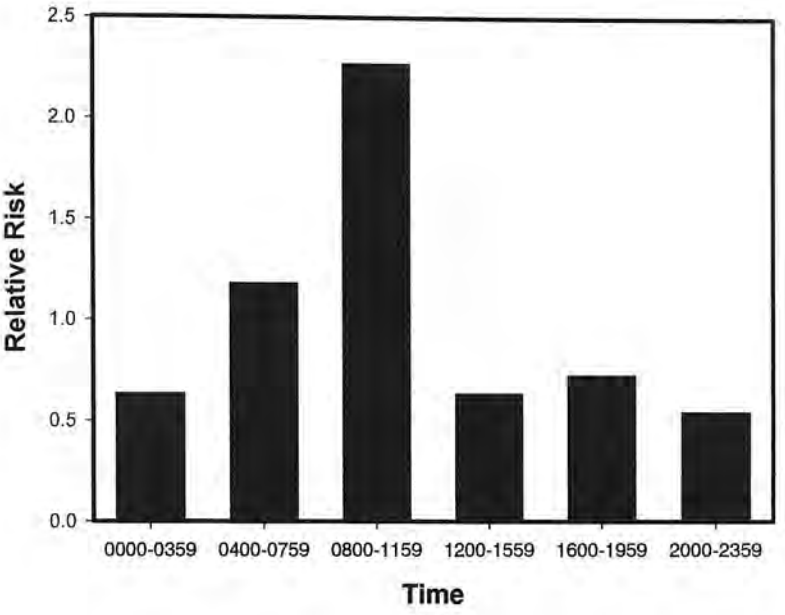
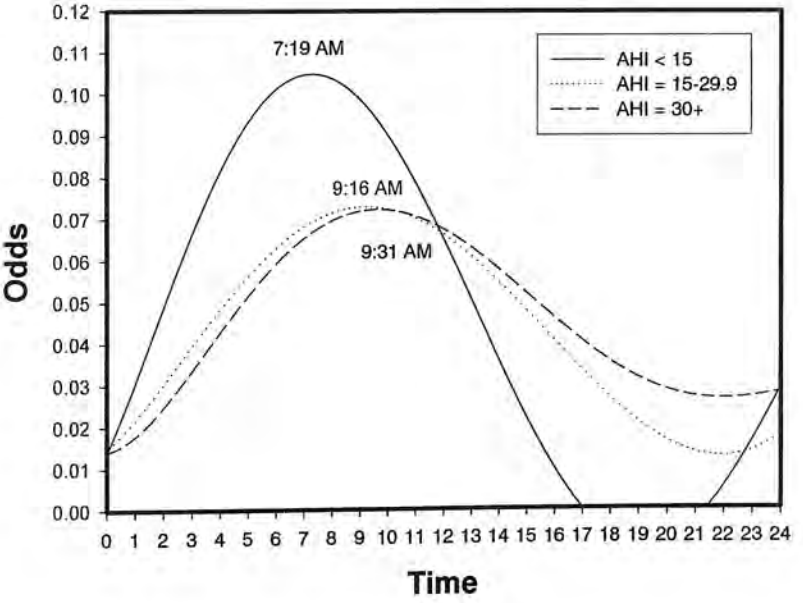


Figure 4.8 Diurnal difference of stroke onset

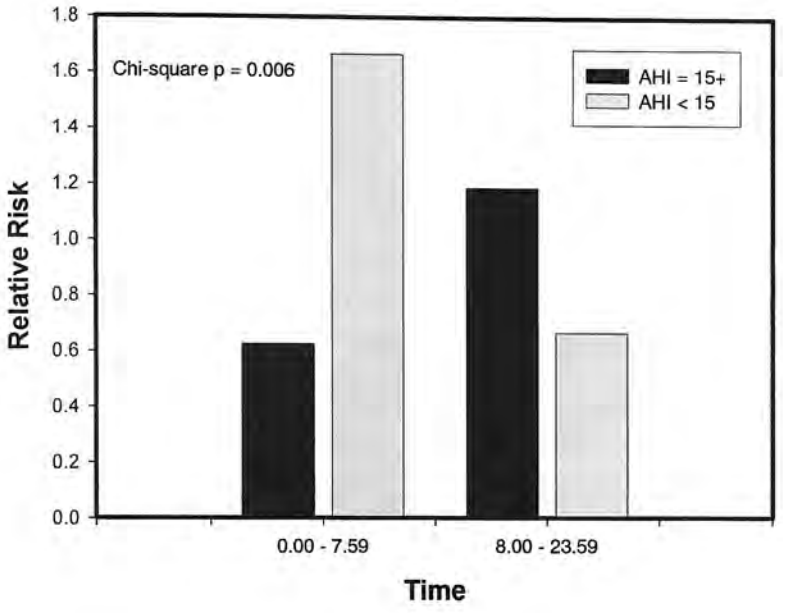
(a) Relative risk of stroke onset displayed in 4-hour interval (n = 66)



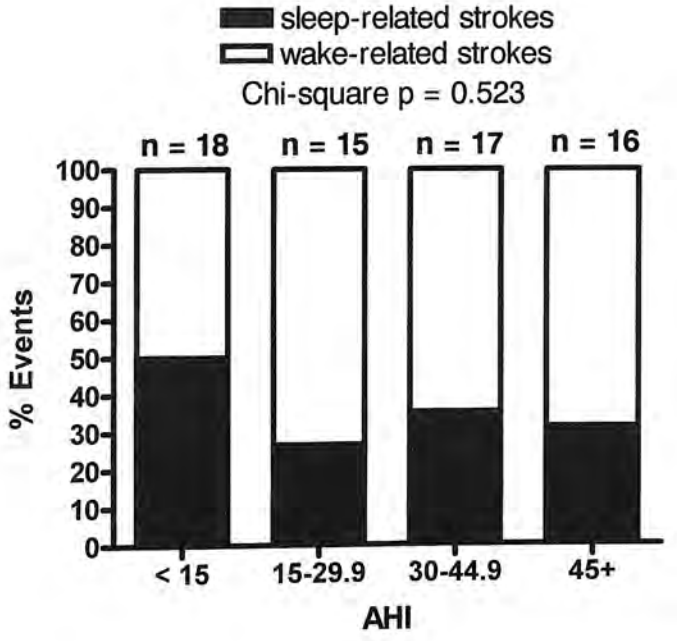
(b) Odds of onset times of stroke in three groups with AHI ≥ 30 (n = 33), AHI = 15 – 29.9 (n = 15) and AHI < 15 (n = 18)



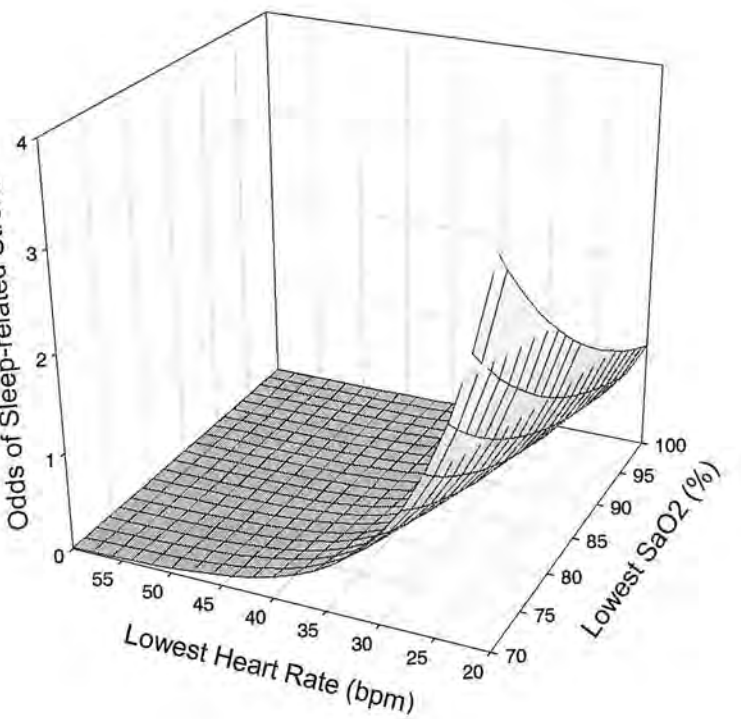
(c) Relative risk of stroke onset in 2 specific time interval between patients with $(A+H)\cdot h^{-1} \geq 15$ (n = 48) and < 15 (n = 18)



(d) Sleep-related and wake-related stroke between 4 groups from low to high $(A+H)\cdot h^{-1}$



(e) Odds of sleep-related stroke across lowest oxygen saturation and the lowest heart rate in patients with $(A+H)\cdot h^{-1} < 30$ (n = 33)



Chapter 5 Randomized Controlled Trial of Continuous Positive Airway Pressure for Obstructive Sleep Apnoea/Hypopnoea following Stroke

5.1 Abstract

Backgrounds: The prevalence of sleep-disordered breathing (SDB) in stroke is high but there are only four publications dealing with the treatment of obstructive sleep apnoea/hypopnoea syndrome (SDB) in stroke. All of them used nasal continuous positive airway pressure (CPAP) as the choice of intervention but only one of them was a randomized control trial. One randomized controlled trial had outcome measures in the domains of functional capacity, cognition and wellbeing but showed that CPAP only improved wellbeing. Another non-randomized controlled trial found CPAP might improve wellbeing and ambulatory blood pressure. The other two studies had no outcome measure.

Methods: Thus we conducted a randomized controlled trial for stroke patients who had $(A+H)\cdot h^{-1} \geq 30$ with predominant obstructive events, i.e. either central apnoea or Cheyne-Stokes respiration < 30%, starting from 21-25 days after stroke. The duration of treatment was 8 weeks and blind outcome assessment was performed at 3 months and 6 months after stroke.

Results: Thirty patients were recruited in the study with 15 randomized to CPAP and the other 15 to conservative treatment for SDB. Conventional treatment for stroke was maintained in all patients. The result showed compliance to CPAP was poor with mean 1.40 hours and median 0.16 hours per night. Increased length of keeping CPAP was correlated with higher score of language subscale in Addenbrooke's Cognitive Examination (Spearman's rho = 0.544, p = 0.036) and lower score in depression subscale of Hospital Anxiety and Depression Scale (Spearman's rho = -0.538, p = 0.039). Increased CPAP compliance was correlated with a higher Nottingham Extended ADL Index (EADL) score at post-treatment phase but this turned into insignificant after adjusting for baseline Barthel Index (BI).

The outcome assessment showed patients randomized into CPAP had a lower EADL mobility subscale score (p = 0.048) and lower scores of physical function (p = 0.006), role physical (p = 0.025), mental health (p = 0.044) and physical summary (p

= 0.022) in SF-36. The difference in the EADL mobility subscale score became insignificant after adjusting for baseline BI but the difference in physical summary score of SF-36 remained after the same procedure. Imbalance due to chance in functional capacity at baseline between groups was the most likely explanation for outcome difference at post-treatment phase. Post-stroke depression in CPAP group might play a role for poorer functional outcome but this could hardly be explained by negative effect of CPAP treatment. There was no difference between groups at 6 months after stroke which might be due to the effect of regression to mean.

The 24-hour ambulatory blood pressure at post-treatment phase showed that lower systolic blood pressure (SBP, Spearman's rho = 0.490, p = 0.015) and diastolic blood pressure (DBP, Spearman's rho = 0.279, p = 187) were associated with lower EADL total score at the post-treatment phase. Instability in circadian rhythm of blood pressure was defined as either SBP/DBP mismatch (difference of periods > 1 hour) or rapid cyclic pattern (period < 8 hours). This was associated with old age (p = 0.012), lower mean saturation (p = 0.013), higher % time of desaturation < 90% (p = 0.011) and stroke onset at baseline, a lower EADL leisure subscale score (p = 0.013) and a lower role emotional subscale score in SF-36 (p = 0.008) at the post-treatment phase.

Conclusions: I concluded that CPAP compliance was a major problem in this study but might be enhanced on a highly selective basis by choosing patients with higher functional capacity, higher cognitive function especially language and less depression in acute or subacute phase of stroke. For unstable patients or poor compliant, CPAP treatment may be delayed to a more stable chronic phase of stroke as it still can have an effect on controlling blood pressure for secondary prevention. Controlling blood pressure in stroke is a complicated issue and the role of reducing blood pressure of CPAP and its influence on cerebral blood flow in acute and subacute stroke needs further clarification with more randomized controlled trials.

Key words: Sleep-disordered breathing; stroke; randomized controlled trial; continuous positive airway pressure; compliance; outcome

5.2 The aims of the study

Scientific background of this randomized controlled trial (RCT) has been reviewed in chapter 2.11. The hypothesis in this chapter was that continuous positive airway pressure (CPAP) treatment for SDB in patients with stroke could improve outcomes. According to previous reviews, we designed a prospective single blind, randomized control CPAP trial with treatment period of 8 weeks and a longitudinal follow-up with a broad spectrum of outcome measures at 3 months and 6 months after stroke. The aims of this study were to establish the:

- Feasibility of CPAP: to find out the compliance of stroke patients suffering from SDB with CPAP.
- Effectiveness of CPAP: to find out the influence of CPAP on functional, cognitive, emotional outcome and health-related quality of life in stoke.
- Haemodynamic effect of CPAP: to find out the effect of CPAP on 24-hour, day and night blood pressure and heart rate in stroke.

5.3 Methods

The Consolidated Standards of Reporting Trials (CONSORT) comprises a checklist and flow diagram to help improve the quality of reports of randomized controlled trials (RCT) [Begg *et al.* 1996]. RCT in this study was designed and reported in accordance with the CONSORT guidelines.

5.3.1 Participants

Stroke patients were approached and recruited in two acute stroke units and two stroke rehabilitation units located in Edinburgh city. The eligibility criteria have been described in chapter 3.2 and sample size calculation has been described in chapter 3.3.

5.3.2 Interventions

All patients with $(A+H)\cdot h^{-1} \geq 30$ received conservative (behavioural) treatment for SDB. For example, an advice on weight loss and abstinence from alcohol and other sedatives was given when appropriate. Using a randomization schedule 21-25 days after stroke, they were randomised either to CPAP (Autoset T) or conservative treatment only for SDB for 8 weeks. Conservative treatment means both groups received advice on weight loss, alcohol avoidance and conventional rehabilitative and medical therapy for stroke and its complications when appropriate. Throughout the study all medications and programmes for stroke were maintained as usual and were recorded on the Follow-up Form. For example, this might include rehabilitation, changes of drug treatment for hypertension, atrial fibrillation or carotid artery surgery.

I did not choose sham CPAP as control. This involves the use of the nasal mask and CPAP machine, but with inadequate pressure generated to overcome upper airway obstruction during sleep. The reasons of not using sham CPAP were: (1) sham CPAP with subtherapeutic pressure might be harmful to stroke patients; (2) it is not

clear whether sham CPAP is a truly inactive treatment; (3) sham CPAP cost extra-funding.

Nasal CPAP therapy was performed following routine patient education about CPAP, mask fitting and familiarization by an auto-titration device, AutoSet T® (ResMed Ltd., SanDiego USA, Figure 3.2, P. 114). There is a pressure sensor and internal computer to monitor the patient's breathing and a clock in the device to provide objective data on CPAP usage. It adjusts pressure on a breath-by-breath basis to minimize the pressure required for effective therapy.

All patients on CPAP were given intensive support from a highly experience CPAP nursing sister (Marjorie Vennelle). The reasons for any non-compliance were investigated and efforts made to solve problems. Reasons for declining to enter the CPAP study were documented, as should difficulties using CPAP and reasons for withdrawal from trial/abandoning CPAP. A standardized form was filled out by the investigator. If they continued to be non-compliant at the next visit, they were withdrawn from the study. The Withdrawal Form was completed.

Patients who experienced an adverse event were withdrawn at any time from the study at the discretion of the investigator. If a patient was withdrawn wholly or in part because of an adverse event, both the Withdrawal and Adverse Events Forms were completed.

5.3.3 Objectives

The main hypothesises of this study were based on the RCT:

- Nasal CPAP might improve sleepiness, fatigue, cognitive function and mood in stroke patients with SDB so they may be more compliant to their rehabilitation programme and other treatment procedures. This might result in better functional outcome.
- Nasal CPAP may stabilize circadian blood pressure in acute and subacute phase of stroke. This might not only result in better outcome but also prevent recurrence of stroke.

5.3.4 Outcomes

The Barthel Index (BI) and the Nottingham Extended ADL Index (EADL) dealing with functional capacity were chosen as primary outcome measures based on a priori hypothesis. The ambulatory blood pressure (ABP), Mini Mental State Examination (MMSE), Addenbrooke's Cognitive Examination (ACE), Hospital Anxiety and Depression Scale (HADS), EuroQol and SF-36 were chosen as secondary outcome measures.

5.3.4.1 Baseline data

Baseline data collection was done on the day of sleep study and baseline assessment was done on the morning after overnight sleep study but before the analysis of sleep data. The details have been described in chapter 4 including demographic data, basic laboratory data, Modified Rankin Scale (MRS), NIH Stroke Scale (NIHSS), Stanford Sleepiness Scale (SSS), BI, ACE and HADS.

5.3.4.2 Ambulatory blood pressure monitoring

All randomized patients received 24-hour ABP monitoring in the last week of the 8-week treatment phase. ABP monitoring was conducted with Spacelabs 90207 (Spacelabs, Redmond, USA). The device has previously been validated for the elderly [Iqbal *et al.* 1996] and recommended by European Society of Hypertension for clinical use [O'Brien *et al.* 2001]. The detailed description of the device has been given in chapter 3.

ABP monitoring was programmed beforehand to automatically measure blood pressure every 30 minutes for 24 hours. The recording started between 2-3 pm at the bedside or patients' home. Instruction was given before putting on the monitor. Information about current medication, estimated sleep/wake time and daily activity were collected at the end of the recording. Raw data of systolic blood pressure (SBP), diastolic blood pressure (DBP), arterial blood pressures (MAP) and heart rate (HR) were downloaded into a computer. MAP was calculated by the device automatically

according to the formula: MAP = (SBP – DBP)/3 + DBP. Mean SBP, DBP, MAP and HR were calculated for three time intervals: 24 hour, daytime and night time. We defined the interval between 6:00 am and 9:59 pm as daytime and the interval between 10:00 pm and 5:59 am as night time because these were closer to the schedule of stroke patients in the wards. "Dipper" was defined as a drop of at least 5% in both systolic and diastolic blood pressure during the night [Engleman *et al.* 1996b]. "Borderline dipper" was defined as either systolic or diastolic blood pressure fulfilling the criteria of dipper. Others were defined as "non-dippers".

Patients with successful ABP readings > 70% of the recording time were further analyzed by the single Cosinor method to evaluate circadian rhythm of blood pressure. The best-fit cosine model of circadian SBP and DBP rhythm was obtained by regression analysis according to the following formula:

$$\text{ABP (Time)} = \text{Mesor} + \text{Amplitude} \times \cos\left(\frac{2\pi\,(\text{Time} - \text{Acrophase})}{\text{Period}}\right)$$

Three data were derived from the Cosinor model for each patient: (1) mesor of 24h ABP: mean of cosine wave; (2) amplitude of 24h ABP: perpendicular distance from peak or nadir of cosine wave to horizontal line of mean of cosine wave; (3) period of 24h ABP: duration of cosine wave. F-test was applied to test the significance of the best-fit Cosinor model of SBP and DBP by examine the null hypothesis of the amplitude.

Each patient was categorized into one of two groups according to the duration and matched pattern of the period of ABP: (A) Regular ABP rhythm: SBP and DBP were matched in period (difference < 1 hour) in a single patient with duration of period ≥ 12 hours; (B) Irregular ABP rhythm: either SBP and DBP rhythm were mismatched in period (difference ≥ 1 hour) or duration of period in any rhythm < 12 hours. These two groups were compared for demographic, sleep, and outcome variables.

Group A was further divided into three subgroups: (A1) normal 24-hour circadian BP rhythm; (A2) reverse 24-hour circadian BP rhythm; (A3) 12-hour circadian BP rhythm. Group B was further divided into two subgroups: (B1) Both SBP and DBP periods are ≥ 12 hours but mismatched; (B2) Either SBP or DBP period was < 12 hours 9 (rapid cycling). The predicted data of SBP and DBP in group A1, A2 and A3 obtained from the Cosinor model are were plotted according to mean and standard error in each time point. The time of stroke onset is marked and shown on the plot of ABP curves to find its relationship to blood pressure swing. The predicted data of SBP and DBP in group B1 are plotted without calculating the mean and standard error of mean (SEM). Patients in group B2 had rapid cyclic SBP and DBP so the circadian rhythms were biased for comparison with stroke onset.

5.3.4.3 Follow-up

All patients who were successfully randomized received a regular follow-up by face-to-face interview and assessment. Post-treatment follow-up was performed within the last three days before the end of CPAP treatment including repeated measurement of NIHSS, MRS, SSS, BI, HADS and ACE. Three extra scales were given in terms of EADL, EuroQol and MOS Short Form-36 (SF-36). The EADL was developed by the Department of Psychology in the University of Nottingham for assessing functional capacity which consists of four domains of questions in terms of mobility, kitchen, domestic activity and leisure activity [Gladman *et al.* 1993]. It has less ceiling effect than the Barthel Index so is more suitable to be used in mild to moderate stroke. EuroQol and SF-36 assess health-related quality of life. EuroQol is a standard instrument to assess health outcome which consists of two domains of questions, Visual Analogue Scale (VAS) and 5-dimension (5D) score, and has proven validity and reliability in stroke study [Dorman *et al.* 1997]. If the patient was still in the hospital, nursing staff were informed to hide the machine if they were at the bedside before I went to do the assessment. If the patient was at home or in the nursing home, carer was informed beforehand to do the same procedure.

Six-months follow-up were performed at 6th calendar month calculated from the onset of current stroke (± 2 weeks), which focused on functional capacities (MRS, BI, EADL) and health-related quality of life (SF-36).

5.3.5 Randomization

Patients were randomised as long as 21 days after stroke onset. The rationale was to recruit a group of patients who had subacute stroke, i.e. 14-19 days following stroke and might be more stable physically and mentally to tolerate CPAP trial. The effect on the ischaemic penumbra would be minimal by this point of time but patients still had great potential of recovery from stroke based on the neuronal plasticity.

On day 21-25 following stroke, patients who had $(A+H)\cdot h^{-1} \geq 30$ with $< 30\%$ central sleep apnoea or Cheyne-Stokes respiration detected by the overnight sleep study proceeded to randomization conducted by a senior staff member in the Department of Sleep Medicine who was not involved in recruiting and assessing patients. Sequence generation was made using the random permuted block (RPB) method where each block consisted of 6 patients with a 50% chance of being assigned to either CPAP or conservative treatment. There are 64 different possible block arrangements. A random number of sequence was used to choose a particular block which set the order of allocation for consecutive 6 patients. Allocation concealment was maintained during the whole course of the study. I was responsible for recruitment, sleep studies, follow-up and assessment and was completely blind to all information of randomization including details of block size. Patients were unblinded when the final assessment of the last randomized patients was completed.

The senior staff member who conducted randomization was also in charge of performing the CPAP treatment. Patients were either randomized to an add-on nasal CPAP treatment with Autoset T (auto-titrating mode, ResMed, Sidney, Australia) or conservative (behavioural) treatment for SDB. Intensive input by a senior sleep research nurse who was experienced in CPAP treatment was arranged on day 1, day 3, day 5, week 1, week 2, week 4 and week 6 of treatment to optimize compliance. The nurse managed all problems related to the mask, the machine and any

complications of CPAP. The CPAP machine was kept by the patient's side unless they refused to use it anymore and asked for it to be taken away. The treatment period lasted for 8 weeks (56 days). Duration of keeping the CPAP equipment was recorded in days. After 8 weeks of CPAP treatment, hours of CPAP usage on a nightly basis was downloaded from the machine. Compliance with CPAP was calculated as the median and mean hours of CPAP use per night. All medications and programmes for stroke were maintained as usual. For example, this might include rehabilitation, changes drug treatment for hypertension, atrial fibrillation, or carotid artery surgery.

5.3.6 Blinding

I was in charge of overnight sleep study and data analysis. All the baseline and outcome assessments were performed face-to-face. I was blinded to the results of sleep study as I performed baseline assessment on the morning following sleep study but before analysis of sleep data. Follow-up was also arranged and performed by myself so I was not blinded to the results of sleep study when I performed assessment at post-treatment phase and 6 months after stroke. The primary outcome measures dealing with functional capacity were self-administrated including BI and the EADL. Most of the secondary outcome measures except those dealing with cognition, i.e. MMSE and ACE, were also self-administrated including SSS, HADS, EuroQol and SF-36. Thus the bias might be reduced to the minimum.

I was blinded to treatment allocation when I performed follow-up at the post-treatment phase and at 6 months after stroke. As CPAP machines were either apparently left at the bedside if patients were still in the hospitals or easily discovered if patients were at homes or nursing homes, the research nurse contacted with patients or caregivers for me beforehand and asked them to hide the machines when I visited them.

I was unblinded to treatment allocation in the first two patients because at that time formal RCT in this study had not started yet. The data of these two patients were not taken into account in the analysis of RCT.

5.3.7 Statistical methods

Data were analyzed on an intention-to-treat basis including a priori hypothesis-driven and post-hoc exploratory analysis which have been described in chapter 3.6. Psychometric data are rarely normally distributed so were presented as median and interquartile range (IQR). Data from ABP monitoring are mostly normally distributed so were presented as mean ± standard deviation (SD). Statistical analysis was done by the statistical software, SPSS version 11.0 for Windows (SPSS Inc. USA).

Non-parametric tests were conducted including Mann-Whitney U test and Chi-square Test (Fisher's test in case there were less than 20 patients in a category) for between-group comparisons. The $p < 0.05$ was taken as statistically significant. Spearman correlation was used to find out association between variables.

Multivariate analysis was conducted to control confounding factors or for adjustment of interactions. Multiple linear regression with the "enter method" was used if the dependent variable was continuous and normally distributed. All predictors with $p < 0.1$ in univariate regression analysis were entered into the model and coefficient and confidence interval (CI) were expressed. Logistic regression with "forward likelihood method" was used. If dependent variables were binary or non-normally distributed' they were dichotomized before entering into the model. All predictors with $p < 0.1$ in univariate regression analysis were entered into the model and the adjusted odds ratio (OR) and CI were expressed. Those variables with $p < 0.05$ in the final model were taken as statistically significant.

Standardized effect size [Cohen's d, Cohen 1988] instead of mean difference between CPAP and conservative groups was calculated and presented in tables. The formula of calculating effect size is:

$d = M1 - M2 / \sigma_{pooled}$ where:

$$\sigma_{pooled} = \sqrt{[(\sigma_1^2 + \sigma_2^2 / 2]}$$

Confidence interval (CI) of effect size (Hedges' g with CI, bias corrected) [Hedges and Olkin 1985] was also calculated and shown in figures to explain the variables without rejecting the null hypothesis.

5.4 Results

5.4.1 Recruitment

Thirty-three of 66 patients with a successful sleep study had $(A+H)\cdot h^{-1} \geq 30$. Two of the 33 patients with $(A+H)\cdot h^{-1} \geq 30$ had sleep studies before the protocol of randomization was started and another dropped out before randomization. Thus 30 patients were randomized, 15 to CPAP and 15 to conservative treatment for SDB. Flow chart of participants through each stage was shown in Figure 5.1 (P. 220). The trial was terminated before we had recruited our target of 80 patients because recruitment was much more difficult than expected and funding ended. The first patient was randomized in March 2001 and the last patient was randomized in June 2003. I finished follow-up for the last randomized patient at 6 months after his stroke in December 2003.

5.4.2 Baseline data

Patients randomized to CPAP were relatively older (median age = 74, IQR 73-81 vs. median age = 73, IQR 65-77), and had relatively lower $(A+H)\cdot h^{-1}$ (43.1 vs. 47.7), casual blood pressure at admission (151 ± 30 mmHg vs. 164 ± 39 mmHg) in comparison with patients randomized to conservative treatment (Table 5.1, P. 206).

Baseline assessment showed that the CPAP group had relatively poor functional capacity (Barthel Index, BI = 11 vs. 14) and emotional status (Hospital Anxiety and Depression Scale, HADS = 10 vs. 7). However, the conservative group had significantly lower score in Mini Mental State Examination (MMSE, p = 0.033) and on the attention/concentration subscale of Addenbrooke's Cognitive Examination (ACE, p = 0.025, Table 5.2, P. 207). There was no significant difference of daytime sleepiness between groups (Table 5.2, P. 207).

5.4.3 CPAP compliance

Among 15 patients randomized to CPAP, 2 patients rejected treatment after mask fitting and a brief trial in the afternoon on day 1 of treatment phase, 1 patient rejected treatment after the first night of CPAP use, 1 died of adult respiratory distress syndrome (ARDS) on day 4 of CPAP limb and 1 rejected treatment after one week of CPAP use. Seven of 15 patients were happy to keep the machine for more than four weeks under intensive education and encouragement (Figure 5.2a, P. 221). The length of keeping CPAP was negatively correlated with the depression subscale of HADS ($p = 0.039$, Figure 5.3a, P. 222) and positively correlated with the language subscale of ACE ($p = 0.036$, Figure 5.3b, P. 222) at baseline. This suggests that patients who had less depression and language problem were willing to try CPAP for a longer time.

Apart from one fatal case, compliance with CPAP, calculated as mean hours per night of CPAP use, was 7 hours in one patient, 6 hours in one patient, 2 hours in two patients, 1 hour in one patient and less than 1 hour in the other nine patients (Figure 5.2b, P. 221). Mean CPAP use was 1.40 hours and median was only 0.16 hours. The baseline data of five patients with better compliance ($\geq$ 1 hour, mean 3.8 ± 2.8, ranged 1.02-7.27 hours) showed that mean $(A+H)\cdot h^{-1}$ was 46.1 ± 10.1/h (35.6-58.4), BMI was 29.3 ± 5.9 (21.8-38.1), ESS was 6 ± 4 (3-14), SSS was 2 ± 1 (1-3), NIHSS was 6 ± 4 (4-13) and BI was 15 ± 6 (4-19). These were not significantly different from other randomized patients.

Problems with compliance with CPAP in 15 patients were categorized into four domains (Table 5.3, P. 208): (1) Eight patients had problems with either the mask or the machine. Two of four patients who were not able to breathe properly and 2 of 3 patients who were claustrophobic abandoned CPAP quickly. (2) Eight patients developed upper airway symptoms in the following treatment days. Although all symptoms were managed by topical medications 3 patients still withdrew due to these symptoms. (3) Nine patients had problems coming from stroke which caused their non-compliance. Two patients who had total anterior circulation infarct (TACI)

also had problems keeping the mask in position probably due to facial weakness or nocturnal confusion. Two patients had involuntary movement of the head. One patient improved gradually and could keep using CPAP. The other didn't improve and abandoned CPAP quickly. Two patients fell due to gait disturbance with wounds on the face and withdrew from that time on. One patient developed adult respiratory distress syndrome (ARDS) following chest infection on the day of CPAP titration and died 3 days later. (4) Two patients did not think that they needed CPAP on a nightly basis but this was not a major reason for withdrawal after education and encouragement. CPAP compliance was positively correlated with BI and the language subscale of ACE but negatively correlated with depression subscale in HADS at baseline (Table 5.4, P. 209).

5.4.4 Outcomes at post-treatment phase

Post-treatment follow-up showed that patients randomized to CPAP had significantly lower mobility subscale of Nottingham Extended ADL Index (EADL, p = 0.048, Table 5.5, P. 210). As they also had lower BI at baseline multivariate analysis was conducted to deal with this confounder. After adjusting for BI at baseline, randomization to CPAP was no longer an independent predictor (Table 5.6, P. 211). On the other hand, increased mean hours of CPAP use per night was associated with higher EADL total score at post-treatment phase (Figure 5.4a, P. 223) but after adjusting for BI at baseline again, CPAP compliance was no longer an independent predictor either (Table 5.7, P. 212). Of the CPAP-treated patients, there were only two who on most criteria would have been regarded as having adequate compliance; of the five with "better compliance", the other three used the treatment for only two hours per day or less on average.

Figure 5.4b (P. 223) was used to demonstrate the result of regression analysis shown in Table 5.7 (P. 212). The two patients located in the right upper corner of the figure were those who had the best compliance. These two good compliers were relatively younger in CPAP group (age = 65 and 73 vs. 76 year-old) and had less severe stroke (BI = 19 and 18 vs. 11). Among the two good compliers, one had

previous history of habitual snoring, witnessed apnoea and unrefreshed sleep. Another had previous history of unrefreshed sleep and mild EDS (post-prandial). Both of them might have pre-existing obstructive sleep apnoea but their $(A+H)\cdot h^{-1}$ was not higher in CPAP group (35.9 and 35.6 vs. 43.1) and their ESS was normal (4 and 5).

Apart from functional capacity, the CPAP group also had significant lower scores in subscales of SF-36 including physical function ($p = 0.006$), role physical ($p = 0.025$), mental health ($p = 0.044$) and physical summary score ($p = 0.022$, Table 5.8, P. 213). After adjusting for AHI and BI at baseline, the difference remained ($p = 0.008$, Table 5.9, P. 214).

If we take a look at those variables in EADL (Figure 5.5, P. 224), HADS (Figure 5.6, P. 225) and SF-36 (Figure 5.7, P. 226) which did not show statistical significance we can see the confidence intervals of Hedges' effect size (bias corrected, Hedges 1985) between CPAP and conservative groups were wide. The upper confidence limit of effect size in favour of CPAP was mostly less than 0.5 (small or no effect) and the lower confidence limit in favour of conservative treatment was higher than 1 (big effect). The main reason for not rejecting null hypothesis might be due to inadequate statistical power.

5.4.5 Outcomes at 6 months after stroke

At 6-month after stroke the differences between CPAP and control groups disappeared (Table 5.10, P. 215). In terms of NADL and SF-36 scales, previous lower scores in CPAP group increased slightly and previously higher scores in the control group decreased slightly. Both of them were approaching to an average level, nearly identical to the scores in the control group ($(A+H)\cdot h^{-1} < 30$, Figure 5.8a, P.227 to 5.8e, P. 228). From statistical point of view, the effect of "regression to mean" or "wearing off" might be a suitable explanation.

5.4.6 Ambulatory blood pressure monitoring

Ambulatory blood pressure (ABP) monitoring was arranged for 32 patients (30 randomized with $(A+H)\cdot h^{-1} \geq 30$ and 2 non-randomized patients with $(A+H)\cdot h^{-1}$ = 49.8 and 17.7 respectively). Two patients died before ABP monitoring. Three patients refused the study. One patient was too unwell to have the recording. This resulted in 26 of 32 patients (81.3%) accepted ABP monitoring. Among 26 patients, 2 failed to have any reading of ABP due to confusion and detachment of the device.

Excluding 2 non-randomized patients, 22 randomized patients had valid ABP data for comparison between CPAP (n = 12) and the conservative group (n = 10). The median of successful recording in 26 ABP monitoring was 89% (IQR 70-93%, minimum 0% and maximum 100%).

There was no significant difference in 24-hour, daytime and nighttime SBP, DBP, MAP and HR between CPAP and conservative groups. The CPAP group had a relatively lower value of 24-hour ABP and ABP in the daytime (Table 5.11, P. 216) but had relatively higher value of ABP in the night time. The confidence intervals of the mean difference of the ABP between groups was wide, ranging from positive difference up to 27 mmHg to negative difference up to 27 mm Hg. The $(A+H)\cdot h^{-1}$ and oximetric variables were not correlated with ABP variables.

Patients in the conservative group had a significantly bigger day to night dipping of SBP (p = 0.021) and MAP (p = 0.037, Table 5.12, P. 217 and Figure 5.9a and 5.9b, P. 229). According to our definition, 7 of 9 patients in conservative group were dippers, 1 was a borderline dipper and 1 was a non-dipper. On the contrary, 2 of 12 patients in the CPAP group were dippers, 1 was a borderline dipper and 9 were non-dippers. The CPAP group had significantly more non-dippers than the conservative group (Chi-square p = 0.019).

Mean 24-hour SBP was positively correlated with total EADL score at 3 months after stroke (Figure 5.10a, P. 230). A similar trend was also found between mean 24-

hour DBP and total EADL score. No significant correlation was found between mean ABP and EADL at 6 months after stroke (Figure 5.10b, P. 230).

Cosinor analysis was performed for 24-hour circadian rhythm of ABP data in 18 randomized and 2 non-randomized patients who had successful ABP readings > 70% of the recording time. Twelve of 20 patients were categorized into group "A" which indicated regular ABP rhythm (Table 5.12, P. 217). In group "A" six patients had a normal 24-hour circadian ABP rhythm ("cosine" pattern, Figure 5.11a, P. 231). Three patients had 24-hour ABP rhythm which showed day-night reverse ("sine" pattern, Figure 5.11b, P. 231). Three patients had a 12-hour ABP rhythm (double-peak pattern Figure 5.11c, P. 232). Eight of 20 patients were categorized into group "B" which indicated irregular rhythm (Table 5.13, P. 218). In group B two patients had 12/24-hour SBP and DBP mismatch ("mismatch pattern", Figure 5.11d, P. 232). Six patients had less than 12-hour circadian ABP rhythm (rapid cycling pattern) and their ABP data were too irregular to be shown in the figure. The best-fit regression models for a cosinor waveform of ABP rhythm were statistically significant in all patients except those who had rapid cyclic pattern (Table 5.12, P. 217 and 5.13, P. 218).

We examined the relationship between circadian ABP rhythms and stroke onset. As I have mentioned in chapter 4, most of the stroke onset in this group of patients (moderate to severe SDB, $(A+H)\cdot h^{-1} \geq 30$) were located outside the period from 10 pm to 6 am. Eight of 12 patients had stroke onset in the ascending limb of ABP rhythms (Figure 5.11a to 5.11c, P. 231-232). The other two patients in group B1 also had stroke onset in the ascending limb of SBP.

Patients in group B (n = 8) were significantly older and had significantly worse desaturation in baseline sleep study than those in group A (n = 12, Figure 5.12a to 5.12d, P. 233-234). From the viewpoint of functional outcome, they showed a trend of lower scores in mobility, kitchen and domestic subscale of EADL and significant lower score in the EADL leisure subscale ($p = 0.013$, Table 5.14, P. 219). From the viewpoint of health-related quality of life, they had relatively lower scores of physical function, mental health and mental summary and significantly lower score of role emotional ($p = 0.008$, Table 5.14, P. 219).

5.4.7 Adverse events

One patient in CPAP group and one in control group died. The patient randomized to CPAP treatment died on the first day of CPAP trial. He tried CPAP shortly in the afternoon when the research nurse (MV) visited him at stroke rehabilitation ward. He suffered from adult respiratory distress syndrome (ARDS) in the evening and died two days later. The patient randomized to conservative treatment died before follow-up at post-treatment phase. She collapsed and died before being transferred to the hospital.

5.5 Discussion

We had strict criteria for recruiting more stable patients in stroke so only 30 patients who had moderate to severe SDB ($(A+H)\cdot h^{-1} \geq 30$) were enrolled and 15 of them were randomized to nasal CPAP treatment. Even though our patients were in the mild to moderate end of stroke the compliance to CPAP was still poor.

5.5.1 Acceptance of and compliance to nasal CPAP

If we take acceptance of CPAP into account first, 4 of 15 patients who were allocated CPAP in our study withdrew in the first week of treatment limb. This is not much different from the previous study conducted by German group that 30% of their patients rejected CPAP either on titration night or within a few days of titration. Ours is also not worse than the study conducted by the Hong Kong group where 53% of patients rejected CPAP either after a brief trial in the afternoon or during the first night of titration.

Then examining compliance with CPAP, in our study, although 7 of 15 patients were willing to keep CPAP for more than 4 weeks, the compliance with CPAP was very poor (mean = 1.40 and median = 0.16 hours per night). This means that they kept the machine but did not use it. The compliance in our study was quite different from that in Swedish group [Sandberg *et al.* 2001a] which showed 4.1 ± 3.2 mean hours of CPAP use in 31 patients. Half of them used CPAP for more than 4 hours. However our finding was more similar to that reported by the Hong Kong group [Hui *et al.* 2002] which showed mean hours of CPAP use in 4 of 34 patients who were willing to proceed to home therapy was 2.5 ± 0.6 hours. The following factors are considered for poor compliance to CPAP from the viewpoint of study design:

- Is the diagnosis of SDB accurate?
- Is CPAP machine and interface suitable?
- Are intensive education and follow-up successful?

I used a portable semi-attended limited sleep study for the diagnosis of SDB in stroke. The cut-off point of $(A+H)\cdot h^{-1}$ for this device (Embletta) was recommended to be 20/h according to previous validity study [Dingli *et al.* 2003]. I further increased the cut-off point to 30/h to focus on stroke patients who had moderate to severe OSAH breathing abnormality. This might increase the acceptance and compliance of CPAP. I didn't use SDB-related symptoms, for instance, patients having at least two of the major symptoms; as adjunctive criteria to recruit more symptomatic patients because we wished to investigate whether the treatment of the disordered breathing of OSAH would be beneficial. In addition we were concerned that identification of excessive sleepiness in the 2 weeks post stroke would be very difficult in this disabled and largely sedentary elderly population. The standard sleepiness questionnaire the Epworth cannot be used in these circumstances. We used an unattended auto-titrating CPAP for the treatment of SDB in stroke for the following two reasons: (1) it is not easy to transfer stroke patients to the sleep centre for an in-lab CPAP titration. Stroke patients were admitted to four hospitals in Edinburgh city but sleep centre is located in one of them; (2) auto-CPAP has been reported to decrease mean effective pressure so might be more comfortable for old and weak stroke patients. Intensive education and follow-up were maintained by an experienced staff in sleep centre who had been keeping in contact with patients who were randomized to CPAP regularly. If patients didn't comply with the CPAP well, encouragement and reinforcement were given before bringing the machine back. According to these, poor compliance might not be due to study design.

The following factors may explain poor compliance with CPAP in this study:

- Patients were not very sleepy and thus might neither tolerate the obtrusive treatment nor perceive obvious benefit which might reinforce CPAP use.
- They were older.
- They were seriously ill physically and probably psychologically.
- They had problems in comprehension of and cooperation with the treatment.
- They and their family were concerned more about stroke than SDB.
- They had difficulty tolerating the mask and side effects of CPAP.

- Most of them could not manage the mask and machine by themselves.

Admitted stroke patients are usually older and have more severe deficits or complications. They are frequently approached by different medical teams for many procedures and treatment plans. Although patients who had severe dysphasia, confusion or cognitive impairment were mostly excluded in our study, the length of keeping CPAP was still negatively correlated with degree of dysphasia and depression. This means the above problems are very common in stroke and stroke patients find it much more difficult than those without brain damage to understand what SDB is, how it is worthy to have a trial as an extra treatment and how to wear a mask properly.

On the other hand stroke patients are not very sleepy and they usually are not concerned by snoring and daytime sleepiness as these are common in old age. Even in patients who had agreed to attend the study and been randomized to CPAP, two of 15 patients still didn't think they had to use CPAP regularly. Poor compliance of nasal CPAP treatment was present in the early days of treatment. One of the reasons might be that stroke patients had lack of insight into the consequences of untreated SDB.

A mask covering the nose or a full-face mask might be a stressor as stroke patients could have a feeling that they were more seriously ill or getting worse. Stroke patients might not only tolerate adverse nasal and oral symptoms of CPAP less but also more easily get upper airway or chest infections which could make these symptoms more troublesome. All of these factors might reduce compliance.

Problems resulting from stroke itself also have an influence on the compliance. Falling is a common complication in stroke and this could result in facial wounds or bodily pain which shift patients' attention to other more serious problems and prevent them from further using CPAP. Hemiparesis and facial palsy are so common in stroke that patients might have insufficient hand function to put on a mask and turn on the machine by themselves but also have mouth leaks or have their mask coming off easily from original position. They have to be dependent on caregivers for

CPAP. In hospitals, caregivers are nursing staff on night duty; they are other non-professional workers when patients move back home or are transferred to a nursing home. Although we arranged a session to introduce and demonstrate CPAP for nursing staff on night duty in two acute stroke units and two rehabilitation wards they usually were very busy and could not keep a constant eye on patients when they were using CPAP. It was even more difficult when stroke patients were discharged home or moved to nursing homes. In conclusion, all of these factors could explain poor compliance with CPAP in our study.

5.5.2 Outcome assessment at post-treatment phase and 6 months after stroke

We did not measure EDAL and SF-36 at baseline. Questions in SF-36 relate to an inappropriate time frame, i.e. the last 4 weeks, thus spanning stroke onset and activities. Questions in both SF-36 and EADL refer to many activities which cannot be performed by hospitalized patients, i.e. house work, shopping, climbing stairs and walking for more than a mile. For these reasons they were not applied at baseline.

The value of an RCT is that the analysis that is critical is the comparison of the primary outcomes after treatment. The primary variables at baseline is not part of the analysis [Engleman *et al.* 1994a;Engleman *et al.* 1997;Engleman *et al.* 1998;Engleman *et al.* 1999]. It is important that the patients are selected by the same criteria and then truly randomized as they were in this study. If the number of subjects studied is big enough that will result in comparable groups. I accept that in smaller studies than planned differences in baseline may occur by chance and this is one of the limitations that I have pointed out in this study.

We cannot show any beneficial effect of CPAP on all domains of outcome in stroke. Although CPAP compliance (mean hour per night of CPAP use) was positively correlated with functional capacity (total EADL score) at post-treatment phase it was no longer an independent predictor for NADL total score after controlling baseline BI. What we can say is that patients who had better functional

capacity at baseline used CPAP longer and more frequently and their better functional outcome at post-treatment phase could be directly due to baseline difference. That is to say, a chance imbalance still existed with small sample size (N = 15, 15) even though randomization was conducted.

On the other hand, we showed that patients who were randomized to CPAP treatment had a trend toward a worse outcome in functional capacity (EADL), mood (HADS) and health-related quality of life (SF-36) at post-treatment phase. There are two possible explanations: (1) we can explain the results by chance at baseline due to limited sample size as well; (2) CPAP had an adverse effect.

The first point is inadequate sample size. The results showed that the CI of effect size in all domains of outcome between CPAP and conservative groups is wide. Although we can not reject the null hypothesis we also can not exclude that power of the study was too low to tell the difference. We did a priori power analysis. Estimated sample size was 40 patients in each group for a randomized control trial to achieve 90% power to detect a difference with a significant level (alpha) of 0.05 using a two-sided two sample-sample test. We unfortunately only reached a sample size of 15 patients in each group before we stopped after recruiting patients for 27 months or so. The major reason is that this was a two-year research project funded by the British Heart and Lung Association and the accessory reason is that patients randomized to CPAP had a very poor compliance (median hours of CPAP use was 0.16 hours per night), which was far below the compliance in clinical practice defined as more than 5 hours per night.

The second point is chance imbalance. The 95% CI of effect size in EADL and SF-36 is mostly located on the negative side in favour of conservative treatment. The possibility that the difference in functional capacity, mood and health-related quality of life between groups might exist but it is possible that those who were randomized to CPAP were worse in functional capacity and other obscured factors at baseline regardless of the treatment. Even we conducted a standardized randomization chance imbalance might exist if sample side is small (n = 15/15). At 6 months after stroke scores for functional capacity and health-related quality of life increased in

previously lower CPAP but decreased in previously higher conservative groups. This means scores became much closer with no more statistical significance. This could be explained by the effect of "regression to mean". Patients with lower scores and higher scores at baseline tend to get closer to the mean of the scores in the follow-up periods.

Post-stroke depression can result in lower physical score in SF-36 even though there is no deterioration of neurological deficit and functional capacity [Suenkeler *et al.* 2002]. The reason may be that depressed patients in stroke tend to give rating for SF-36 worse scores [Fruhwald *et al.* 2001]. In our study we found lower CPAP compliance was independently associated with lower physical summary score in SF-36 at post-treatment phase after adjusting for baseline BI. Post-stroke depression might be one of the explanations because patients randomized to CPAP also had lower depression sub-score of HADS and mental sub-score of SF-36 at post-treatment phase. One of the possibilities is that CPAP treatment might be more stressful for non-compliant patients in my study so resulted in or enhanced pre-existing psychological problems, for instance, anxiety and depression. More than half of our patients were willing to keep CPAP for longer period. This means they did not reject trying CPAP but they couldn't use it because of their physical, psychological illness or complications from either stroke or CPAP.

A non-randomized control trial in stroke showed better outcome following CPAP treatment in terms of well-being and 24-hour ABP [Wessendorf *et al.* 2001]. Although they had 105 patients recruited in the study only 41 of them had results for well-being which was assessed by a simple Visual Analogue Scale only. Only 16 of them had results for ABP. The major bias in this study was that they used noncompliant patients as controls. Noncompliant might have more psychological or physical problems than compliant. Thus they might have lower score in wellbeing and higher ambulatory blood pressure which were independent of allocation. In my study I also found CPAP non-compliant patients had similar problems which have been described in the previous paragraph.

The other study with a randomized control trial for SDB in stroke found that only depressive symptom was improved following CPAP treatment (n = 31) in comparison with conventional stroke treatment only (control, n = 28). According to their description, the CPAP group decreased 5 points of MADRS (CI = -8.2 to -1.8) but the control group, on the contrary, increased 2.6 points of MADRS (CI = 0.1 to 5.1). The effectiveness of CPAP treatment is statistically significant. The effect took place in the assessment on day 7 [Sandberg *et al.* 2001a]. The validity and reliability of MADRS and HADS [Aben *et al.* 2002] are both satisfactory in assessing depression in the elderly ill patients. MADRS consists of 10 questions related with depression with 6-level of Likert scale in each question. The maximum score is 60. Depression subscale of HADS consists of 7 questions related with depression with 4-level Likert scale. The total depression subscale is 21. Sensitivity and specificity in predicting moderate to severe depression in non-stroke patients seemed to be higher in MADRS (sensitivity = 93.5%, specificity = 83.3%) [Muller *et al.* 2003] than HADS (sensitivity = 85%, specificity = 76%) [Lowe *et al.* 2004] from two separate study without comparing each other. Their randomized controlled trial of CPAP in stroke further supports their previous finding that depression associated with SDB in stroke can be counteracted by CPAP intervention. The only drawback was that they conducted a parametric test (repeated measure ANOVA with contrast analysis) but they didn't mention whether MADRS in the study was normally distributed. It is very common for a psychological variable to be not normally distributed. Their sample size for comparison is about the lower limit for which the "central limit theorem" can be applied regardless of whether it is normally distributed.

The other studies with CPAP trials in stroke didn't have any outcome assessment so it not possible to compare my data to theirs. I have two significant findings regarding ABP monitoring and functional outcome:

- The higher the blood pressure the better the functional outcome and the lower the blood pressure the worse the functional outcome in the post-treatment phase.

- The older the patient and the more severe the desaturation at baseline, the less stable the circadian BP rhythm and the worse the functional outcome in the post-treatment phase.

These will be discussed in the following two sections:

5.5.3 Ambulatory blood pressure and functional outcome of stroke

As ambulatory SBP and DBP are about 10 mmHg lower than those measured by sphygmomanometer [Bur *et al.* 2002], a new classification of ABP based on the risks of cardiovascular diseases was proposed: (1) normal (< 132/81 mmHg); (2) stage I (< 140/88 mmHg); (3) stage II (< 148/94 mmHg); (4) stage III (≥ 148/94 mmHg). According to the above definition, mean SBP and DBP in both the CPAP and the conservative groups in our study were basically within a normal range. The upper confidence limit of SBP/DBP was around 160/90 mmHg and lower confidence limit of SBP/DBP was around 90/55 for both groups of patients. This means that the higher end of ABP in our patients is still acceptable in acute and subacute phase of stroke but the lower end of ABP might be at risk of compromising cerebral perfusion pressure.

Controlling blood pressure is an important issue in stroke. A large sample (n = 308) cross-sectional study showed low blood pressure below 180 mmHg was harmful in acute stroke [Castillo *et al.* 2004]. They found the lower the BP below that point, the worse the neurological deficit. The other randomized controlled trial was conducted on a group of stroke patients who had bigger ischaemic penumbra defined by perfusion diffusion mismatch in magnetic resonance image (MRI) [Hillis *et al.* 2003]. Patients were randomized to either blood pressure elevation or conventional treatment. The results showed beneficial effect of elevation of blood pressure on functional outcome in acute and subacute stage. It is still not clear whether blood pressure reducing effect of CPAP in patients with SDB is also observed in patients with stroke but it is important to think over this issue especially in acute or subacute phase of stroke as lower level of blood pressure may be harmful to stroke patients.

One study using ABP monitoring for 219 stroke patients found that 24-hour SBP higher than 160 mmHg might predict long-term mortality after a median follow-up for 2.5 years [Robinson *et al.* 2001]. This supports that reduction of blood pressure in the chronic phase of stroke is beneficial. The other study using ABP monitoring showed that the odds ratio of early neurological improvement was higher in patients with a day to night decrease of SBP and DBP [Bhalla *et al.* 2001], This means that dippers had a better outcome even in the acute phase of stroke although extreme blood pressure dipping at night might be worse [Kario *et al.* 2001]. The other study also showed lower risk of stroke in dippers [Phillips *et al.* 2000;Yamamoto *et al.* 1998]. One of the beneficial effect of CPAP is to convert non-dippers into dippers [Akashiba *et al.* 1999;Engleman *et al.* 1994b]. All of these are good points supporting CPAP treatment for SDB in stroke from a long-term point of view.

As I have described in chapter 2, CPAP increases intrathoracic pressure and decreases venous return to the heart. This further increases intracranial pressure (IICP). The systemic effect of IICP is increased mean arterial pressure but this can be counteracted by vasoconstriction in the brain through autoregulation. The BP subsequently decreased. So the effect of blood pressure elevation induced by CPAP disappears. On the other hand CPAP abolishes SDB, hypoxia and arousal response. This can decrease sympathetic tone and systemic blood pressure. The effect of blood pressure reduction by CPAP is stronger especially in the night time during the treatment. The net effect of CPAP is to reduce blood pressure. In our study patients randomized to CPAP had relatively lower ambulatory SBP, DBP and MAP in 24-hour and in the daytime but higher in the night time. This can hardly be explained by the treatment of CPAP.

The group randomized to CPAP in our study had significantly more non-dippers than dippers which is in contrast to previous study [Wessendorf *et al.* 2001]. Non-dippers are commonly seen in stroke regardless of SDB [Lip *et al.* 1997;Jain *et al.* 2004]. My patients were not different in type, location and risks (hypertension, diabetes) of stroke to patients in previous studies. Those who were randomized to CPAP but could not tolerate it might have more mask-fitting problem or air leak.

This could turn true CPAP into sham CPAP (CPAP with subtherapeutic pressure) and have a negative effect on blood pressure at night [Pepperell *et al.* 2002]. Stroke patients who were not compliant with CPAP could have psychological stress during CPAP usage and this might increase their blood pressure at night. I don't think the above two possibilities are high as our patients had very poor compliance. It is hard to say that CPAP kept on the bedside can increase blood pressure psychologically. The most possible explanation is chance imbalance as well. That is to say, we incidentally randomized a small group of patients into CPAP limb who had an unclear reason for lower blood pressure at baseline and follow-up period and this was associated with poorer functional outcome. There is probably nothing related to CPAP treatment.

5.5.4 Instability of circadian ABP rhythm

One study found that two peak of stroke onset in the morning and evening were associated with surge of blood pressure and increased physical activity at that time [Stergiou *et al.* 2002]. SDB is one of the trigger factors for surge of blood pressure either at night or in the daytime which might explain the link between SDB and long standing hypertension. One of the possible mechanisms for stroke onset in the daytime for patients with SDB is sympathetic activation which could result in circadian BP swing. This is compatible with our findings described in the chapter 4 that patients with $(A+H)\cdot h^{-1} \geq 30$ had more stroke onset in the daytime and onset time of stroke was mostly located in the ascending limb of circadian BP rhythm in this chapter.

We also found both SBP/DBP mismatch (B1) and rapid cycling of ABP with period less than 12 hours (B2) were also associated with poor functional outcome. Age and desaturation are two significant factors resulting in these two types of circadian BP rhythm. We showed in chapter 4 that older stroke patents (apart from those in their 80s) had more severe SDB which could result in more severe desaturation. In this chapter we found that more severe desaturation was associated with more unstable circadian BP swing (B1 and B2). We propose a hypothesis

through the post-hoc exploratory analysis that this kind of blood pressure instability may be associated with stroke onset. This is also compatible with previous publications that, stroke onset which is located in the morning might be associated with surges of blood pressure.

5.6 Conclusions

We have the following conclusions in this single blind randomized controlled trial:

- We cannot show any beneficial effect of CPAP on the outcome of stroke but one of the reasons is that our sample size was too small which resulted in wide confidence interval.
- Compliance with CPAP treatment was poor even we had strict criteria to recruit more stable stroke patients and performed an intensive CPAP education and follow-up.
- Compliance with CPAP may be enhanced in further studies on a even more highly selective basis by choosing patients with higher functional capacity, higher cognitive function especially language and less depression in the acute or subacute phase of stroke.
- Rapid swing of ambulatory blood pressure in stroke may be associated with increased age, more severe SDB, more profound desaturation and stroke onset.
- If stroke patients are unstable in the acute or subacute phase, CPAP treatment may be delayed to a more stable chronic phase, i.e. 3 months after stroke. At this stage CPAP may still be useful in secondary prevention of stroke through controlling blood pressure and cardiovascular risk factors. This needs further randomized controlled trials to evaluate.
- The effect of CPAP on blood pressure reduction and CBF need to be clarified in acute and subacute stroke as I showed that the lower the blood pressure the poorer the functional outcome.

Table 5.1 Baseline demographic, sleep and laboratory data in patients randomized to CPAP (n = 15) and conservative treatment (n = 15)

	Control	CPAP	p Value ¶
Age	72 (58-84)	76 (65-87)	0.173
Male/Female, N	9/6	11/4	0.439
Body mass index, kg/m^2	25.1 (22.1-33.1)	26.8 (21.9-28.5)	0.548
OCSP classification			0.465
TACI, n	4	4	
PACI, n	7	9	
POCI, n	1	2	
LACI, n	2	0	
ICH, n	1	0	
Hypertension, n	11	7	0.136
Diabetes mellitus, n	3	1	0.283
Previous stroke or TIA, n	4	4	1.000
Current smoking, n	3	2	0.624
Systolic BP at admission	164 ± 39	151 ± 30	0.307
Diastolic BP at admission	87 ± 11	85 ± 14	0.723
Apnoea Hypopnoea Index, n/hr	47.7 (36.5-60.2)	43.1 (35.6-51.8)	0.237
Desaturation Index, n/hr	25.5 (7.0-40.3)	15.8 (8.1-22.7)	0.330
Mean SaO2, %	93.2 (92.5-95.0)	93.3 (91.8-94.3)	0.678
Lowest SaO2, %	81 (76-86)	80 (66-85)	0.360
% Time SaO2 < 90%	3 (0.9-10.0)	4.9 (2.1-20.9)	0.561
Haemoglobin	145 (133-153)	139 (135-150)	0.648
Haematocrit	42.3 (37.9-43.2)	41.9 (39.3-45.0)	0.950
Platelet	209 (196-236)	21.7 (21.0-25.8)	0.271
Plasma glucose	6.3 (5.9-7.3)	6.4 (5.5-8.3)	0.726
Total cholesterol	5.1 (4.0-6.6)	4.9 (4.3-6.2)	0.771

¶ Mann-Whitney U test or Chi-square test

§ OCSP: Oxford Classification of Stroke project; TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; POCI: Posterior circulation infarct; LACI: Lacunar infarct; ICH: Intracerebral haemorrhage

Table 5.2 Baseline assessment in patients randomized to CPAP (n = 15) and conservative treatment (n = 15)

	Control	CPAP	p Value ¶
Pre-stroke Modified Rankin Score	0 (0-0)	0 (0-0)	0.654
Pre-stroke Epworth Sleepiness Scale	6 (2-10)	6 (4-14)	0.373
Stanford Sleepiness Scale (1-7)	3 (1-4)	2 (2-3)	0.966
NIH Stroke Scale (0-42)	6 (5-8)	5 (4-9)	0.736
Barthel Index (0-20)	14 (9-17)	11 (7-16)	0.358
Mini-mental Status Examination (0-30)	25 (23-28)	28 (26-29)	0.033*
Addenbrooke's Cognitive Exam (0-100)	79 (61-85)	84 (69-88)	0.245
Orientation (1-10)	10 (8-10)	10 (8-10)	0.963
Attention and concentration (0-8)	7 (5-8)	8 (7-8)	0.025*
Memory (0-35)	23 (15-32)	32 (21-33)	0.103
Verbal fluency (0-14)	6 (4-8)	5 (4-9)	0.950
Language (0-28)	25 (21-27)	26 (22-27)	0.690
Visual spatial (0-5)	3 (1-4)	3 (2-4)	0.391
Hospital Anxiety Depression Scale (0-42)	7 (5-15)	10 (6-15)	0.479
Anxiety (0-21)	4 (2-5)	5 (2-6)	0.402
Depression (0-21)	5 (3-9)	5 (2-9)	0.983

¶ Mann-Whitney U test

* $P < 0.05$

Table 5.3 Problems of compliance to nasal CPAP treatment (n = 15) ¶

Category	Total N	N	Details	Management
Problems with machine	8	4	Air leakage through mouth	Full face mask, chin strap, education
		3	Claustrophobic	Education, changing masks
		2	Air leakage through mask	Mask fitting*
		2	Unable to sleep with mask	Education
		1	Noisy machine	Education
		1	Feeling cold air	Humidifier*
Complications of CPAP	8	5	Stuffy or running nose	Medication*
		3	Harsh on the throat or cough	Humidifier*
		2	Dry mouth	Humidifier*
		1	Pressure sores	Wound care*
Complications of stroke	9	4	Problem to put on mask	Education, help from caregivers*
		2	Problem to keep mask in position	Full face mask, help from caregivers
		2	Involuntary movement of head	1 patient recovered spontaneously*
		2	Fall with bruise or wound on face	Wound care (refused to use then)
		1	ARDS †	Ventilator
No insight for treatment	2			Education*

¶ Each patient might have more than one problem so the column total does not equal the number of patients

* Able to solve the problem

† Adult respiratory distress syndrome

Table 5.4 Factors correlated with CPAP compliance (mean hours of use per night, n = 14) at baseline

	Coefficient	p Value ¶
Age	-0.259	0.371
Education	0.061	0.837
AHI	0.121	0.679
Pre-stroke Epworth Sleepiness Scale (n = 11)	-0.377	0.253
Stanford Sleepiness Scale	0.022	0.941
NIH stroke scale	-0.487	0.077
Barthel Index	0.565	0.035*
Mini-mental Status Exam	-0.050	0.864
Addenbrooke's Cognitive Exam total	0.248	0.392
Orientation	0.257	0.375
Attention and concentration	-0.282	0.329
Memory	0.003	0.991
Verbal fluency	0.231	0.426
Language	0.643	0.013*
Visual spatial	0.471	0.089
Hospital Anxiety Depression Scale total	-0.132	0.653
Anxiety	0.166	0.571
Depression	-0.574	0.032*

¶ Spearman correlation

*P < 0.05

Table 5.5 Comparison of sleepiness, neurological and functional outcomes between CPAP and conservative treatment at post-treatment phase

	Direction of Improvement	N	Control	N	CPAP	Effect size	p Value ¶
Stanford sleepiness scale (0-7)	–	14	2 (1-3)	14	3 (1-4)	-0.72#	0.119
NIH stroke scale (0-42)	–	13	3 (1-6)	14	2 (1-4)	-0.10	0.622
Barthel ADL (0-20)	+	15	19 (16-20)	15	17 (14-18)	-0.27	0.166
Nottingham Extended ADL total (0-66)	+	15	30 (16-41)	15	18 (11-27)	-0.36	0.229
Mobility (0-18)	+	15	6 (4-13)	15	3 (1-6)	-0.72*	0.048
Kitchen (0-10)	+	15	12 (4-14)	15	8 (1-13)	-0.37	0.317
Domestic (0-10)	+	15	1 (0-5)	15	0 (0-9)	0.09	0.822
Leisure (0-18)	+	15	8 (6-9)	15	6 (5-8)	-0.24	0.251
Mini-mental State Examination (0-30)	+	13	29 (25-30)	14	29 (25-29)	0.25	0.980
Addenbrooke's Cognitive Exam total (0-100)	+	13	88 (74-90)	14	86 (75-91)	0.27	0.827
Orientation (1-10)	+	13	10 (9-10)	14	10 (9-10)	0.09	0.885
Attention and concentration (0-8)	+	13	8 (6-8)	14	8 (6-8)	0.06	0.764
Memory (0-35)	+	13	30 (20-32)	14	34 (25-35)	0.73#	0.062
Verbal fluency (0-14)	+	13	8 (7-9)	14	6 (4-9)	-0.40	0.249
Language (0-28)	+	13	28 (26-28)	14	27 (25-28)	0.09	0.659
Visual spatial (0-5)	+	13	4 (3-5)	14	4 (3-4)	-0.29	0.394

¶ Mann-Whitney U test

$P < 0.05$, # $P \geq 0.05$ but effect size > 0.5

Table 5.6 Factors predicting mobility subscale of Nottingham Extended ADL Index at post-treatment phase in stroke patients under randomization ¶

Dependent variable	NADL Mobility Subscale ≥ 5		
Predictors	Age (p = 0.061), randomization (p = 0.014), Barthel ADL score at baseline (p = 0.010)		
Variables	Odds Ratio	Confidence Interval	p Value
Age	0.854	0.716-1.019	0.081
Treatment allocation	0.142	0.016-1.234	0.077
Baseline Barthel ADL	1.492	1.065-2.091	0.020*
Model Chi-Square		18.851	< 0.001
Correct Predictions		50%	
Nagelkerke-R^2		0.622	

¶ Logistic regression with enter method

* P < 0.05

The parenthesis following predictor shows p value in univariate regression analysis. Only those with p < 0.1 are entered into full model.

Table 5.7 Factors predicting Nottingham Extended ADL total score at post-treatment phase in patients randomized to CPAP treatment

Dependent variable	Nottingham ADL Total score			
Predictors	CPAP compliance (p = 0.023), Barthel ADL at baseline (p < 0.001)			
Significant Variables	Coefficient	Standard error	t Value	p Value
CPAP compliance †	8.484	6.397	1.326	0.212
Baseline Barthel ADL	2.273	0.597	3.807	0.003**
Full model F (df)		14.471 (2,11)		< 0.001
Full model R^2		0.845		

¶ Multiple linear regression with enter method

† CPAP compliance is treated as dichotomous variable (≥ 1h/night and < 1h/night)

** P < 0.01, * P < 0.05

Table 5.8 Comparison of well-being between CPAP and conservative treatment at post-treatment phase

	Direction of Improvement	Control (N = 14)	CPAP (N = 14)	Effect size	p Value ¶
Hospital Anxiety Depression Scale total (0-42)	–	7 (3-10)	9 (6-13)	-0.44	0.249
Anxiety (0-21)	–	3 (1-5)	3 (2-5)	0.18	0.981
Depression (0-21)	–	4 (3-5)	5 (4-9)	-0.60#	0.236
EuroQol Visual Analogue Scale (0-100)	+	80 (70-83)	70 (70-76)	-0.59#	0.099
EuroQol 5-Dimention (0-1)	+	0.81 (0.67-0.91)	0.59 (0.49-0.70)	-0.70#	0.022
SF-36 Health transition (1-5)	–	4 (3-4)	4 (3-4)	-0.11	0.546
SF-36 Physical function (0-100)	+	45 (35-66)	20 (14-35)	-1.08**	0.006
SF-36 Role physical (0-100)	+	0 (0-50)	0 (0-0)	-0.88*	0.025
SF-36 Role emotional (0-100)	+	100 (33-100)	83 (25-100)	-0.34	0.318
SF-36 Bodily pain (0-100)	+	84 (62-100)	72 (59-100)	-0.43	0.354
SF-36 Mental health (0-100)	+	86 (68-96)	68 (52-84)	-0.83*	0.044
SF-36 Social function (0-100)	+	63 (34-91)	44 (25-53)	-0.73#	0.119
SF-36 General health (0-100)	+	67 (58-80)	60 (44-76)	-0.41	0.300
SF-36 Vitality (0-100)	+	60 (48-75)	53 (35-66)	-0.61#	0.159
SF-36 Physical summary (0-100)	+	30.8 (25.3-42.6)	23.7 (18.5-26.1)	-0.85*	0.022
SF-36 Mental summary (0-100)	+	56.4 (48.3-61.1)	49.8 (39.0-60.2)	-0.47	0.232

¶ Mann-Whitney U test; ** $P < 0.01$, * $P < 0.05$, # $P \geq 0.05$ but effect size > 0.5

Table 5.9 Factor predicting physical summary score of SF-36 at post-treatment phase in stroke patients under randomization ¶

Dependent variable	Post-treatment SF-36 Physical Summary Score			
Predictors	AHI (p = 0.1), Randomization (p = 0.032), Barthel ADL at baseline (p = 0.011)			
Significant Variables	Coefficient	Standard error	t Value	p Value
AHI	-0.361	0.134	-2.685	0.013
Randomization	-9.819	3.370	-2.913	0.008
Baseline Barthel ADL	0.898	0.356	2.524	0.019
Full model F (df)		7.641 (3,24)		0.001
Full model R^2		0.489		

¶ Multiple linear regression with enter method

* $P < 0.05$

The parenthesis following predictor shows p value in univariate regression analysis. Only those with $p \leq 0.1$ are entered into full model.

Table 5.10 Comparison of outcomes between CPAP and conservative treatment at 6 months after stroke

	Direction of Improvement	N	Control	N	CPAP	Effect size	p Value ¶
Barthel ADL (0-20)	+	15	18 (16-19)	14	19 (11-20)	-0.06	0.640
Nottingham Extended ADL total (0-66)	+	15	28 (18-39)	14	23 (12-33)	-0.14	0.498
Mobility (0-18)	+	15	6 (4-12)	14	4 (2-6)	-0.53#	0.053
Kitchen (0-10)	+	15	9 (6-14)	14	11 (1-13)	-0.07	0.930
Domestic (0-10)	+	15	2 (0-7)	14	3 (0-7)	0.20	1.000
Leisure (0-18)	+	15	7 (5-9)	14	8 (4-10)	0.03	0.912
SF-36 Health transition (1-5)	–	13	4 (3-4)	13	3 (3-4)	0.74#	0.076
SF-36 Physical function (0-100)	+	13	40 (20-53)	13	25 (10-33)	-0.58#	0.095
SF-36 Role physical (0-100)	+	13	0 (0-13)	13	0 (0-25)	0.00	0.767
SF-36 Role emotional (0-100)	+	13	100 (0-100)	13	67 (0-100)	-0.23	0.379
SF-36 Bodily pain (0-100)	+	13	100 (42-100)	13	72 (37-100)	-0.15	0.721
SF-36 Mental health (0-100)	+	13	68 (54-88)	13	76 (72-80)	0.26	0.471
SF-36 Social function (0-100)	+	13	88 (38-88)	13	50 (13-75)	-0.70#	0.066
SF-36 General health (0-100)	+	13	62 (50-77)	13	67 (38-86)	0.07	0.662
SF-36 Vitality (0-100)	+	13	50 (35-73)	13	50 (40-58)	-0.14	0.857
SF-36 Physical summary (0-100)	+	13	28.4 (18.5-35.9)	13	19.8 (15.9-32.6)	-0.47	0.248
SF-36 Mental summary (0-100)	+	13	54.3 (39.7-61.3)	13	52.8 (43.2-58.9)	-0.08	0.798

¶ Mann-Whitney U test

** $P < 0.01$, * $P < 0.05$, # $P \geq 0.05$ but effect size > 0.5

Table 5.11 Comparison of ABP between CPAP and conservative treatment at post-treatment phase

	N	Control	N	CPAP	Mean difference (95% CI)	p Value ¶
Systolic BP	10	130.0 ± 18.4	12	126.2 ± 21.5	3.8 (-14.2-21.8)	0.666
Diastolic BP	10	73.7 ± 12.3	12	71.6 ± 6.7	2.1 (-6.5-10.7)	0.618
Mean arterial BP	10	94.4 ± 13.0	12	90.7 ± 11.4	3.7 (-7.2-14.5)	0.490
Heart rate	10	70.4 ± 11.9	12	69.9 ± 12.5	0.4 (-10.5-11.4)	0.934
Day systolic BP	9	132.5 ± 20.2	12	124.9 ± 22.6	7.6 (-12.3-27.6)	0.433
Night systolic BP	9	120.0 ± 18.8	12	127.9 ± 22.7	-7.9 (-27.4-11.6)	0.408
Day-Night SBP difference	9	12.5 ± 13.2	12	-3.1 ± 13.8		0.018*
Day-Night SBP difference (%)	9	8.9 ± 10.6	12	-3.1 ± 10.9		0.021*
Day diastolic BP	9	77.6 ± 14.6	12	71.7 ± 8.0	5.9 (-4.5-16.4)	0.926
Night diastolic BP	9	68.3 ± 12.2	12	71.2 ± 7.0	-2.9 (-11.7-5.9)	0.497
Day-Night DBP difference	9	9.3 ± 10.3	12	0.4 ± 6.9		0.029*
Day-Night DBP difference (%)	9	10.9 ± 14.6	12	0.1 ± 9.7		0.055
Day mean arterial BP	9	97.6 ± 16.0	12	90.3 ± 12.5	7.4 (-5.6-20.4)	0.248
Night mean arterial BP	9	87.3 ± 13.0	12	91.2 ± 12.2	-3.9 (-15.5-7.7)	0.492
Day-night MAP difference	9	10.4 ± 11.7	12	-0.9 ± 9.2		0.023*
Day-night MAP difference (%)	9	9.7 ± 12.8	12	-1.6 ± 10.3		0.037*
Day heart rate	9	74.1 ± 14.7	12	72.7 ± 13.3	1.5 (-11.4-14.3)	0.815
Night heart rate	9	65.1 ± 9.0	12	65.9 ± 12.2	-0.8 (-11.0-9.3)	0.862
Day-night HR difference	9	9.0 ± 7.7	12	6.7 ± 6.8		0.475
Day-night HR difference (%)	9	11.1 ± 7.5	12	8.9 ± 8.2		0.534

¶ Student's T test; * $P < 0.05$

Table 5.12 Circadian ABP rhythm with normal 24-hour (A1, n = 6) period, reverse 24-hour period (A2, n = 3) and 12-hour period (A3, n = 3) by Cosinor method

ID	SBP			Full model			DBP			Full model		
	Mesor	Amp	Period	F (df=3)	R^2	p Value	Mesor	Amp	Period	F (df=3)	R^2	p Value
Group A1												
SW	125.4	6.9	25.4	5.19	0.21	0.003	73.9	3.9	25.8	2.35	0.11	0.011
JM	164.5	15.5	24.9	8.05	0.32	< 0.001	83.5	11.1	25.5	6.81	0.29	< 0.001
AK1	115.6	17.1	25.6	14.3	0.45	< 0.001	64.5	14.7	25.3	15.4	0.47	< 0.001
JC	134.7	12.3	25.0	11.74	0.39	< 0.001	89.7	13.4	25.9	18.6	0.50	< 0.001
DM	141.0	21.4	24.9	35.0	0.68	< 0.001	88.2	16.8	25.6	24.0	0.59	< 0.001
TA2	115.6	7.8	26.0	6.22	0.26	0.001	72.5	5.5	26.5	2.95	0.14	0.040
Group A2												
SD	103.2	14.2	20.8	25.9	0.68	< 0.001	65.5	10.8	20.8	9.31	0.43	< 0.001
AK2	136.8	23.9	24.1	45.7	0.73	< 0.001	78.1	5.6	25.6	5.88	0.26	0.002
PD	106.5	9.5	24.7	4.28	0.19	0.009	59.2	8.5	23.0	6.41	0.30	< 0.001
Group A3												
WS	123.5	11.7	11.8	5.32	0.24	0.003	66.8	7.4	11.8	6.02	0.26	0.001
TA1	139.7	12.5	11.7	8.44	0.33	< 0.001	93.6	7.6	11.4	5.10	0.23	0.004
PR	143.0	10.0	11.6	10.02	0.37	< 0.001	70.6	5.0	11.9	7.00	0.29	< 0.001

Table 5.13 Circadian ABP rhythm with either SBP/DBP mismatch (B1, n = 2) or period < 12 hours (B2, n = 6) by Cosinor method

ID	SBP			Full model			DBP			Full model		
	Mesor	Amp	Period	F (df=3)	R^2	p Value	Mesor	Amp	Period	F (df)	R^2	p value
Group B1												
AS	127.5	17.9	25.6	9.43	0.35	< 0.001	69.0	10.8	11.6	9.23	0.34	< 0.001
PH	109.7	11.2	11.7	6.14	0.27	0.001	59.2	8.5	23.0	7.65	0.32	< 0.001
Group B2												
GC	125.0	7.1	10.9	2.99	0.15	0.039	68.6	3.8	4.9	2.57	0.13	0.064
JS	132.2	6.4	2.4	4.08	0.19	0.011	79.9	6.6	3.0	8.50	0.33	< 0.001
JD	106.7	6.1	4.8	2.81	0.16	0.050	68.6	2.9	2.0	0.67	0.04	0.576
TM	100.6	6.6	3.0	5.06	0.25	0.004	69.7	3.6	8.2	2.36	0.13	0.084
BS	131.6	11.0	8.3	6.73	0.29	< 0.001	78.8	7.4	8.4	5.58	0.25	0.002
VM	107.0	8.9	7.8	8.94	0.33	< 0.001	62.1	4.3	7.8	3.60	0.17	0.019

Table 5.14 Comparison of outcomes in patients with (group A) and without (group B) stable circadian ABP rhythm

	Direction of Improvement	Group A (n = 12)	Group B (n = 8)	Effect size	p Value ¶
Nottingham Extended ADL total (0-66)	+	41 (15-56)	19 (13-26)	0.75#	0.164
Mobility (0-18)	+	11 (4-16)	4 (2-7)	0.82#	0.088
Kitchen (0-10)	+	14 (4-15)	8 (4-11)	0.51#	0.243
Domestic (0-10)	+	5 (0-14)	1 (0-5)	0.58#	0.311
Leisure (0-18)	+	9 (7-12)	6 (5-6)	1.01	0.013*
Hospital Anxiety Depression Scale total (0-42)	–	6 (4-9)	6 (4-12)	0.20	0.907
Addenbrooke's Cognitive Exam total (0-100)	+	89 (82-92)	90 (77-91)	0.08	0.786
SF-36 Physical function (0-100)	+	55 (31-85)	28 (16-43)	0.75#	0.088
SF-36 Role physical (0-100)	+	0 (0-19)	0 (0-19)	0.82	0.919
SF-36 Role emotional (0-100)	+	100 (100-100)	83 (8-100)	1.27	0.008**
SF-36 Mental health (0-100)	+	84 (73-95)	72 (55-84)	0.81#	0.111
SF-36 Physical summary (0-100)	+	26 (19-43)	24 (20-30)	0.27	0.487
SF-36 Mental summary (0-100)	+	60 (55-63)	53 (40-61)	0.84#	0.217

¶ Mann-Whitney U test

*P < 0.05, * P < 0.01, # P ≥ 0.05 but effect size > 0.5

Figure 5.1 Diagram of randomized controlled trial of CPAP treatment for obstructive sleep apnoea/hypopnoea after stroke

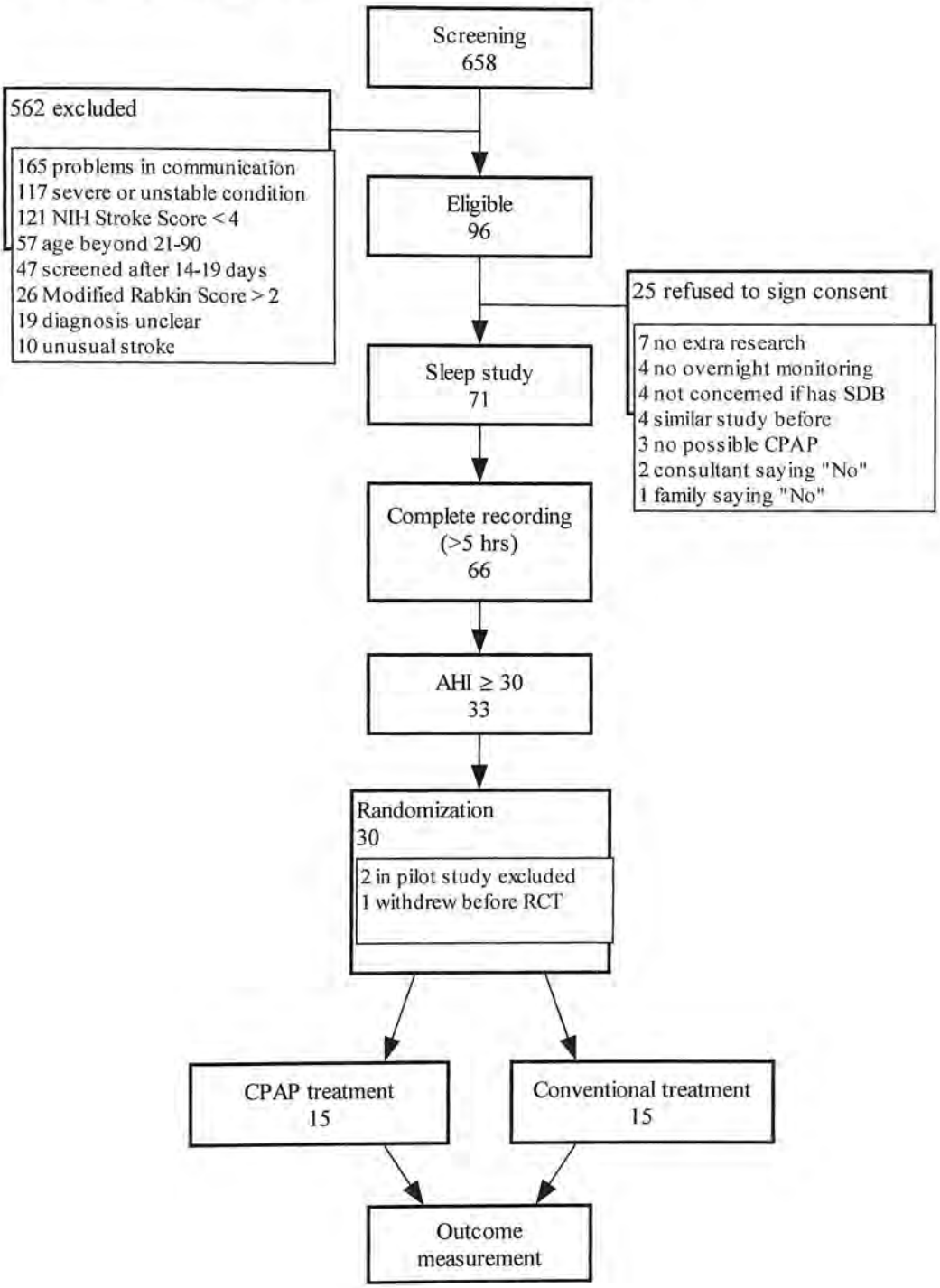
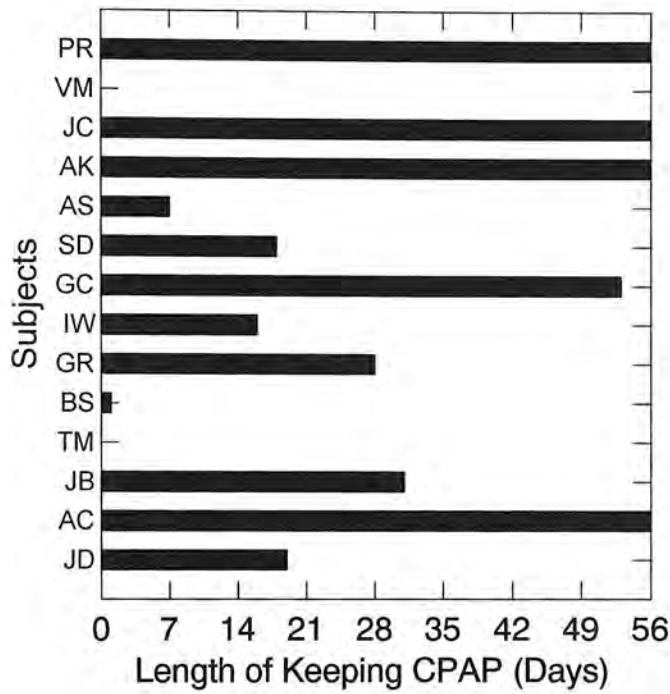


Figure 5.2 Length of keeping CPAP in days (a) and mean hours of CPAP use in hours per night (b)



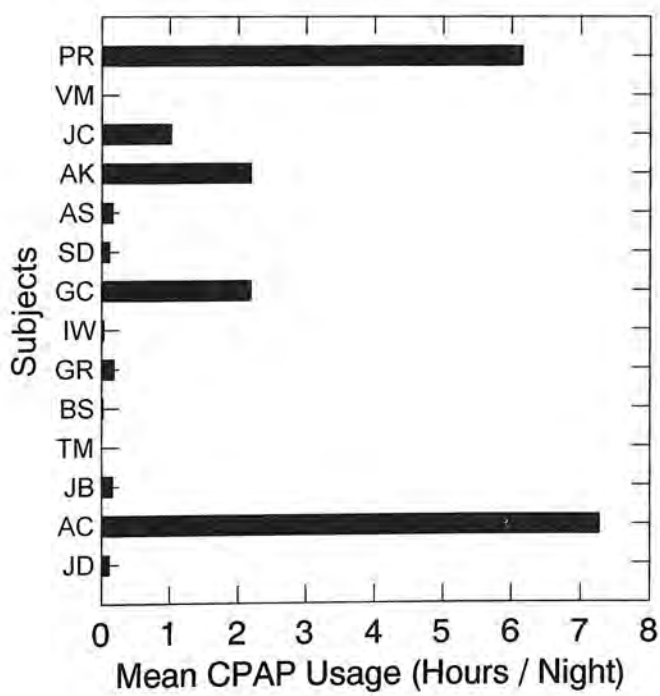
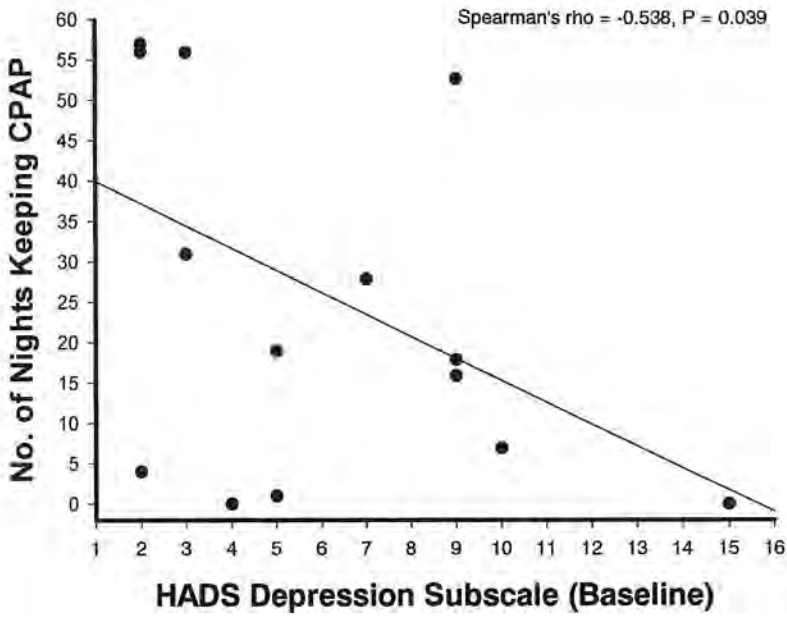


Figure 5.3 Correlation of length of keeping CPAP with depression subscale of Hospital Anxiety Depression Scale (a, N = 15) and language subscale of Addenbrooke's Cognitive Examination (b, N = 15) at baseline



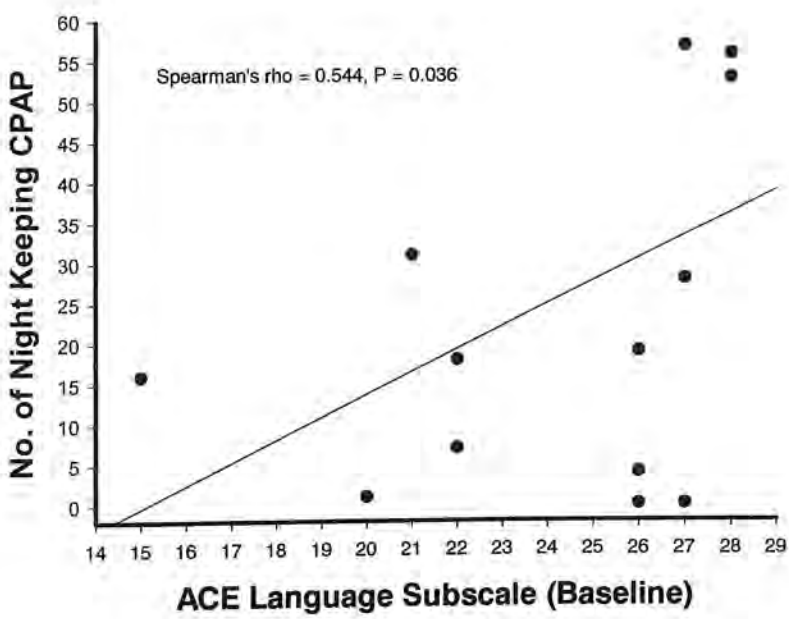
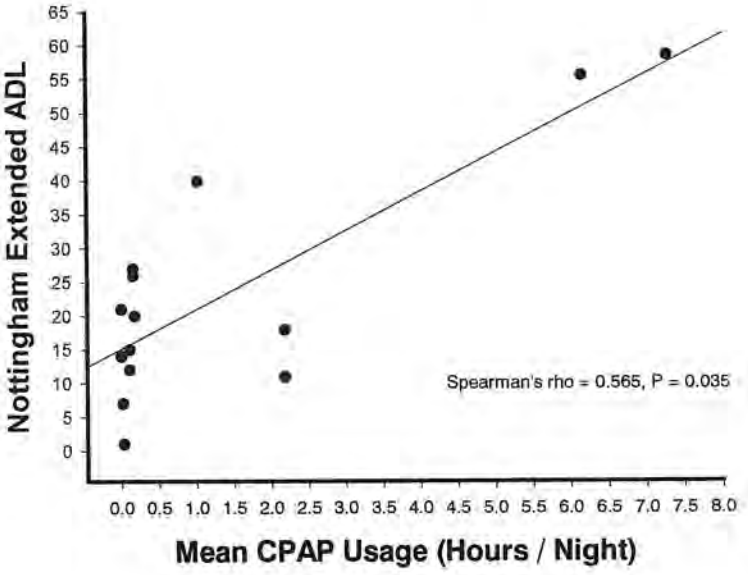


Figure 5.4 Correlation of CPAP compliance with Nottingham Extended ADL total score at post-treatment phase (a, N = 15) and after adjusting for Barthel Index at baseline (b)



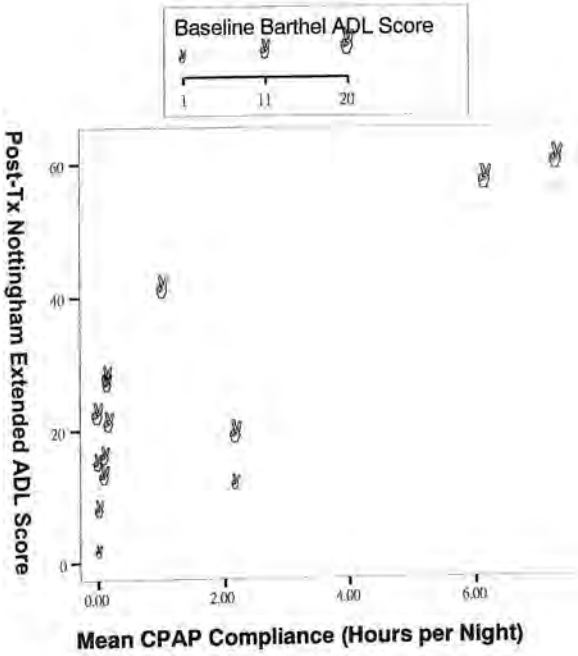


Figure 5.5 Effect size (bias corrected) with 95% CI in Nottingham Extended ADL Scale between CPAP and conservative groups

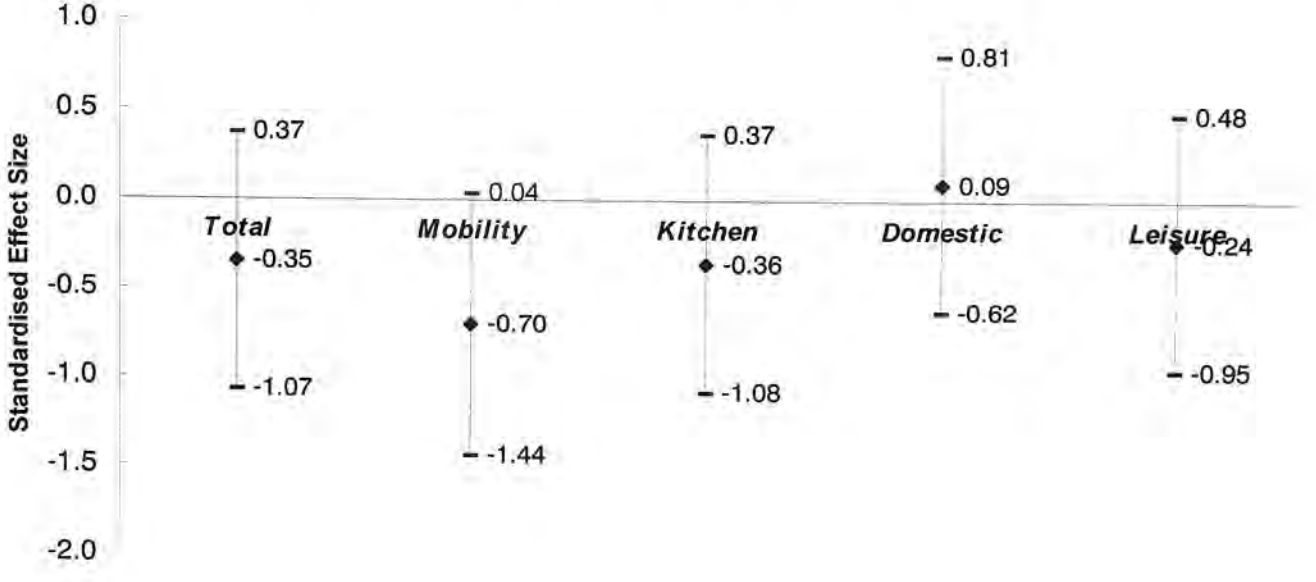


Figure 5.6 Effect size (bias corrected) with 95% CI in Hospital Anxiety and Depression Scale and EuroQol between CPAP and conservative groups

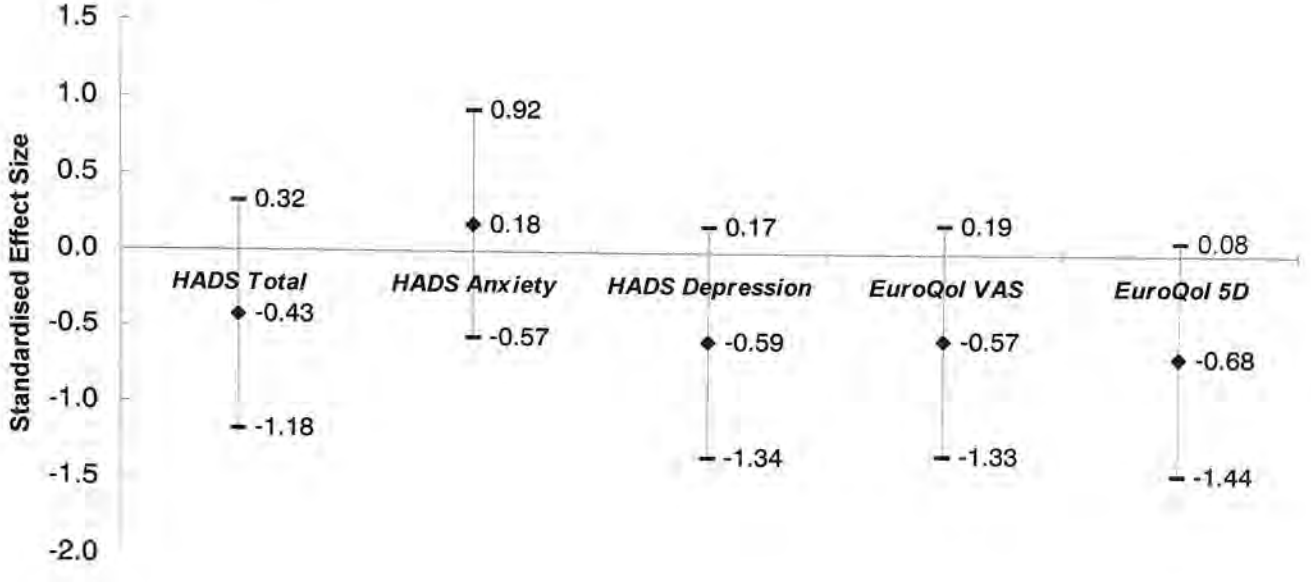
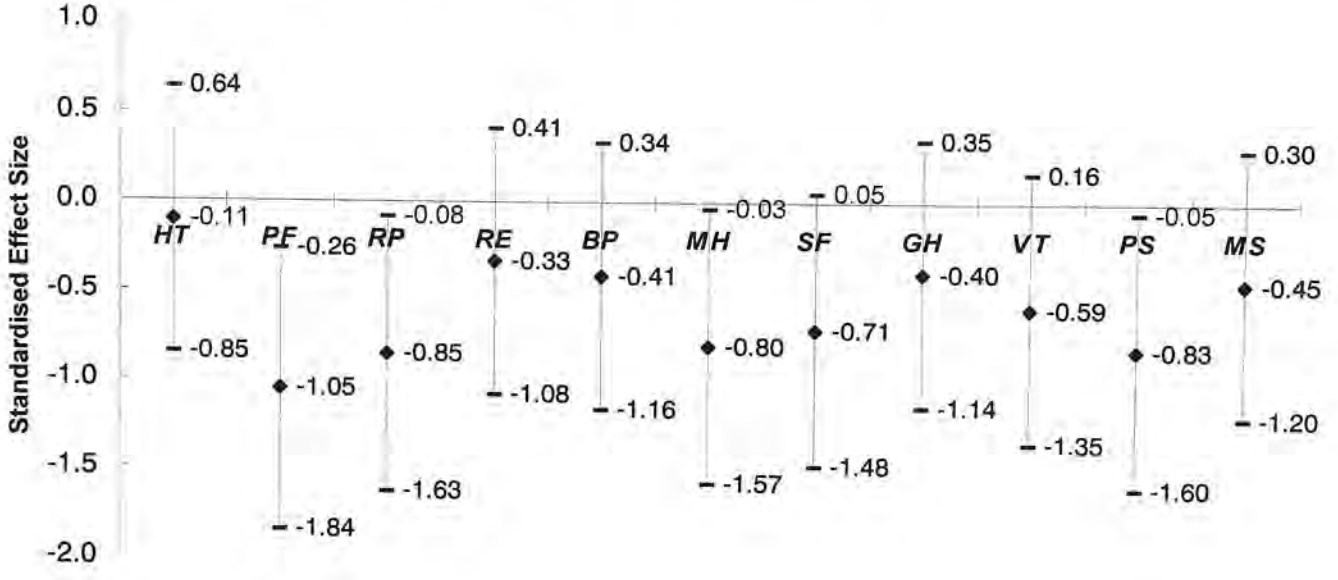
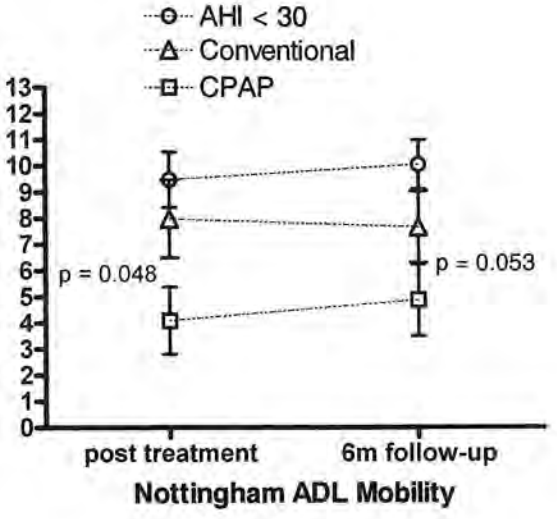


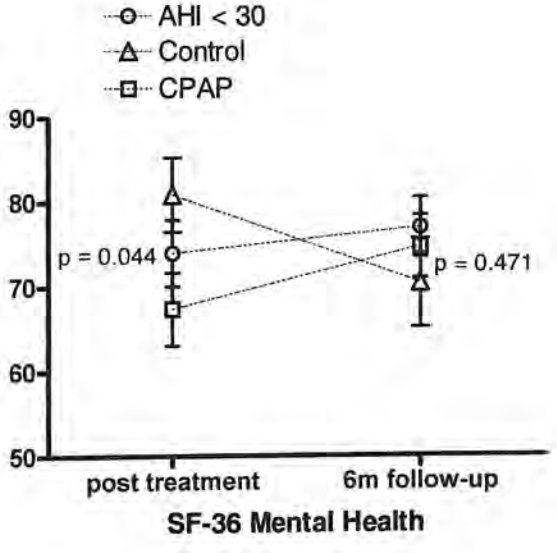
Figure 5.7 Effect size (bias corrected) with 95% CI in SF-36 between CPAP and conservative groups

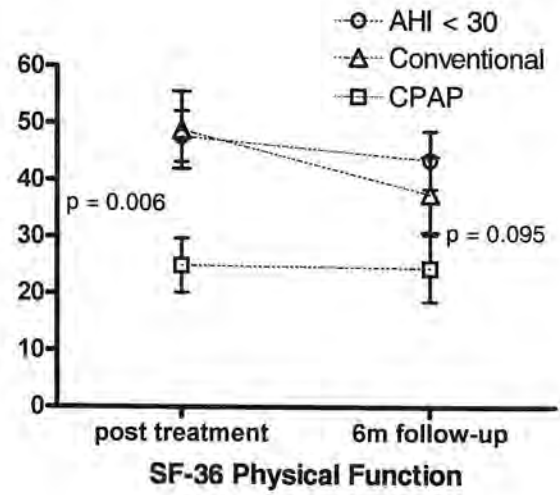


HT: health transition; PF: physical function; RP: role physical; RE: role emotional; BP: body pain; MH: mental health; SF: social function; GH: general health; VF: vitality; PS: physical summary score; MS: mental summary score

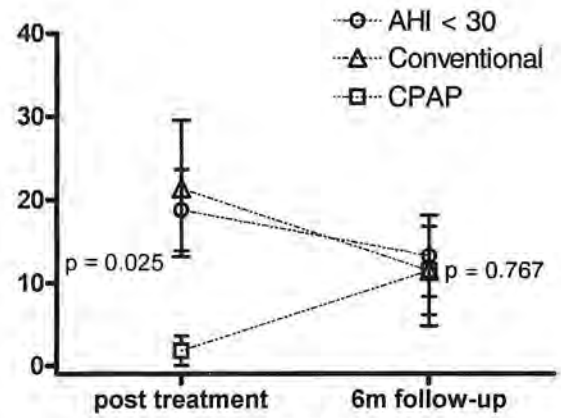
Figure 5.8 Longitudinal changes of mobility subscale in (a) Nottingham Extended ADL Index and (b) mental health, (c) physical function, (d) role physical, (e) physical summary score of SF-36 between CPAP and conservative groups (patients with AHI < 30 used as control)



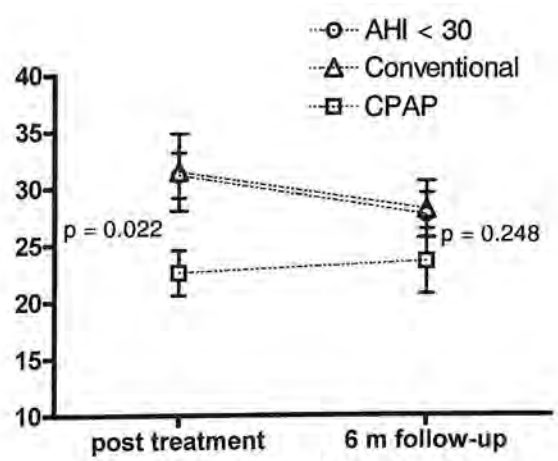




SF-36 Physical Function

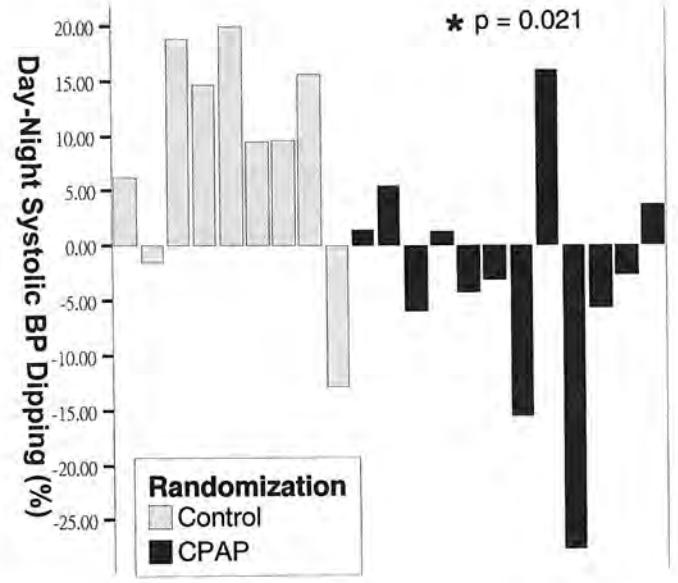


SF-36 Role Physical



SF-36 Physical Summary

Figure 5.9 Systolic (a) and diastolic (b) blood pressure dipping in patients randomized to CPAP and conservative treatment



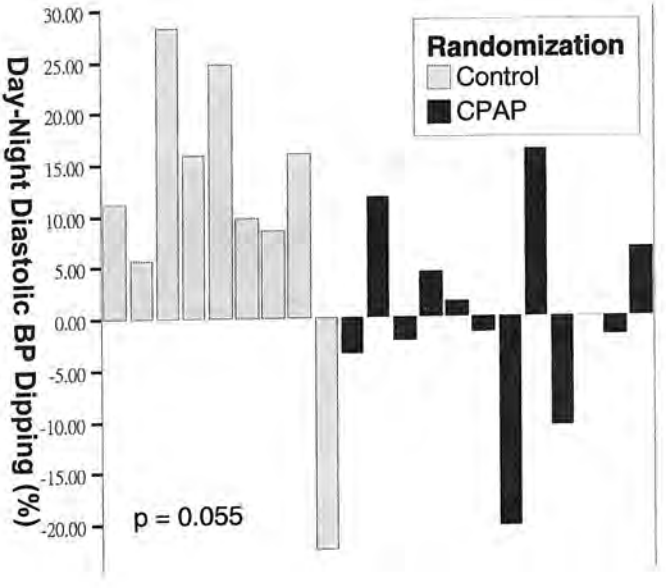
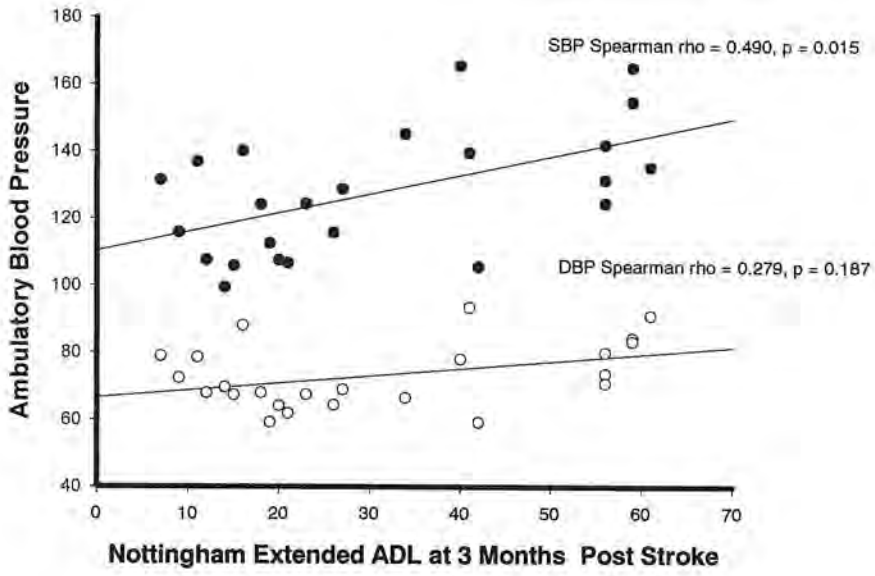


Figure 5.10 Correlation of ambulatory blood pressure and Nottingham Extended ADL Index at post-treatment phase (a) and 6 months after stroke (b)



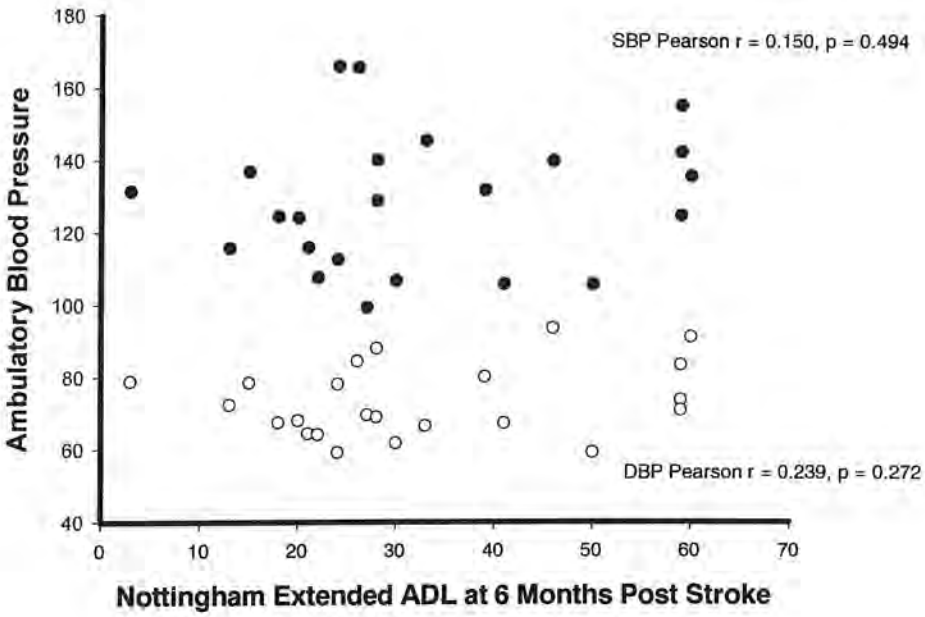
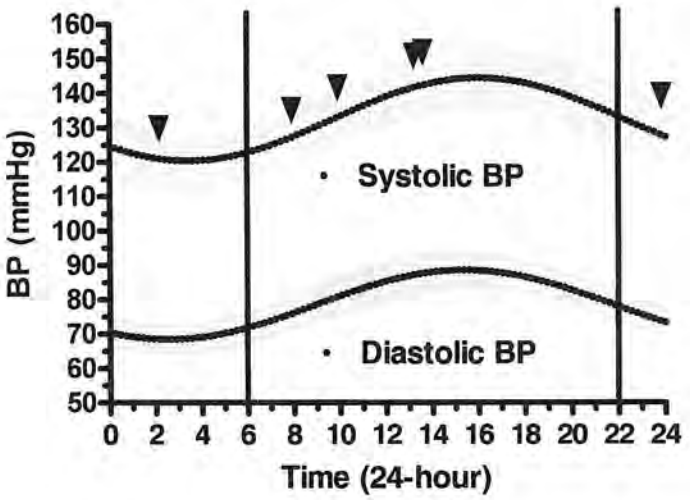
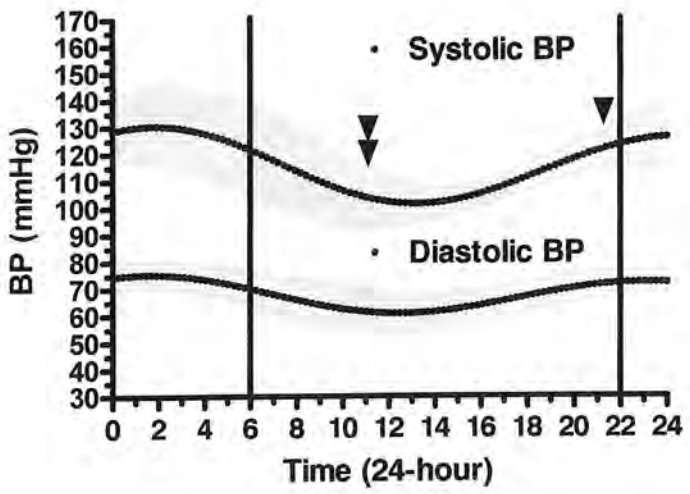
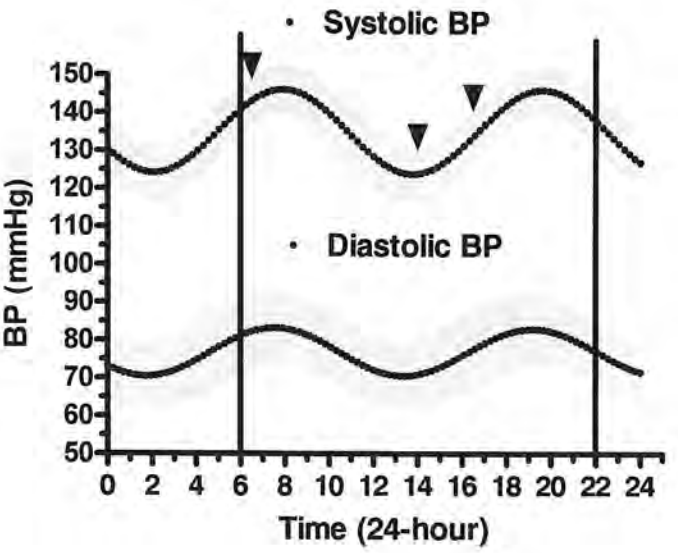


Figure 5.11 Circadian rhythm of blood pressure and its association with stroke onset: (a) normal 24-h circadian ABP rhythm, n = 6 (b) Reverse 24-h circadian ABP rhythm, n = 3 (c) 12-h circadian ABP rhythm, n = 3 (d) Circadian ABP rhythm with 12/24-h SBP/DBP mismatch, n = 2






Systolic BP
Diastolic BP
BP (mmHg)
150
140
130
120
110
100
90
80
70
60
50
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (24-hour)

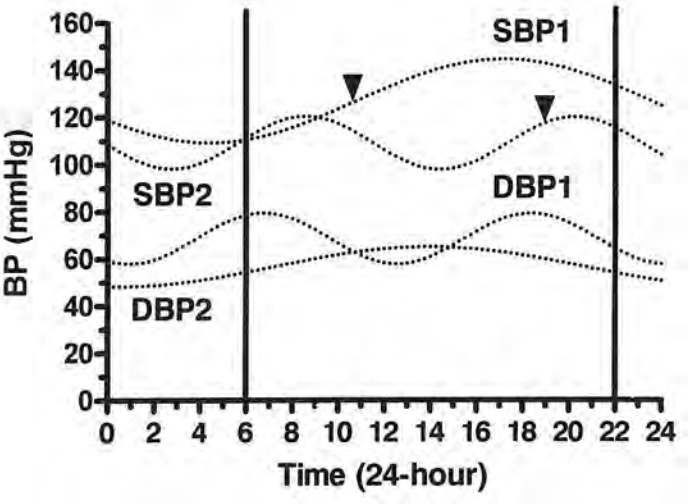
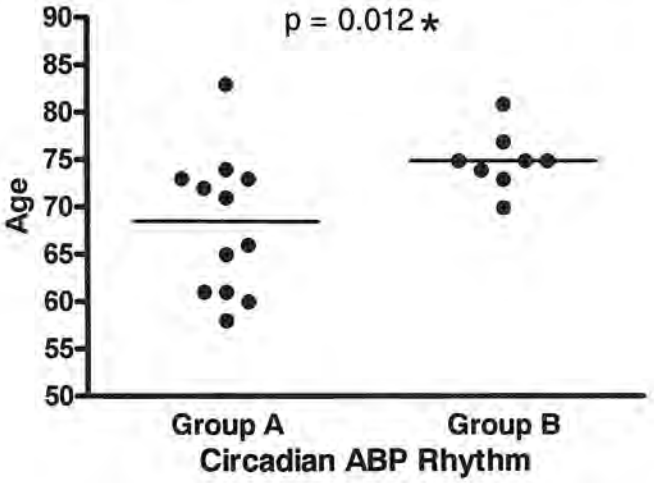
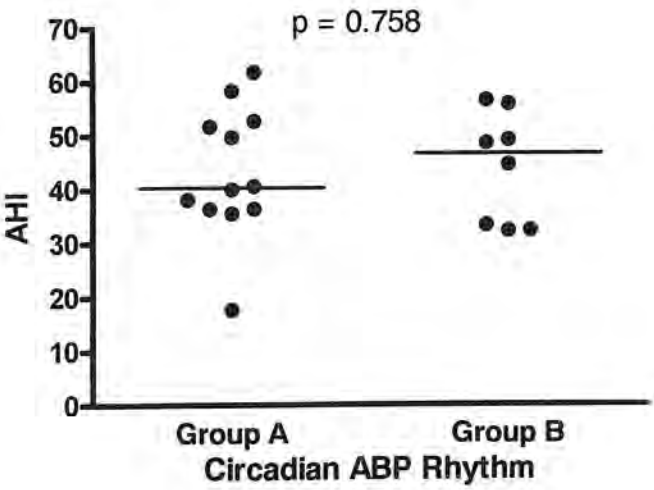
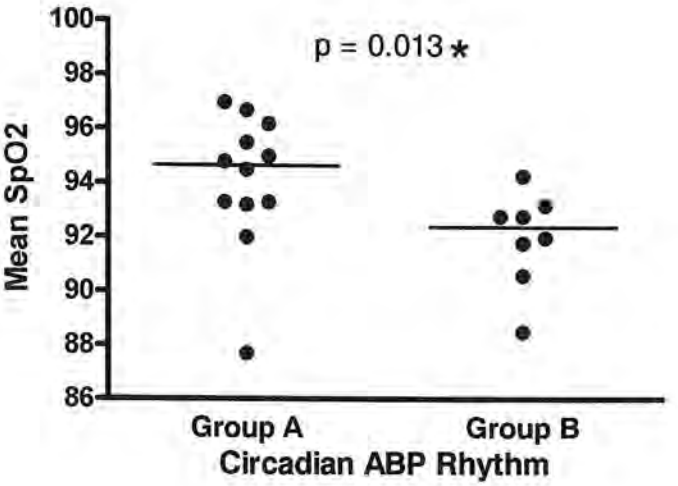
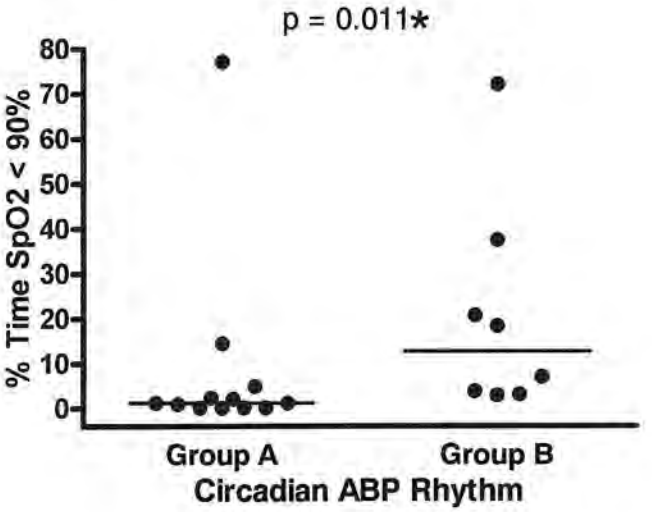

SBP1
SBP2
DBP1
DBP2
BP (mmHg)
160
140
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (24-hour)

Figure 5.12 The association between stable circadian ABP rhythm (group A), unstable circadian ABP rhythm (group B) and (a) age (b) AHI (c) mean SpO2 (d) % time with SpO2 < 90% at baseline






p = 0.013 *
Mean SpO2
100
98
96
94
92
90
88
86
Group A
Group B
Circadian ABP Rhythm


p = 0.011*
% Time SpO2 < 90%
80
70
60
50
40
30
20
10
0
Group A
Group B
Circadian ABP Rhythm

Chapter 6 The Impact of Obstructive Sleep Apnoea/Hypopnoea on the Outcome of Stroke: A Longitudinal Follow-up

6.1 Abstract

Backgrounds: Sleep-disordered breathing (SDB) is common in stroke. More evidence is needed to support the small number of publications showing that SDB has a significant impact on the functional and emotional outcomes of stroke. The impact of SDB on other outcome domains in terms of cognition and health-related quality of life is also not clear. Whether the influence of SDB is more prominent in mild or in severe stroke is still waiting to be clarified.

Methods: Sixty-six patients with successful overnight sleep study were recruited for longitudinal follow-up at 3, 6 12 and 18 months following stroke. Outcome measures at 3 months consisted of NIH Stroke Scale (NIHSS), Stanford Sleepiness Scale (SSS), Barthel Index (BI), Nottingham Extended ADL Index (EADL), Addenbrooke's Cognitive Examination (ACE), Hospital Anxiety and Depression Scale (HADS), EuroQol and MOS Short Form-36 (SF-36). Outcome measures at 6 months consisted of BI, EADL and SF-36. A Modified Rankin Scale (MRS) and status of independence were recorded during the whole course of follow-up.

Results: The results showed patients with $(A+H)\cdot h^{-1} \geq 30$ had a trend of worse functional capacity in both BI and EADL than patients with $(A+H)\cdot h^{-1} < 30$. There was a significant difference in mobility subscale of EADL between the groups ($p = 0.033$). Multivariate analysis after adjusting for gender, baseline BI and ACE showed that $(A+H)\cdot h^{-1}$ was an independent predictor for mobility subscale of EADL (> 6, cut-off by median) at 3 months after stroke ($p = 0.011$).

The negative influence of SDB on functional capacity and health-related quality of life following stroke was more prominent in patients with mild stroke (NIHSS < 7) at both 3 and 6 months after stroke, including total score ($p < 0.01$), mobility ($p < 0.01$), kitchen ($p < 0.05$), domestic ($p < 0.05$), leisure ($p < 0.05$) subscale of EADL and physical function ($p < 0.01$), social function ($p = 0.01$), physical summary score ($p < 0.01$) of SF-36. There was no difference in cognitive and emotional outcome but patients who had $(A+H)\cdot h^{-1} < 30$ also had significant higher total EADL score than

patients who had $(A+H)\cdot h^{-1} \geq 30$ in the subgroup with lesser emotional distress (HADS < 8) at both 3 and 6 months and in the subgroup with lesser cognitive impairment (Mini Mental State Examination, MMSE ≥ 28) at 6 months after stroke.

Lowest SaO2 obtained from the sleep study was significantly correlated with MMSE ($p = 0.016$) and orientation subscale of ACE ($p = 0.015$) at 3 months after stroke. Mean SaO2 was significantly correlated with orientation subscale of ACE ($p = 0.029$). There was no significant correlation between $(A+H)\cdot h^{-1}$ and cognitive outcome.

There was no clear change of MRS scores in patients with $(A+H)\cdot h^{-1} \geq 30$ over time but MRS scores were gradually decreased from 3 months to 12 months after stroke in patients with $(A+H)\cdot h^{-1} < 30$. The difference of MRS between groups was significant at 6 months after stroke ($p = 0.026$). There was a higher proportion of "independence at home" in patients with $(A+H)\cdot h^{-1} < 30$ than those with $(A+H)\cdot h^{-1} \geq 30$ which was significant at 6 months after stroke ($p = 0.033$). No significant difference of mortality rate was noted.

Conclusions: In my study I focused on a group of patients with mild to moderate neurological deficits (median NIH Stroke Scale = 6) in a narrow time span (14-19 days) following stroke. We concluded that SDB is independently associated with poor functional outcome in stroke but the effect of SDB on cognitive and emotional outcomes, health-related quality of life, and mortality is small. Hypoxaemia might play a more important role than sleep fragmentation in cognitive outcome. Many other factors resulting from brain damage or complications of stroke might have a stronger influence on functional outcome and length of hospitalization than SDB. Initial severity of stroke is a strong confounding factor. Cognitive function and mood might be two accessory factors. We propose that SDB may start to play a role when these factors are getting more stable or under control.

Key words: Sleep-disordered breathing; stroke; outcome; activities of daily living; mood; cognition; health-related quality of life

6.2 The aims of the study

Scientific background of this randomized controlled trial (RCT) has been reviewed in chapter 2.12. The hypothesis in this chapter was that untreated SDB predicted poor outcome. According to previous reviews, some questions still need to be clarified regarding the association of SDB with the outcome of stroke:

- I focused on SDB instead of oxygen desaturation. Although oximetric variables (e.g. DI) and apnoea hypopnoea index (AHI) are closely related with each other the former reflects the degree of hypoxaemia and the latter, sleep apnoea and hypopnoea. Strictly speaking, they do not reflect the same thing but whether they have same association with outcome of stroke is still not clear.
- I did multivariate analysis instead of univariate analysis. Many previous paper using univariate analysis to predict the outcome of stroke have had serious methodological shortcomings. Thus multiple linear regression or logistic regression analysis was essential and used in my study.
- I did a broad spectrum of outcome measures. Although functional outcome is a major factor determining whether a patient with stroke can live independently, stroke patients can have impaired health-related quality of life because of depression, anxiety, cognitive impairment, fatigue, sleepiness and poor social relationship even they have relatively better functional outcome. A broad spectrum of outcome measures including neurological deficits, functional capacity, daytime sleepiness, cognitive function, emotional status and health-related quality of life might be more helpful than functional outcome alone.
- I followed up stroke patients for at least six months after stroke. Some stroke patients are getting better but others may die or deteriorate to a status that institulization is needed in the following couple of months or years. Whether SDB plays a role in the natural course of recovery of stroke is also not clear.

Thus we performed a longitudinal follow-up for the same cohort of stroke patients described in chapter 4 and chapter 5. I performed an extensive follow-up including face-to-face interviews at 3 and 6 months and telephone interviews at 12 and 18 months after stroke. We measured several domains of outcome including stroke severity, functional, cognitive, emotional outcome, health-related quality of life, status of independence and mortality. We conducted a multivariate analysis to adjust for confounders at baseline. All the details are presented and discussed in this chapter.

6.3 Methods

Recruitment of patients and performance of sleep study have been described in chapter 4. Criteria used for recruiting patients were based on our randomized controlled trial of CPAP which has also been described in chapter 5.

6.3.1 Subjects

Sixty-six patients with valid overnight sleep studies were followed up in this study. Patients were divided into two groups according to the cut-off point of $(A+H)\cdot h^{-1} \geq 30$ and $(A+H)\cdot h^{-1} < 30$.

6.3.2 Treatment

Conventional treatment for stroke was maintained in all 66 patients. Regular medications (Aspirin, Statin, anti-hypertensive drugs etc.) and rehabilitation programmes (physiotherapy, occupational therapy and speech language therapy etc.) were given which depended on each patient's physical or neurological condition.

Thirty of 33 patients with $(A+H)\cdot h^{-1} \geq 30$ were included in the randomized controlled trial (RCT) and 15 of them were allocated to nasal CPAP. The compliance with CPAP and outcome measures between CPAP and control groups have been described in chapter 5. Three of 33 patients (two were enrolled before starting project of RCT and one declined after allocation) with $(A+H)\cdot h^{-1} \geq 30$ and 33 patients with $(A+H)\cdot h^{-1} < 30$ received conventional treatment for stroke only.

6.3.3 Assessment and follow-up

6.3.3.1 Baseline

Baseline assessment performed at 14-19 days of stroke was used for adjustment in multivariate analysis including Modified Rankin Scale (MRS), NIH Stroke Scale (NIHSS), SSS, BI, ACE and HADS. The detail has been described in chapter 4. All

missing data were checked, questions were read out and patients were asked to fill in or choose the most suitable answer.

6.3.3.2 3 months after stroke

As patients with and without RCT were not on the same schedule the definition of "3 months after stroke" was not based on calendar month. For randomized patients ($(A+H)\cdot h^{-1} \geq 30$), 3-month follow-up was performed within the last three days before due of 8 weeks of CPAP treatment but after ambulatory blood pressure (ABP) monitoring. For non-randomized patients ($(A+H)\cdot h^{-1} < 30$), 3-month follow-up was performed in the 12^{th} week of stroke.

Three months follow-up included repeated measurement of patients on scales previously conduced at baseline: NIHSS, MRS, SSS, BI, HADS and ACE. Three extra scales were provided in terms of EADL, EuroQol (Visual Analogue Scale and 5-dimension score) and SF-36. The 6-level "Status of Independence" was assessed by me as follows: home without social or nursing support, home with social or nursing support, residential home, nursing home, hospital and death.

6.3.3.3 6 months after stroke

Six months follow-up were performed at the 6th calendar month calculated from the onset of current stroke (± 2 weeks), which focused on functional capacities (MRS, BI, EADL) and health-related quality of life (SF-36). The 6-level "Status of Independence" was also recorded.

6.3.3.4 12 and 18 months after stroke

A regular telephone interview was performed at 12 and 18 calendar months (± 2 weeks) after stroke, which included MRS and "Status of Independence". If telephone contact was not available a letter was sent for collecting data. If there was no reply of the letter, the patient was taken as "lost follow-up". No further attempt was made to discover whether the patients lost to follow-up were still alive.

6.3.4 Statistical methods

All continuous data were presented as median and interquartile range (IQR). Non-parametric tests were conducted including Mann-Whitney U test and Chi-square Test (Fisher's test in case there were less than 20 patients in a category) for between-group comparisons. The $p < 0.05$ was taken as significant. Effect size (ES) was also expressed. The ES of ≥ 0.2 was taken as mild, ≥ 0.5 as moderate and ≥ 0.8 as marked difference.

For a more conservative statistical analysis, non-parametric statistics were still used to compare all scale-related measurements. Mann-Whitney U Test was conducted for between-group comparisons ($(A+H)\cdot h^{-1} \geq 30$ and < 30) at 3 months and 6 months after stroke. A scatter plot and Spearman correlation were conducted to confirm the linear relationship between sleep variables and two groups or outcome measure at 3 months after stroke: (1) functional capacity: BI and EADL; (2) cognitive function: MMSE and ACE.

Multivariate analysis was conducted to control confounding factors. Multiple linear regression was used if dependent variables were continuous and normally distributed. All predictors with $p < 0.1$ in univariate regression analysis were entered into the model and coefficient and its standard error (SE) were expressed. Logistic regression was used if dependent variables were binary or not normally distributed. All predictors with $p < 0.1$ in univariate regression analysis were entered into the model and adjusted odds ration and CI were expressed. Those predictors with $p < 0.05$ in final model were taken as significant.

Post-hoc subgroup analysis was conducted for functional outcome between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 in the following three domains: severity of stroke (NIHSS), cognitive function (MMSE) and mood (HADS). The cut-off points for the above three variables are based on previous publications instead of arbitrarily chosen: (1) NIHSS ≥ 7 and < 7 [Adams, Jr. *et al.* 1999]; (2) MMSE ≥ 28 and < 28 [Mathuranath *et al.* 2000]; (3) HADS ≥ 7 and < 7 [Dennis, O'Rourke, Lewis, Sharpe, and Warlow2000]. Original p value was expressed in the tables and p value

following Bonferroni correction were compared and discussed. The data from post-hoc analysis were used to explain the results more conservatively as they were biased in multiple statistical testing with small sample size.

The patients followed up for up to 18 months are essentially those from the RCT (i.e. $(A+H)\cdot h^{-1} \geq 30$) with the addition of those ineligible for the RCT because of $(A+H)\cdot h^{-1} < 30$. So half of the patients with $(A+H)\cdot h^{-1} \geq 30$ were allocated to CPAP. Further regression analysis was done to take into account allocation to CPAP.

Statistical analysis was done by the statistical software, SPSS version 11.0 (SPSS Inc. USA).

6.4 Results

Upon completion of the study, 8 patients in total had recurrent stroke with a confirmed diagnosis in the hospitals. Five of 8 patients had $(A+H)\cdot h^{-1} \geq 30$. Among these 5 patients 1 was randomized to CPAP (compliance 0.16 hours / night).

In total, 9 patients died. Two died before 3 months post-stroke, 2 patients died between 6-12 months and 5 patients died between 12-18 months post-stroke. Five of 9 patients who died had $(A+H)\cdot h^{-1} \geq 30$. Of these 5 patients 1 was randomized to CPAP but died within a few days of initiation of treatment and the other one died after 6 months which was a long time after the end of CPAP treatment. On the other hand, 4 of 9 patients who died had $(A+H)\cdot h^{-1} < 30$. Two of them had $(A+H)\cdot h^{-1}$ between 20 and 29.9. Among 4 patients who had $(A+H)\cdot h^{-1} \geq 30$ and died, 3 had cardiovascular mortality and 1 died before she was sent to hospital. Among 4 patients who had $(A+H)\cdot h^{-1} < 30$ and died, 3 had cardiovascular mortality and 1 died of complication of pneumonia.

6.4.1 Outcome assessment at 3 months after stroke

Sixty-six patients were contacted for a 3-month follow-up. Two patients with $(A+H)\cdot h^{-1} \geq 30$ died before 3 months after stroke. They were scored "0" on the Barthel Index (BI) and Nottingham Extended ADL Index (EADL). Other scales were not scored. Three patients accepted telephone interviews for partial assessment only. Three of them had scores of Stanford Sleepiness Scale (SSS), BI, and EADL. One patient also had Hospital Anxiety and Depression Scale (HADS) and EuroQol. One patient with $(A+H)\cdot h^{-1} \geq 30$ refused a telephone interview so only the Modified Rankin Scale (MRS) and State of Independence were obtained from brief communication. Sixty patients completed all the outcome assessments. Thirty-two had $(A+H)\cdot h^{-1} < 30$ and 28 had $(A+H)\cdot h^{-1} \geq 30$.

Comparisons of length of hospitalization between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 are shown in Figure 6.1 (P. 275). There was no significant difference in

length of hospitalization between groups although patients with $(A+H)\cdot h^{-1} \geq 30$ had about 1 day longer of staying in an acute stroke unit and 5 days longer in a rehabilitation ward (Figure 6.1a, P. 275). The correlation between $(A+H)\cdot h^{-1}$ and length of hospitalization was also not significant (Figure 6.1b, P. 275). After controlling for severity of stroke and functional capacity at baseline (Table 6.1, P. 262), $(A+H)\cdot h^{-1}$ was an independent but weak predictor for the total length of hospitalization (coefficient = 0.006, SE = 0.003, p = 0.044) in comparison with the NIH Stroke Scale (coefficient = 0.085, SE = 0.026, p = 0.002) and Barthel Index (coefficient = -0.014, SE = 0.016, $p < 0.001$). Further regression analysis adjusting for allocation was shown in Table 6.2 (P. 263). The $(A+H)\cdot h^{-1}$ remained significant (coefficient = 0.010, SE = 0.004, p = 0.025) after adjusting for the factor of allocation. On the contrary, allocation factor was not independently associated with length of hospitalization.

The results of sleepiness, neurological deficits, cognitive and functional outcome are shown (Table 6.3, P. 264). Patients with $(A+H)\cdot h^{-1} \geq 30$ had a trend of worse functional capacity in both BI and EADL than patients with $(A+H)\cdot h^{-1} < 30$. The effect size of BI between two groups was moderate (0.47) and the difference was not statistically significant (p = 0.246). There was a significant difference in the EADL mobility subscale between groups (p = 0.033). Multivariate analysis after adjusting for gender, baseline BI and ACE showed that $(A+H)\cdot h^{-1}$ was an independent predictor for the EADL mobility subscale > 6 (median) at 3 months after stroke (p = 0.011, Table 6.4, P. 265). Further regression analysis adjusting for allocation was also shown in Table 6.5 (P. 266). The odds ratio of EADL mobility subscale > 6 in the group who had $(A+H)\cdot h^{-1} < 30$ was 25.056 (95% CI = 2.423-259.095, p = 0.007) when compared to the group who had $(A+H)\cdot h^{-1} \geq 30$ allocated to CPAP treatment. On the contrary, the odds ratio of EADL mobility subscale > 6 in the group who had $(A+H)\cdot h^{-1} \geq 30$ allocated to conservative treatment was 7.510 (95% CI = 0.693-81.376, p = 0.097) when compared to the group who had $(A+H)\cdot h^{-1} \geq 30$ allocated to CPAP treatment. This means there was no significant difference of functional outcome between those allocated to CPAP and allocated to conservative treatment.

In the subgroup of mild stroke (NIHSS < 7 at baseline, Table 6.3, P. 264 and Figure 6.2a, P. 276), patients with $(A+H)\cdot h^{-1} \geq 30$ had significantly lower scores in total score ($p = 0.003$) and all subscales (mobility, $p = 0.002$, kitchen, $p = 0.021$, domestic, $p = 0.018$, leisure, $p = 0.039$) of EADL than patients with $(A+H)\cdot h^{-1} < 30$. The effect size of total EADL between groups was 0.40 in the whole group of patients but increased to 0.99 in the subgroup of mild stroke. The mean difference of total EADL was about 5 (95% CI = 1-20) in the whole group and about 8 (95% CI = 4-29) in the subgroup of mild stroke. Multivariate analysis after adjusting for baseline BI also showed that $(A+H)\cdot h^{-1}$ was an independent predictor for total EADL score > 36 (median) in the subgroup of mild stroke ($p = 0.005$, Table 6.6, P. 267). There was no significant difference between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 in the subgroup of moderate to severe stroke (NIHSS ≥ 7 at baseline).

The results of well-being are shown (Table 6.7, P. 268). Patients with $(A+H)\cdot h^{-1} \geq 30$ had significant lower score in subscale of social function in SF-36 than patients with $(A+H)\cdot h^{-1} < 30$ ($p = 0.045$). In the subgroup of mild stroke, patients with $(A+H)\cdot h^{-1} \geq 30$ also had significantly lower scores on the subscale of 5-dimension in EuroQol ($p = 0.014$), subscales of physical function ($p = 0.002$), social function ($p = 0.010$) and physical summary in SF-36 ($p = 0.004$). There was also no significant difference in the subgroup with moderate to severe stroke.

Subgroup analyses were also conducted for cognitive function (MMSE) and mood (HADS) at baseline. When patients were stratified according to MMSE (cut-off < 28 and ≥ 28, Figure 6.3a, P. 277) and HADS (cut-off < 8 and ≥ 8, Figure 6.4a, P. 278), the difference of total EADL score between $(A+H)\cdot h^{-1} \geq 30$ and < 30 at 3 months after stroke was significant in the subgroup with HADS < 8 ($p = 0.014$, Figure 6.4a, P. 278).

Correlations between sleep variables and functional capacities are shown (Table 6.8, P. 269). Mobility subscale of EADL was significantly correlated with $(A+H)\cdot h^{-1}$ ($p = 0.029$) and index of hypopnoea ($p = 0.028$) but there was no significant

correlation between oximetric variables and variables of functional outcome (BI and EADL).

Correlations between sleep variables and cognitive functions are shown (Table 6.9, P. 270). In contrast to the above findings, oximetric variables are significantly correlated with cognitive functions. Lowest SaO2 was significantly correlated with MMSE ($p = 0.016$) and ACE orientation subscale ($p = 0.015$). Mean SaO2 was significantly correlated with ACE orientation subscale ($p = 0.029$). Heart rate variability defined as standard deviation (SD) of mean heart rate obtained by pulse oximetry was significantly correlated with total score ($p = 0.011$), memory ($p = 0.008$) and language subscales ($p = 0.024$) of ACE. Lowest heart rate was significantly correlated with ACE memory subscale ($p = 0.035$).

Gender difference at 3 months after stroke is shown (Table 6.10, P. 271). Female patients had lower scores in ACE which was significant in visuospatial subscale ($p = 0.004$) and lower scores in EADL which was significant in leisure subscale ($p = 0.041$). Female patients also had lower scores in well-being including HADS, Euro-Q which was significant in 5-dimension score (EQ-5D, $p = 0.044$) and lower scores in SF-36 which was significant in subscales of social function ($p = 0.046$) and vitality ($p = 0.014$).

6.4.2 Outcome assessment at 6 months after stroke

Sixty-four patients were contacted for 6-month follow-up. One patient in the group of $(A+H)\cdot h^{-1} \geq 30$ was lost follow-up. No patients died between 3 and 6 months. Two patients who accepted telephone interview at 3-month assessment also received telephone interview for BI and EADL. Two patients who refused telephone interview at 3-month assessment were also contacted to collect brief information about MRS and "Status of Independence". The other two patients who had complete assessment at 3 months after stroke were not available for both face-to-face assessment and telephone interview. One patient in the group of $(A+H)\cdot h^{-1} < 30$ was diagnosed and treated for post-stroke depression and her daughter refused my visit and telephone interview. The other patient who had $(A+H)\cdot h^{-1} \geq 30$ had bad temper

and refused to talk much. Brief information about MRS and State of Independence was collected from both of them. The BI and EADL of two patients who died before 3 months were also scored "0" as I did at 3-month assessment. Fifty-seven of 63 patients completed all the outcome assessments. Thirty had $(A+H)\cdot h^{-1} < 30$ and 27 had $(A+H)\cdot h^{-1} \geq 30$.

The results of outcome assessment at six months after stroke are shown (Table 6.11, P. 272). The effect sizes of functional capacity between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 increased slightly in BI (0.47 to 0.48), total (0.40 to 0.51) and mobility subscale (0.52 to 0.62) of EADL but there was no change of statistical significance. In the subgroup analysis of mild stroke (NIHSS < 7), the differences between these 2 groups in total score ($p = 0.016$, Table 6.11, P. 272 and Figure 6.2b, P. 276), mobility ($p = 0.004$) and leisure ($p = 0.006$) subscales of EADL were still statistically significant (Table 6.11, P. 272). Subgroup analyses for cognitive function (MMSE) and mood (HADS) are also shown (Figure 6.3b, P. 277 and 6.4b, P. 278). The differences of total EADL between $(A+H)\cdot h^{-1} \geq 30$ and < 30 was significant in the subgroup with MMSE ≥ 28 ($p = 0.006$) and subgroup with HADS < 8 ($p = 0.014$).

Multivariate analysis after adjusting for gender, BI and Addenbrooke's Cognitive Examination (ACE) at baseline also showed $(A+H)\cdot h^{-1}$ was an independent predictor for total EADL score at 6 months after stroke in the subgroup with NIHSS < 7 ($p = 0.009$, Table 6.12, P. 273).

Gender difference at 6 months after stroke is shown (Table 6.13, P. 274). The difference of EADL between male and female was bigger at 6 months. Female patients had significantly lower total score ($p = 0.033$), mobility subscale ($p < 0.001$) and leisure subscale ($p = 0.029$) of EADL. On the contrary, the difference of SF-36 was less prominent and insignificant apart from vitality subscale ($p = 0.012$).

6.4.3 Time course of functional outcome in stroke

The longitudinal study was terminated when the last recruited patient received 6-month follow-up so there was limited follow-up of patients at 12 and 18 months.

Sixty-three patients were contacted for 12-month follow-up through telephone. Two extra patients were lost. Two extra patients died. Fifty-nine patients had rating of "status of independence" and MRS. Forty-one patients were contacted for 18-month follow-up through telephone. No extra patient was lost but five extra patients died. Forty-one patients had rating of "status of independence" and MRS.

Time course of BI is shown in Figure 6.5 (P. 279). There was a trend of improvement from 3 weeks to 6 months and it was more prominent from 3 weeks to 3 months after stroke. At 3-month time most patients had BI > 10 and at 6-month time most patients had BI > 15 with ceiling effect. Although there was no statistical significance of BI between groups at both 3 months and 6 months as mentioned previously, the score of BI was higher, distribution was more homogenous and changes from 3 to 6 months were bigger in the group with $(A+H)\cdot h^{-1} < 30$ than $(A+H)\cdot h^{-1} \geq 30$.

Time course of EADL is shown in Figure 6.6 (P. 280). We did not assess EADL at baseline (3 weeks) because at that time patients, even with mild to moderate stroke, usually had a floor effect on this scale. The distribution of total score and mobility subscale of EADL was wide in both groups but there was a trend of increased EADL from 3 to 6 months which was more prominent in the group with $(A+H)\cdot h^{-1} < 30$. Although there was a significant difference of EADL mobility subscale between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30, the changes of total and mobility subscale of EADL from 3 to 6 months between groups were not significant. It was bigger in the group with $(A+H)\cdot h^{-1} < 30$.

Time course of MMSE and ACE is shown in Figure 6.7 (P. 281). As described in chapter 4 patients with $(A+H)\cdot h^{-1} < 30$ had a relatively higher cognitive scores than those with $(A+H)\cdot h^{-1} \geq 30$. There was also a trend of improvement of ACE and MMSE from 3 weeks to 3 months in both groups but changes were similar between groups.

Time course of HADS is shown in Figure 6.8 (P. 282). On the contrary, changes of HADS were more heterogeneous with some going up and the others going down.

There was a net trend of minimal improvement of mood (decreased anxiety and depression scores of HADS) associated with concomitant improvement of neurological deficit and functional capacity described previously.

Longitudinal follow-up of MRS is shown in Figure 6.9 (P. 283). MRS was higher in patients with $(A+H)\cdot h^{-1} < 30$. There was no clear change of MRS scores in patients with $(A+H)\cdot h^{-1} \geq 30$ from 3 months to 12 months after stroke but MRS scores were gradually decreased from 3 months to 12 months in patients with $(A+H)\cdot h^{-1} < 30$ which means improvement of functional capacity. The difference of MRS between groups with $(A+H)\cdot h^{-1} \geq 30$ and $(A+H)\cdot h^{-1} < 30$ was significant at 6 months after stroke ($p = 0.026$). At 18 months after stroke, sample size was too small to tell the difference.

6.4.4 Status of independence and mortality

Longitudinal follow-up of "status of independence" is shown (Figure 6.10a and 6.10b, P. 284). There was a higher proportion of "independence at home" in patients with $(A+H)\cdot h^{-1} < 30$ than those with $(A+H)\cdot h^{-1} \geq 30$ at each time point of follow-up but the only significant difference was at 6 months after stroke by Chi-square test ($p = 0.033$, Figure 6.10a, P. 284). There was no significant difference of mortality rate between groups at each time point of follow-up by the Chi-square test (Figure 6.10b, P. 284).

6.5 Discussion

In this study I focused on a group of patients with mild to moderate neurological deficits (median NIH stroke score = 6) in a narrow time span (14-19 days) following stroke. As recovery from stroke is an ongoing process stroke patients should be compared at a set time following stroke. My study is different from previous two outcome studies which recruited patients in a much wider time span between one and two months after stroke [Cherkassky *et al.* 2003;Kaneko *et al.* 2003b]. I also expanded the spectrum of outcome assessment from physical and functional domains to include the following:

- A more detailed cognitive assessment, i.e. Addenbrooke's Cognitive Examination (ACE) rather than Mini-mental State Examination (MMSE)
- Emotional outcome and health-related quality of life as they are practical issues in the life of stroke patients.

6.5.1 The prognostic implication of SDB in physical and functional outcome of stroke

By conducting a longitudinal follow-up we found patients with $(A+H)\cdot h^{-1} < 30$ had higher score in Barthel Index (BI) at baseline, higher Nottingham Extended ADL Index (EADL) at 3 months and 6 months after stroke and bigger improvement during the follow-up periods than $(A+H)\cdot h^{-1} \geq 30$. Patients with $(A+H)\cdot h^{-1} < 30$ also had higher scores in Modified Rankin Scale (MRS) and physical domains of SF-36 than $(A+H)\cdot h^{-1} \geq 30$. The difference between groups was small with effect size around 0.2-0.5. It was only significant in EADL mobility subscale at 3 months and 6 months, MRS at 6 months and 12 months and SF-36 social function subscale at 3 months after stroke, mostly in subscales or post-hoc subgroup analysis. All of these should be interpreted more conservatively as they depend on post-hoc analysis.

An obvious objection to comparing the outcome in the two severity groups is that half of the more severe group (i.e. $(A+H)\cdot h^{-1} \geq 30$) were allocated to CPAP

treatment. As it appears that patients treated with CPAP fared worse in some ways than those not treated this might have artificially exaggerated any apparent adverse prognostic effects of patients with $(A+H)\cdot h^{-1} \geq 30$. After adjusting for the confounding factor of allocation, the results showed allocation was not independently associated with length of hospitalization and poor functional outcome at 3 months after stroke. This means since CPAP treatment had little effect, this had probably made little difference.

6.5.1.1 Controlling baseline confounders

I found in my study that the difference in functional capacities between groups with $(A+H)\cdot h^{-1} < 30$ and $(A+H)\cdot h^{-1} \geq 30$ was getting bigger from 3 weeks (baseline) to 3 months after stroke according to the following results:

- There was no significant difference of baseline severity of stroke (NIHSS) and functional capacity (BI) between groups although we could not completely exclude the possibility that there might be a small difference but sample size was not big enough to tell.
- The difference of mobility subscale of EADL between groups at 3 months after stroke was still significant after adjusting for baseline confounders including gender, functional capacity (BI) and cognitive function (Addenbrooke's Cognitive Examination, ACE).

Controlling severity of stroke or functional capacity at baseline is important as these have a major impact on the outcome. One study based on oximetry showed the correlation between oximetric variables and BI existed as early as admission but they didn't do further multivariate analysis to adjust for confounders at baseline [Good *et al.* 1996]. In their study patients who had more severe stroke also had more severe hypoxemia and this could have resulted in a poor functional outcome. They used an uncommon statistical method, Pearson's correlation with mortality as a dichomatous variable, to show a significant association between mortality at 12 months after stroke and two oximetric variables, namely, mean SaO2 and percentage of time with SaO2 < 90%. Only 5 of their 47 patients died at 12 months which is quite similar to

my findings. I applied the Chi-square test for comparison of mortality between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 and the difference between groups were not statistically significant. A more appropriate analysis of mortality might be the Cox regression model instead of simple correlation. We didn't use this because the mortality rate was low (9 of 66 patients).

6.5.1.2 Distinction between hypoxaemia and sleep apnoea/hypopnoea syndrome in outcome study of stroke

The other study dealing with SDB and the outcome of stroke was also based on oximetry only [Cherkassky *et al.* 2003;Good *et al.* 1996]. Good et al. measured outcome with the BI and Cherkassky et al. used the Functional Independence Measure (FIM). The former found a significant correlation between oximetric variables and BI and the latter showed that the respiratory disturbance index (RDI) was an independent predictor for FIM gain after controlling baseline FIM data. The RDI they calculated was based on oximetry so it relates to desaturation (DI) rather than to the true apnoea hypopnoea index (AHI).

Although both Good et al. and Cherkassky et al. highlighted the association between SDB and the functional outcome of stroke, they actually focused on hypoxia instead of SDB. By using oximetry only they might have recruited a certain proportion of Cheyne-Stokes respiration (CSR) and central sleep apnoea (CSA), which are common in stroke. Many sequelae or complications of stroke might cause hypoxaemia as well. Thus the major finding of their studies is only the association between functional outcome of stroke and hypoxemia, and not between functional outcome and SDB, although most of the hypoxemia might be caused by SDB.

I didn't find any correlation between oximetric variables and two functional outcome measures, including BI and EADL. A significant correlation was only noted between oximetric variables and cognitive outcome measured by ACE. A plausible explanation in our study might be that the functional outcome measure (EADL) was more sensitive to AHI and the cognitive outcome measure (ACE) was more sensitive

to oximetric variables. I didn't perform full polysomnography so there was no electroencephalography (EEG) information to know whether impaired functional outcome in patients with $(A+H)\cdot h^{-1} \geq 30$ was mainly due to sleep fragmentation.

The difference between our study and the study conducted by Good et al. regarding desaturation and outcome of stroke needs to be clarified in further studies which should clearly separate hypoxaemia and sleep apnoea/hypopnoea syndrome into two distinct domains before studying their association with the outcome of stroke.

6.5.1.3 Comparison between EADL in our study and FIM in previous publications

Unlike the study conducted by Good et al., although we found a trend of difference in BI between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 this was not statistically significant. One other study which applied BI as a measure of functional outcome in the randomized control trial of nasal CPAP in stroke did not show any significant difference in BI either [Sandberg *et al.* 2001a].

I added the other scale to measure functional outcome, EADL, which is more sensitive than BI and similar to FIM used in previous two publications [Cherkassky *et al.* 2003;Kaneko *et al.* 2003b]. Although we all showed a negative impact of SDB on functional outcome the size of this impact varied between our studies. Kaneko et al. showed there was about 10% of difference (mean difference / total score × 100%) in total score of FIM between patients with (AHI ≥ 10) and without (AHI < 10) sleep apnoea at discharge from rehabilitation ward which was statistically significant. By using linear regression they also showed that obstructive AHI was an independent predictor for total FIM score and length of hospitalization. On the other hand, Cherkassky et al. showed the difference in total FIM score between patients with RDI > 10 and ≤ 10 was not significant. There was actually about 14% of difference between these two groups of patients which was quite similar with Kaneko's result. In our study, there was no significant difference of total EADL score and length of

hospitalization between groups with $(A+H)\cdot h^{-1} \geq 30$ and < 30 but there was about 14% of difference between these two groups which was also quite similar to the previous two studies.

The sample size in our study (n = 66) was more than Kaneko's (n = 50) but the standard deviation (SD) of EADL in our study was much bigger. Although percentage of mean difference in our study was similar to Kaneko's the effect size was much smaller. We might need more patients to achieve statistical significance in total EADL score. This also means our patients had higher variation of EADL score. From the other point of view the level of functional capacity assessed by EADL might be higher than that in FIM. As FIM is usually used in assessing the outcome of in-patient rehabilitation and EADL deals with more after-discharge activities this explanation might be reasonable. The sample size in Cherkassky's study (n = 30) was much less than Kaneko's (n = 50) and SD of FIM in Cherkassky's study was also as big as ours. Type II error might be more prominent in their study than Kaneko's and our study.

My patients were relatively older than Kaneko's patients (74 vs. 66). The FIM (score 18-126) was 80-95 at admission and 100-110 at discharge in Kaneko's study. On the other hand, the BI (score 0-20) of our patients was 12 at admission and EADL (score 0-66) was 20-30 at 3 months after stroke. According to a rough estimation, we recruited a group of more severe stroke patients than they did even though the median of NIHSS (0-42) in our patients was only 6. According to our results described previously, difference of functional outcome between patients with and without SDB might be bigger in the group of milder stroke severity.

6.5.2 The prognostic implication of SDB in mental outcomes

I didn't find any significant difference in cognitive function and mood between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 either at baseline or at 3 months after stroke. The effect size of MMSE, ACE and its subscales at 3 months after stroke was small (0-0.38). The effect size of HADS at 3 months and mental summary subscale of SF-

36 at both 3 and 6 months was very small (mostly < 0.1). There are five plausible explanations:

- There was no difference of cognitive and emotional outcome between groups.
- Type II error might occur in our patients with small difference of mean between groups, big SD and small effect size.
- ACE, MMSE, Hospital Anxiety and Depression Scale (HADS) and mental domains of SF36 were not sensitive enough to detect the difference.
- The influence of SDB was masked by cognitive deficits and emotional symptoms resulted from stroke itself.
- About half of the patients with $(A+H)\cdot h^{-1} \geq 30$ who were randomized to CPAP treatment had improvement in these symptoms so the difference disappeared. This is less likely as compliance to CPAP was very poor.

In terms of cognitive outcome, my findings are similar to the few previous publications but in terms of emotional outcome, quite different. All previous studies applied MMSE as the only cognitive measure [Kaneko *et al.* 2003b;Sandberg *et al.* 2001a]. We added ACE which also includes MMSE but there was still no significant difference between groups. ACE, like MMSE is still a screening tool. Although ACE covers a broad spectrum of cognitive function there is only one test (verbal fluency) to deal with executive function which might be important in SDB and stroke. It is not easy to perform a comprehensive neuropsychological assessment in stroke. If we do apply more difficult tests to differentiate subtle cognitive changes in patients with SDB we doubt this difference, even it is statistically significant, has a clinically significant influence on the functional outcome of stroke.

Only one research group identified an association between SDB and distinct depressive symptoms in stroke [Sandberg *et al.* 2001b]. They conducted a sleep study at 23 ± 7 days (11-41 days) of stroke when patients were admitted to rehabilitation ward. They also measured Montgometry-Åsberg Depression Rating Scale (MADRS, score 0-60) and Organic Brain Syndrome (OBS) Scale including one item for depressed mood (score 0-3). The mean difference of MADRS between patients with

AHI ≥ 10 and < 10 was 5.2 (p = 0.013) and effect size was 0.47 (mild to moderate). The mean difference of "depressed mood" in OBS Scale was 0.41 (p = 0.004) and the effect size was 0.52 (moderate). The difference between groups was moderate and significant.

On the other hand, patients with AHI ≥ 10 also had more severe strokes as measured by BI (7.6 ± 6.0 vs. 11.5 ± 6.8, p = 0.001) and delirium (75.3% vs. 55.6%, p = 0.018). In order to control baseline severity of stroke, they used a logistic regression model with AHI as the dependent variable and, BI and "depressed mood" in OBS Scale as independent variables. The result showed "depressed mood" in OBS Scale was still independently associated with AHI after adjusting for the association between BI and AHI. There are still some points which need to be clarified in their study:

- "Depressed mood" is only one item of the 39 neuropsychiatric features (suspiciousness, delusion, hallucination, personality changes etc.) in OBS Scale regarding depressive symptoms thus its validity for the diagnosis of depression should be tested beforehand. This finding might be by chance due to multiple statistical testing.
- A better way to know whether AHI is independently associated with depressed mood is to put "depressed mood" in OBS Scale as a dependent variable and AHI as an independent variable in the regression model and control for the association between BI and "depressed mood".
- The percentage of delirium was very high in their patients. The answers of delirious patients to psychometric measures are questionable because the patients are confused.
- The odds ratio of "depressed mood" in OBS Scale calculated from the regression model was not high (1.74, CI = 1.02-2.94).

Sandberg et al. conducted the first randomized controlled trail of CPAP in stroke and showed that depressive symptoms measured by MADRS were significantly decreased. They didn't mention whether MADRS in the study was normally

distributed but they conducted a parametric test which might increase the chance of getting a significant finding. This part has been discussed in chapter 5.

There was no direct evidence in our study that poor functional outcome in stroke patients with $(A+H)\cdot h^{-1} \geq 30$ could be explained by poor emotional outcome which resulted in low motivation to attend rehabilitation or other treatment programmes. The underlying mechanisms for poor functional outcome could be the direct impact of SDB through intermittent hypoxemia, sleep fragmentation or impaired cerebral blood flow. In summary, ours is the second ever study dealing with SDB and emotional outcome in stroke which generated a different result from the first publication. Further studies in this field are required. Mood might not be an important factor when the outcome of stroke is simply defined as "alive and independent" but might be more important when outcome is assessed by a more detailed scale like EADL. Although SDB didn't play a significant role in the cognitive and emotional outcome of stroke I think that SDB might play a more significant role in functional outcome in patients with higher cognitive function and stable mood. This will be discussed in the following section.

6.5.3 The interaction of SDB with other factors on functional outcome

When we consider mild stroke only (NIHSS < 7), the differences of outcome between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 were larger and more significant in terms of total score and all subscales of EADL, role physical, social and physical summary subscale of SF-36 and length of hospitalization. The difference of EADL score was also more prominent in patients with either mild cognitive impairment (MMSE ≥ 28) or less emotional distress (HADS < 8). If this finding is correct CPAP treatment would be easier and more practically useful. This is in contrast to a previous study which showed that SDB affected functional outcome of stroke more significantly in more severe stroke (FIM < 70) [Cherkassky *et al.* 2003]. If so CPAP treatment would be more difficult and less practically useful. Cherkassky et al. showed that only 2 of 6 patients with SDB and FIM < 70 improved by ≥ 30 points

whereas this occurred in 7 of 9 patients without SDB. However, their sample size was small and their finding was not statistically significant (P = 0.085).

We would rather take the above findings in the subgroup analysis with caution because they were obtained from a post-hoc exploratory analysis. This was with at least six independent multiple statistical tests according to three cut-off points (NIH < 7 and ≥ 7; MMSE < 28 and ≥ 28; HADS < 8 and ≥ 8) and two Mann-Whitney U tests for the difference between patients at both 3 and 6 months after stroke for each cut-off point. If we apply the "6p" value (original p value times 6) as the cut-off point of statistical significance by Bonferroni correction, total score and mobility subscale of EADL and physical function of SF-36 were still significant in the subgroup of NIHSS < 7 at 3 months after stroke (Table 6.3). Mobility and leisure subscale were still significant in the subgroup of NIHSS < 7 at 6 months after stroke. Total scores of EADL were still significant in the subgroups of MMSE > 28 and HADS < 8 at 6 months after stroke.

Many other factors resulting from brain damage or complications of stroke have stronger influence on the functional outcome and length of hospitalization than SDB. Initial severity of stroke and functional capacity at admission is one of them. Cognitive function and mood might be accessory factors. We think that SDB starts to play its role when these factors are getting more stable or under control.

6.5.4 The SDB and mortality after stroke

Only 9 patients died in our study so we did not perform Kaplan-Meir analysis and Cox's regression model for further analysis. A simple Chi-square showed that there was no significant difference of mortality between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30. The study conducted by the Spanish group had a larger sample size (n = 161) and longer longitudinal follow-up (mean 22.8 months) than others [Parra *et al.* 2004]. They found that SDB was an independent predictor for mortality after stroke.

On the other hand, the study conducted by the Spanish group did not have a very homogenous cohort as they recruited patients from both stroke and TIA. The

mortality rate may be higher in stroke than in TIA. The characteristics of mortality may be different in stroke from that in TIA. Stroke patients would have more mortality resulted from complications than TIA patients. There was no data showing whether the mortality group had a higher proportion of stroke patients. The study also found age was the strongest predictor for mortality. Another predictor, CAD, is highly associated with old age. The hazard ratio and 95% CI of AHI in the prediction model was small. There was also no data showing whether older patients had a higher proportion of stroke than younger ones. Further studies can be designed to recruit only young stroke patients (excluding TIA and old age) to clarify whether SDB does play a more significant role in mortality after stroke.

6.6 Conclusions

We have the following conclusions in this prospective cohort study:

- SDB is independently associated with poor functional outcome in stroke.
- The effect of SDB on cognitive, emotional outcomes, health-related quality of life, and mortality is small.
- Oximetric variables, but not $(A+H)\cdot h^{-1}$, are significantly correlated with cognitive functions. Hypoxaemia might play a more important role than sleep fragmentation in cognitive outcome.
- The difference of functional outcome between patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 might be more prominent in the subgroup of patients with mild stroke, lesser cognitive impairment or lesser emotional distress.
- Many other factors might have a stronger influence than SDB on the functional outcome and length of hospitalization. The initial severity of stroke is a strong confounding factor. Cognitive function and mood might be two accessory factors. We think that SDB starts to play its role when these factors are getting more stable or under control.

Table 6.1 Factors at baseline (3 weeks) predicting length of hospitalization

Dependent variable	Logarithm (Ln) of Length of Hospitalization			
Predictors	Age (p = 0.014), classification of stroke (p = 0.012), NIH Stroke Scale (p < 0.001), Barthel Index (p < 0.001), Stanford Sleepiness Score (p = 0.062), Addenbrooke's Cognitive Exam (p = 0.078), Hospital Anxiety and Depression Score (p = 0.024)			
Significant Variables	Coefficient	Standard error	t Value	P Value
NIH Stroke Scale	0.085	0.026	3.245	0.002
Barthel ADL	-0.104	0.016	-6.577	< 0.001
AHI	0.006	0.003	2.060	0.044
Full model F (df)		47.152 (3,57)		< 0.001
F change with AHI		4.244		0.044
Full model R^2		0.713		
R^2 change with AHI		0.021		

1. Stepwise multiple linear regression with forced entry of AHI.
2. Length of hospitalization is log transformed into normal distribution.
3. The parenthesis following predictor shows p value in univariate analysis. Only those with p < 0.1 are entered.

Table 6.2 Factors at baseline (3 weeks) predicting length of hospitalization after adjusting for allocation

Dependent variable	Logarithm (Ln) of Length of Hospitalization			
Predictors	Age ($p = 0.014$), classification of stroke ($p = 0.012$), NIH Stroke Scale ($p < 0.001$), Barthel Index ($p < 0.001$), Stanford Sleepiness Score ($p = 0.062$), Addenbrooke's Cognitive Exam ($p = 0.078$), Hospital Anxiety and Depression Score ($p = 0.024$)			
Significant Variables	Coefficient	Standard error	t Value	P Value
NIH Stroke Scale	0.081	0.026	3.126	0.003
Barthel ADL	-0.105	0.016	-6.735	< 0.001
AHI	0.010	0.004	2.302	0.025
Allocation	-0.093	0.101	-0.923	0.360
Full model F (df)		36.433 (4,55)		< 0.001
Full model R^2		0.726		

1. Stepwise multiple linear regression with forced entry of AHI and allocation.

2. Length of hospitalization is log transformed into normal distribution.

3. The parenthesis following predictor shows p value in univariate analysis. Only those with $p < 0.1$ are entered.

Table 6.3 Sleepiness, neurological deficits, cognitive and functional outcome in patients with AHI < 30 and AHI ≥ 30 at three months post-stroke ¶

	DOI	AHI < 30	N	AHI ≥ 30	N	Effect size	P value	Mild stroke (N=19/20) Effect Size (P value)
Stanford sleepiness score (1-7)	–	2 (2-3)	33	2 (1-3)	29	0.20	0.258	NS
NIH stroke score (0-42)	–	3 (1-7)	32	2 (1-5)	28	0.13	0.564	NS
Barthel ADL (0-20)	+	18 (16-20)	33	17 (15-19)	31	0.47	0.246	0.60 (0.051)#
Nottingham Extended ADL (0-66)	+	32 (14-54)	33	23 (12-40)	31	0.40	0.116	0.99 (0.003)**
Mobility (0-18)	+	8 (4-16)	33	5 (1-13)	31	0.52	0.033*	1.14 (0.002)**
Kitchen (0-10)	+	11 (4-15)	33	11 (3-14)	31	0.17	0.271	0.66 (0.021)*
Domestic (0-10)	+	5 (0-12)	33	0 (0-8)	31	0.37	0.175	0.89 (0.018)*
Leisure (0-18)	+	7 (5-12)	33	6 (6-9)	31	0.35	0.267	0.73 (0.039)*
Mini-mental Status Exam (0-30)	+	29 (27-30)	32	29 (25-29)	28	0.25	0.461	NS
Addenbrooke's Cognitive Exam (0-100)	+	87 (81-93)	32	88 (76-90)	28	0.15	0.553	NS
Orientation (0-10)	+	10 (9-10)	32	10 (9-10)	28	0.38	0.466	NS
Attention (0-8)	+	8 (7-8)	32	8 (6-8)	28	0.01	0.807	NS
Memory (0-35)	+	31 (26-34)	32	31 (25-34)	28	0.10	0.988	NS
Verbal fluency (0-14)	+	8 (6-10)	32	8 (5-9)	28	0.14	0.492	NS
Language (0-28)	+	28 (25-28)	32	28 (26-28)	28	0.00	0.811	NS
Visuospatial (0-5)	+	4 (3-4)	32	4 (3-5)	28	0.08	0.939	NS

¶ Mann-Whitney U test; ** P < 0.01, * P < 0.05, # P ≥ 0.05 but effect size > 0.5

DOI: direction of improvement; NS: not significant

Table 6.4 Factors at baseline predicting mobility subscale of Nottingham Extended ADL Index (EADL) at 3 months after stroke

Dependent variable	EADL mobility subscale > 6			
Predictors	Gender (p = 0.066), AHI (p = 0.026), NIH Stroke Scale (p = 0.006), Barthel Index (p < 0.001), Addenbrooke's Cognitive exam (p = 0.071) at baseline			
Variables	Wald	Odds Ratio	CI	p Value
Gender	2.810	3.791	0.798-18.012	0.094
AHI	6.233	0.145	0.032-0.660	0.013
Barthel Index	14.242	1.502	1.216-1.856	< 0.001
Addenbrooke's Cognitive Exam	0.363	1.016	0.965-1.069	0.547
Model Chi-Square		36.400		< 0.001
Correct Predictions		77.8%		
Nagelkerke-R^2		0.585		

1. Full model logistic regression.

2. EADL mobility subscale is converted into dichotomous variable according to its median. AHI is converted into dichotomous variable according to the cut-off point (30).

3. The parenthesis following predictor shows p value in univariate analysis. Only those with p < 0.1 are entered.

4. NIH Stroke Scale is not put in the model to prevent from multicollinearity with Barthel Index.

Table 6.5 Factors at baseline predicting mobility subscale of Nottingham Extended ADL Index (EADL) at 3 months after stroke after adjusting for allocation

Dependent variable	EADL mobility subscale > 6			
Predictors	Gender (p = 0.066), AHI (p = 0.029), Barthel Index (p < 0.001), Addenbrooke's Cognitive exam (p = 0.071) at baseline			
Variables	Wald	Odds Ratio	CI	p Value
Gender	3.294	4.677	0.884-24.746	0.070
AHI				0.024
AHI < 30 vs. AHI ≥ 30 (CPAP)	7.304	25.056	2.423-259.095	0.007
AHI ≥ 30 (Con) vs. AHI ≥ 30 (CPAP)	2.750	7.510	0.693-81.376	0.097
Barthel Index	13.346	1.520	1.214-1.903	< 0.001
Addenbrooke's Cognitive Exam	0.963	1.026	0.974-1.081	0.326
Model Chi-Square		39.498		< 0.001
Correct Predictions		81%		
Nagelkerke-R^2		0.621		

1. Full model logistic regression.

2. EADL mobility subscale is converted into dichotomous variable according to its median. AHI is converted into dichotomous variable according to the cut-off point (30).

3. Regression analysis taking allocation into account is done by dividing AHI into three groups: (1) AHI < 30; (2) AHI ≥ 30 with conventional treatment for stroke only (Con); (3) AHI ≥ 30 with conventional treatment for stroke plus CPAP treatment (CPAP). The results are presented as odds ratio of (1) AHI < 30 to AHI ≥ 30 (CPAP) and (2) AHI ≥ 30 with conventional treatment only (Con) to AHI ≥ 30 with conventional treatment plus CPAP treatment (CPAP).

4. The parenthesis following predictor shows p value in univariate analysis. Only those with p < 0.1 are entered.

Table 6.6 Factors at baseline predicting total score of Nottingham Extended ADL Index (EADL) at 3 months after stroke in patients with mild stroke (NIHSS < 7)

Dependent variable	EADL total score > 36 at 3 months			
Predictors	AHI (p = 0.009), Barthel Index (p = 0.006) at baseline			
Variables	Wald	Odds Ratio	CI	p Value
AHI	6.653	0.055	0.007-0.407	0.005
Barthel Index	6.737	1.536	1.103-2.137	0.011
Model Chi-Square		19.221		< 0.001
Correct Predictions		84.6		
Nagelkerke-R^2		0.519		

1. Full model logistic regression.
2. EADL total score is converted into dichotomous variable according to its median in the group with NIHSS < 7.
3. The parenthesis following predictor shows p value in univariate analysis. Only those with p < 0.1 are entered.

Table 6.7 Outcome of well-being in patients with AHI < 30 and AHI ≥ 30 at 3 months post-stroke ¶

	DOI	AHI < 30	N	AHI ≥ 30	N	Effect size	P value	Mild stroke (N=19/20) Effect Size (P value)
Hospital Anxiety Depression (0-42)	–	8 (3-14)	32	8 (5-12)	29	0.09	0.868	NS
Anxiety score (0-21)	–	4 (2-6)	32	3 (2-5)	29	0.11	0.711	NS
Depression score (0-21)	–	4 (1-8)	32	5 (3-6)	29	0.08	0.828	NS
Euro-Q Visual Analogue (0-100)	+	70 (60-80)	32	75 (70-80)	29	-0.22	0.424	NS
Euro-Q 5-Dimention (0-1)	+	0.75 (0.54-0.96)	32	0.69 (0.56-0.85)	29	0.20	0.450	0.63 (0.014)*
SF-36 Health transition (1-5)	–	4 (4-5)	32	4 (3-4)	29	-0.51	0.060#	NS
SF-36 Physical function (0-100)	+	50 (25-65)	32	35 (20-55)	29	0.39	0.121	1.09 (0.002)**
SF-36 Role physical (0-100)	+	0 (0-25)	32	0 (0-13)	29	0.29	0.145	0.50 (0.058)#
SF-36 Role emotional (0-100)	+	100 (33-100)	32	100 (33-100)	29	0.15	0.560	NS
SF-36 Bodily pain	+	84 (62-100)	32	84 (61-100)	29	0.06	0.724	NS
SF-36 Mental health	+	82 (54-92)	32	72 (64-92)	29	-0.04	0.873	NS
SF-36 Social function	+	75 (31-100)	32	50 (31-75)	29	0.53	0.045*	0.92 (0.010)*
SF-36 General health	+	67 (47-77)	32	67 (50-77)	29	-0.09	0.954	NS
SF-36 Vitality	+	60 (39-70)	32	55 (40-70)	29	0.12	0.514	NS
SF-36 Physical score	+	28.4 (21.9-40.1)	32	25.8 (20.5-31.3)	29	0.37	0.168	0.95 (0.004)**
SF-36 Mental score	+	55.8 (48.2-61.6)	32	54.7 (40.9-61.1)	29	0.08	0.745	NS

¶ Mann-Whitney U test; ** P < 0.01, * P < 0.05, # P ≥ 0.05 but effect size > 0.5

DOI: direction of improvement; NS: not significant

Table 6.8 Correlations between sleep variables and functional outcome at 3 months after stroke

	AHI	OAI	HI	ODI	Mean SaO2	CT90
Barthel Index	r = -1.555	r = -0.105	r = -0.148	r = 0.008	r = -0.047	r = -0.044
	p = 0.220	p = 0.409	p = 0.243	p = 0.949	p = 0.711	p = 0.730
Nottingham Extended ADL Index	r = -0.194	r = -0.122	r = -0.189	r = -0.110	r = 0.072	r = -0.066
	p = 0.125	p = 0.335	p = 0.136	p = 0.388	p = 0.574	p = 0.602
Mobility	r = -0.273	r = -0.218	r = -0.275	r = -0.140	r = 0.059	r = -0.096
	p = 0.029*	p = 0.084	p = 0.028*	p = 0.269	p = 0.645	p = 0.452
Kitchen	r = -0.109	r = -0.061	r = -0.048	r = -0.047	r = 0.067	r = -0.063
	p = 0.391	p = 0.630	p = 0.704	p = 0.712	p = 0.598	p = 0.619
Domestic	r = -0.169	r = -0.039	r = -0.173	r = -0.168	r = 0.083	r = -0.095
	p = 0.182	p = 0.757	p = 0.171	p = 0.184	p = 0.515	p = 0.455
Leisure	r = -0.131	r = -0.161	r = -0.117	r = -0.111	r = 0.120	r = -0.032
	p = 0.302	p = 0.205	p = 0.357	p = 0.382	p = 0.344	p = 0.800

Table 6.9 Correlations between sleep variables and cognitive function at 3 months after stroke

	AHI	ODI	Lowest SaO2	Mean Desat	HRV †	Min HR
Mini-mental Status Exam	r = -0.099	r = -0.106	r = 0.309	r = -0.234	r = -0.304	r = 0.147
	p = 0.449	p = 0.422	p = 0.016*	p = 0.072	P = 0.018	p = 0.262
Addenbrooke's Cognitive Exam	r = 0.036	r = 0.003	r = 0.154	r = -0.117	r = -0.325	r = 0.217
	p = 0.787	p = 0.982	p = 0.241	p = 0.374	P = 0.011*	p = 0.095
Orientation	r = -0.144	r = -0.113	r = 0.313	r = -0.283	r = -0.215	r = 0.078
	p = 0.274	p = 0.388	p = 0.015*	p = 0.029*	P = 0.098	p = 0.555
Attention and concentration	r = 0.068	r = -0.011	r = 0.178	r = -0.195	r = -0.112	r = -0.013
	p = 0.608	p = 0.935	p = 0.175	p = 0.136	P = 0.396	p = 0.919
Memory	r = 0.132	r = 0.111	r = 0.144	r = -0.103	r = -0.340	r = 0.272
	p = 0.315	p = 0.932	p = 0.274	p = 0.436	p = 0.008**	p = 0.035*
Verbal fluency	r = 0.007	r = 0.047	r = -0.028	r = -0.026	r = -0.153	r = 0.035
	p = 0.960	p = 0.723	p = 0.835	p = 0.841	p = 0.245	p = 0.789
Language	r = 0.099	r = 0.009	r = 0.242	r = -0.170	r = -0.291	r = 0.140
	p = 0.452	p = 0.946	p = 0.063	p = 0.195	p = 0.024*	p = 0.286
Visual spatial	r = -0.021	r = -0.045	r = 0.161	r = -0.183	r = -0.017	r = -0.110
	p = 0.870	p = 0.731	p = 0.221	p = 0.162	p = 0.899	p = 0.404

Table 6.10 Gender difference in outcome at 3 months after stroke

	Male	Female	p Value
Stanford Sleepiness Scale	3 (2-3)	3 (1-3)	0.808
NIH Stroke Scale	2 (1-5)	2 (1-7)	0.936
Barthel Index	18 (16-20)	18 (14-20)	0.586
Mini-mental Status Exam	29 (27-29)	29 (25-30)	0.890
Addenbrooke's Cognitive Exam	87 (82-91)	81 (68-92)	0.259
Orientation	10 (9-10)	10 (9-10)	0.609
Attention and concentration	8 (7-8)	8 (6-8)	0.667
Memory	31 (26-34)	29 (23-33)	0.190
Verbal fluency	8 (6-10)	7 (4-10)	0.209
Language	28 (27-28)	26 (24-28)	0.071
Visual spatial	4 (3-5)	3 (3-4)	0.004**
Nottingham Extended ADL	29 (15-56)	26 (9-37)	0.148
Mobility	8 (3-16)	5 (1-10)	0.052
Kitchen	11 (4-15)	11 (3-14)	0.332
Domestic	3 (0-12)	1 (0-8)	0.363
Leisure	8 (6-12)	6 (4-9)	0.041*
Hospital Anxiety Depression Scale	8 (3-11)	10 (6-15)	0.089
Anxiety	3 (2-5)	5 (3-6)	0.078
Depression	4 (2-6)	6 (3-11)	0.088
Euro-Q Visual Analogue	75 (67-80)	70 (61-80)	0.160
Euro-Q 5-Dimention	0.76 (0.59-1.00)	0.69 (0.42-0.79)	0.044*
SF-36 Health transition	4 (3-4)	4 (4-5)	0.151
SF-36 Physical function	45 (25-68)	35 (20-50)	0.058
SF-36 Role physical	0 (0-25)	0 (0-25)	0.494
SF-36 Role emotional	100 (33-100)	100 (33 -100)	0.489
SF-36 Bodily pain	84 (62-100)	72 (61-100)	0.237
SF-36 Mental health	84 (64-92)	64 (49-87)	0.022
SF-36 Social function	60 (50-75)	56 (25-75)	0.046*
SF-36 General health	67 (49-82)	64 (48-72)	0.171
SF-36 Vitality	60 (50-75)	53 (26-60)	0.014*
SF-36 Physical summary	28.1 (21.6-39.3)	25.8 (21.9-30.8)	0.293
SF-36 Mental summary	56 (51-64)	49.9 (38.2-57.8)	0.073

¶ Mann-Whitney U test

Table 6.11 Functional outcome and well-being in patients with AHI < 30 and AHI ≥ 30 at 6 months post-stroke

	DOI	AHI < 30	N	AHI ≥ 30	N	Effect size	p value ¶	Mild stroke (N=17/20) Effect Size (p value)
Barthel ADL score	+	19 (17-20)	31	19 (15-19)	30	0.48	0.271	0.52 (0.060)#
Nottingham extended ADL score	+	41 (16-48)	31	27 (17-40)	30	0.51	0.055#	0.89 (0.016)*
Mobility	+	9 (6-16)	31	5 (3-11)	30	0.62	0.017*	1.02 (0.004)**
Kitchen	+	11 (4-15)	31	10 (5-14)	30	0.12	0.358	0.40 (0.086)
Domestic	+	6 (1-13)	31	3 (0-7)	30	0.45	0.119	0.62 (0.084)#
Leisure	+	9 (7-11)	31	8 (5-9)	30	0.57	0.062#	0.97 (0.006)**
SF-36 Health transition	–	4 (3-5)	30	4 (3-4)	27	-0.37	0.087	NS
SF-36 Physical function	+	43 (25-72)	30	30 (15-45)	27	0.40	0.130	0.63 (0.103)#
SF-36 Role physical	+	0 (0-6)	30	0 (0-25)	27	0.05	0.772	NS
SF-36 Role emotional	+	100 (33-100)	30	67 (0-100)	27	0.29	0.333	NS
SF-36 Bodily pain	+	72 (49-100)	30	63 (25-88)	27	-0.03	0.805	NS
SF-36 Mental health	+	82 (63-92)	30	84 (41-100)	27	0.21	0.272	NS
SF-36 Social function	+	50 (25-78)	30	76 (64-88)	27	-0.10	0.766	NS
SF-36 General health	+	62 (51-83)	30	65 (50-82)	27	0.06	0.930	NS
SF-36 Vitality	+	50 (34-60)	30	50 (35-65)	27	-0.16	0.547	NS
SF-36 Physical summary	+	26.1 (20.3-37.5)	30	27.6 (17.4-35.9)	27	0.13	0.626	NS
SF-36 Mental summary	+	55.7 (45.1-59.1)	30	53.3 (42.6-61.1)	27	0.04	0.943	NS

¶ Mann-Whitney U test; ** $p < 0.01$, * $p < 0.05$, # $p \geq 0.05$ but effect size > 0.5

DOI: direction of improvement; NS: not significant

Table 6.12 Factors predicting Nottingham Extended ADL Index (EADL) at 6 months after stroke in patients with mild stroke (NIHSS < 7)

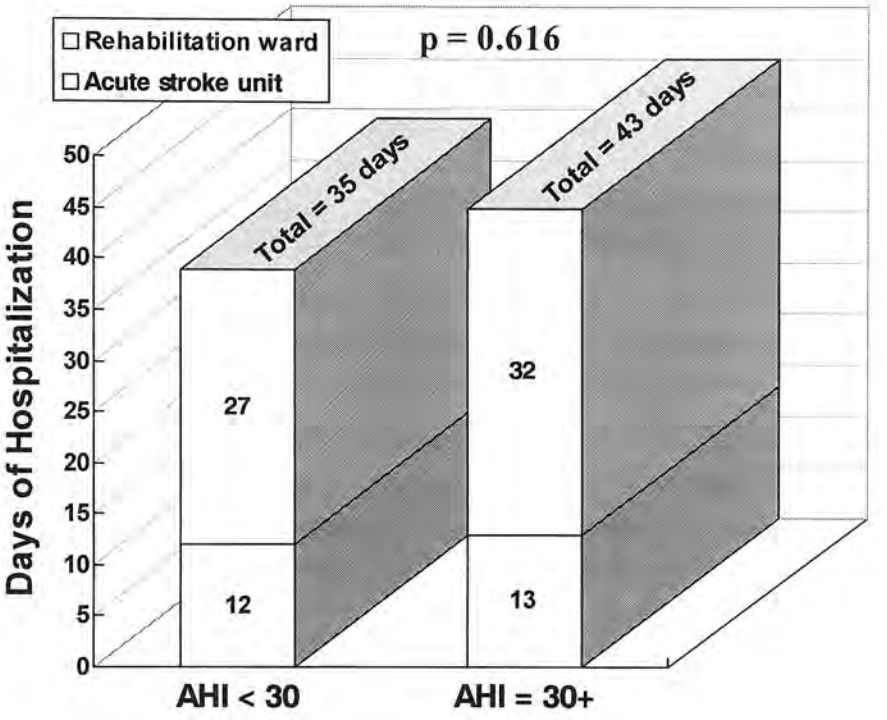
Dependent variable	EADL total score at 6 months			
Predictors	Gender (p = 0.020), AHI (p = 0.017), Barthel Index (p = 0.001), Addenbrooke's Cognitive Exam (p = 0.021) at baseline			
Variables	Coefficient	Standard error	t Value	p Value
Gender	5.455	4.881	1.118	0.272
AHI	-0.323	0.116	-2.783	0.009
Barthel Index	2.359	0.627	3.760	0.001
Addenbrooke's Cognitive Exam	0.249	0.144	1.724	0.095
Full model F (df)		9.759 (4,31)		< 0.001
Full model R^2		0.557		

1. Full model multiple regression.
2. The parenthesis following predictor shows p value in univariate analysis. Only those with p < 0.1 are entered.

Table 6.13 Gender difference in outcome at 6 months after stroke

	Male	Female	p Value
Barthel Index	19 (17-20)	18 (14-19)	0.159
Nottingham Extended ADL	36 (21-53)	25 (10-39)	0.033*
Mobility	10 (5-17)	4 (2-9)	< 0.001***
Kitchen	11 (8-15)	11 (2-14)	0.122
Domestic	4 (0-12)	4 (0-8)	0.431
Leisure	9 (7-11)	8 (5-9)	0.029*
SF-36 Health transition	4 (3-4)	4 (3-4)	0.560
SF-36 Physical function	45 (20-70)	28 (14-40)	0.065
SF-36 Role physical	0 (0-25)	0 (0-6)	0.609
SF-36 Role emotional	67 (33-100)	100 (25-100)	0.536
SF-36 Bodily pain	72 (42-100)	100 (49-100)	0.264
SF-36 Mental health	80 (64-92)	72 (67-88)	0.259
SF-36 Social function	63 (25-88)	38 (22-88)	0.126
SF-36 General health	62 (47-77)	69 (52-88)	0.256
SF-36 Vitality	55 (40-70)	38 (29-53)	0.012*
SF-36 Physical summary	27.4 (18.2-36.8)	21.8 (19.5-35.9)	0.525
SF-36 Mental summary	55.9 (45.7-59.9)	51.7 (40.2-59.5)	0.487

Figure 6.1 Length of hospitalization between AHI ≥ 30 and < 30 (a) and correlation with AHI (b)



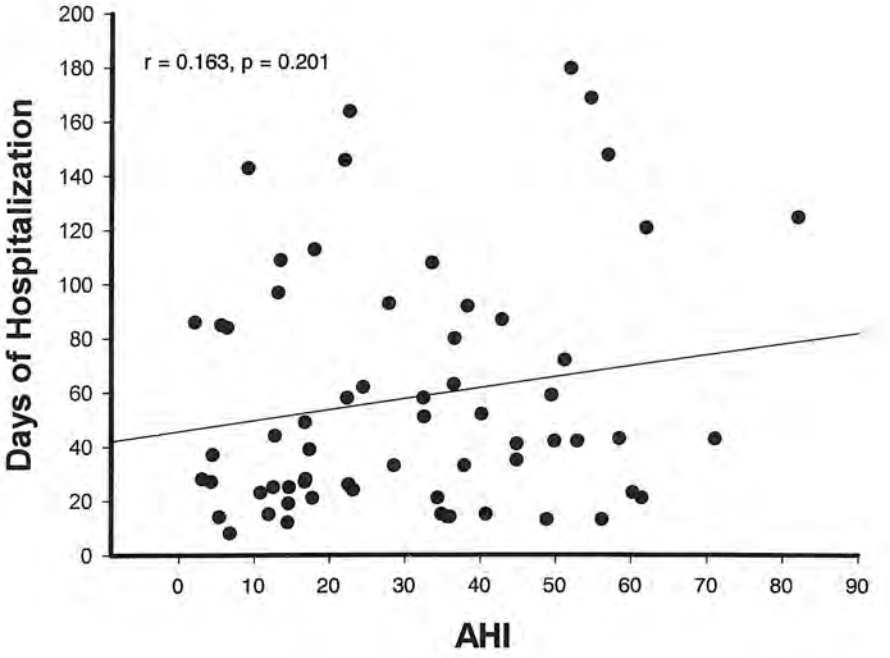
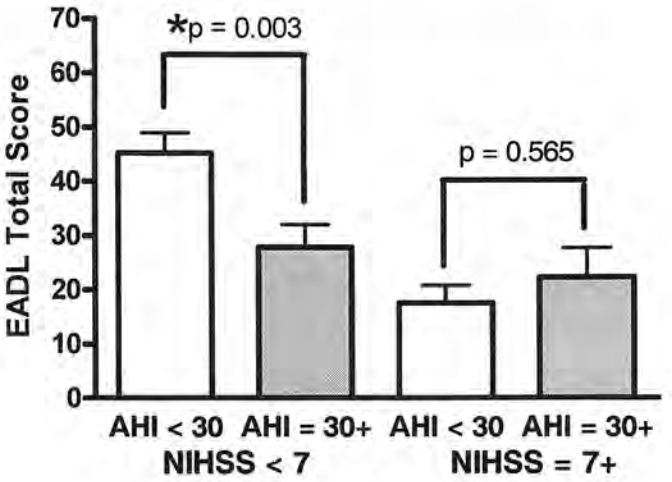


Figure 6.2 Subgroup analysis of Nottingham Extended ADL Index (EADL) between AHI ≥ 30 and AHI < 30 based on NIH Stroke Scale (NIHSS) at 3 months (a) and 6 months (b) after stroke



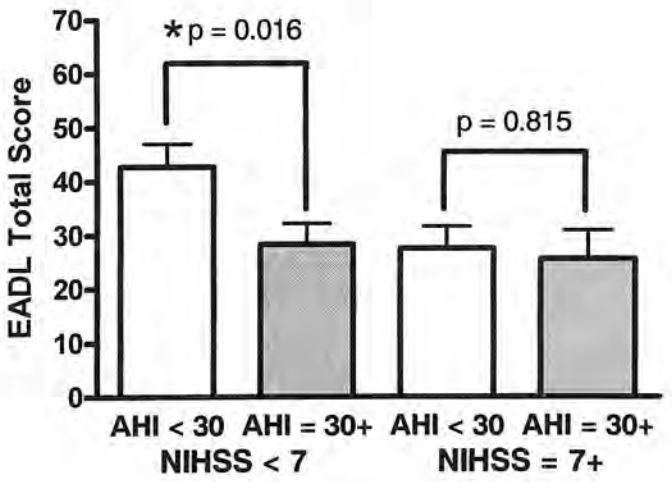
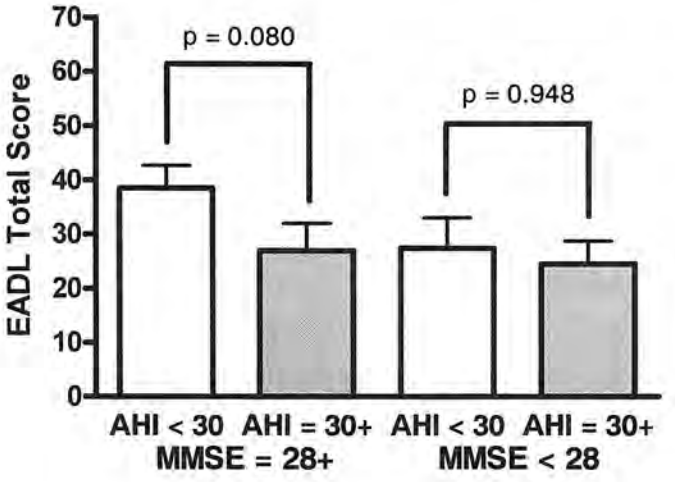


Figure 6.3 Subgroup analysis of Nottingham Extended ADL Index (EADL) between AHI ≥ 30 and AHI < 30 based on Mini-mental State Examination (MMSE, b) at 3 months (a) and 6 months (b) after stroke



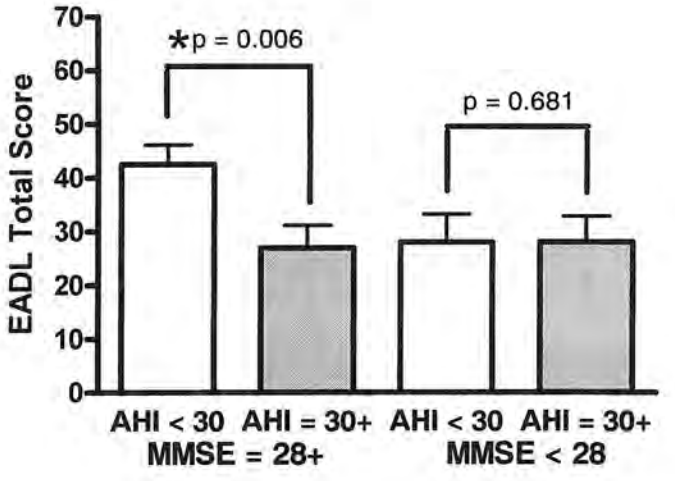
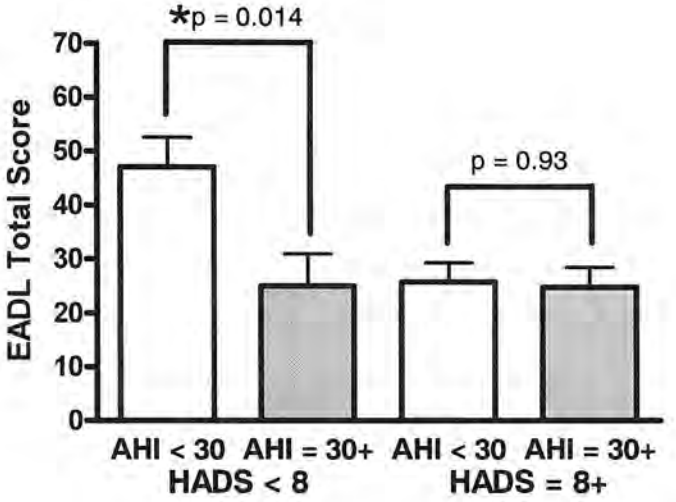


Figure 6.4 Subgroup analysis of Nottingham Extended ADL Index (EADL) between AHI ≥ 30 and AHI < 30 based on Hospital Anxiety and Depression Scale (HADS) at 3 months (a) and 6 months (b) after stroke



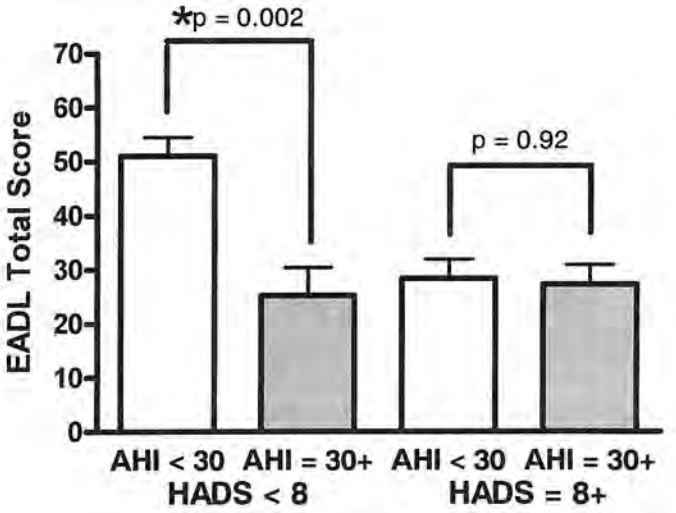
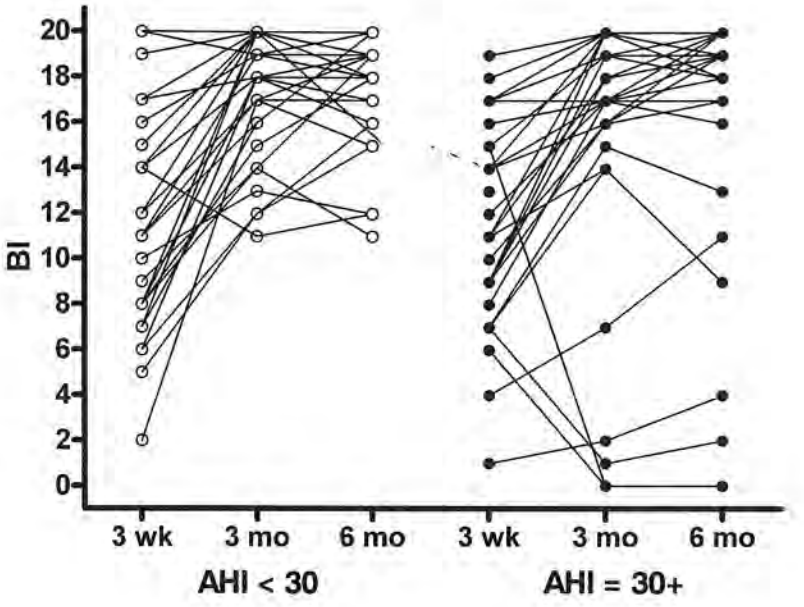


Figure 6.5 Time course (a) and changes (b) of Barthel Index (BI) between patients with AHI < 30 and AHI ≥ 30



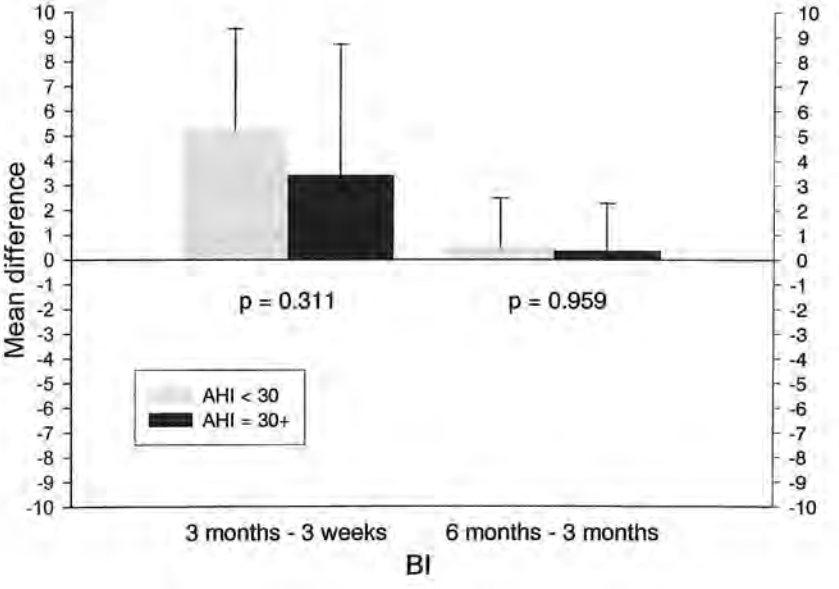
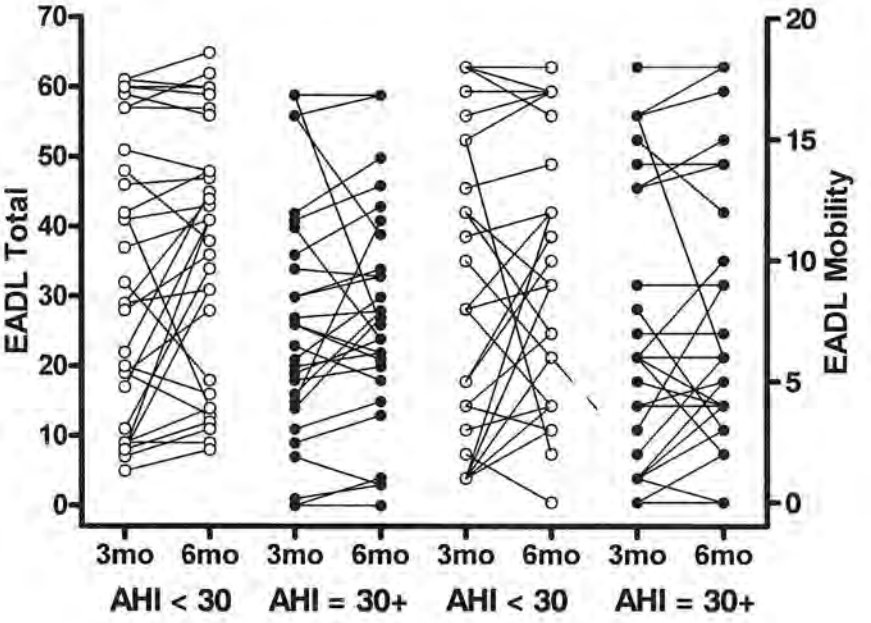


Figure 6.6 Time course (a) and changes (b) of Nottingham Extended ADL Index between patients with AHI < 30 and AHI ≥ 30



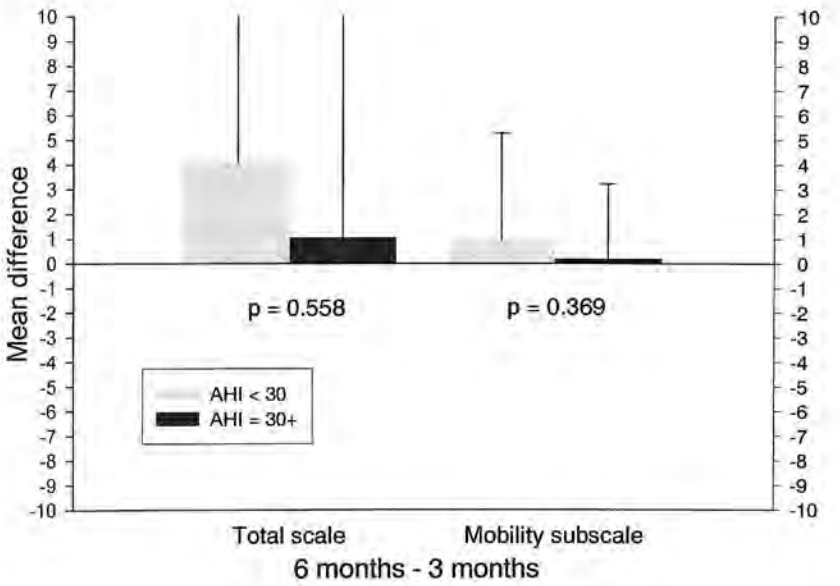
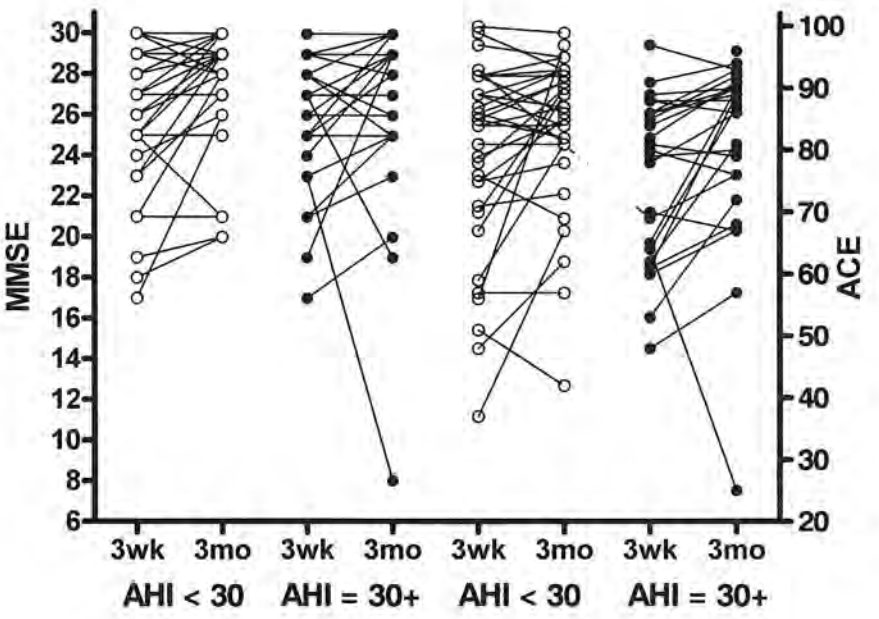


Figure 6.7 Time course (a) and changes (b) of Mini-mental State Examination (MMSE) and Addenbrooke's Cognitive Examination (ACE) between patients with AHI < 30 and AHI ≥ 30



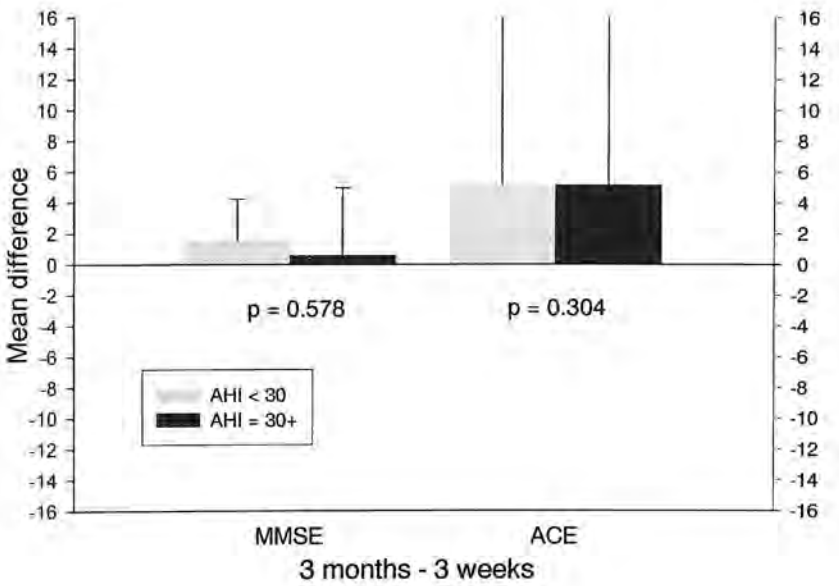
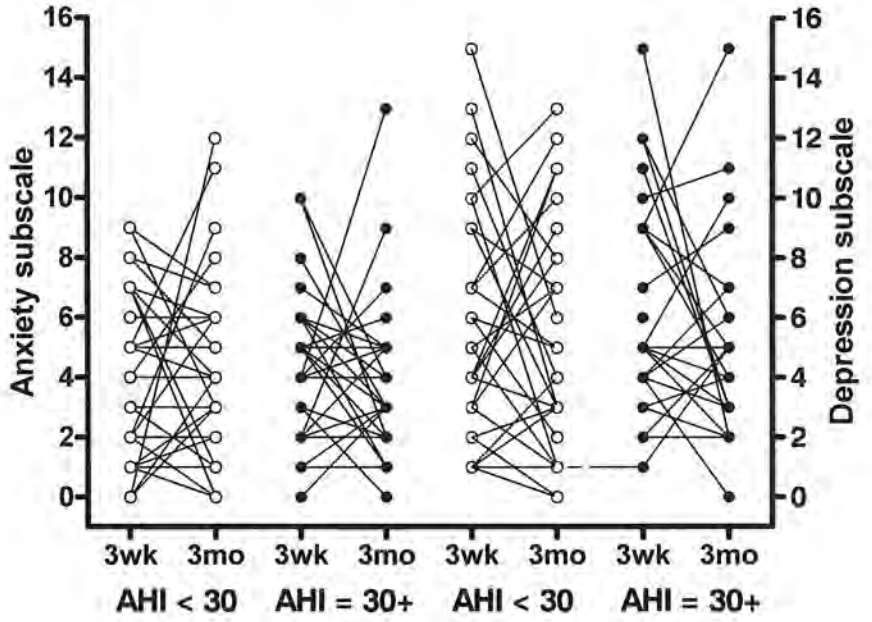


Figure 6.8 Time course (a) and changes (b) of Hospital Anxiety and Depression Scale between patients with AHI < 30 and AHI ≥ 30



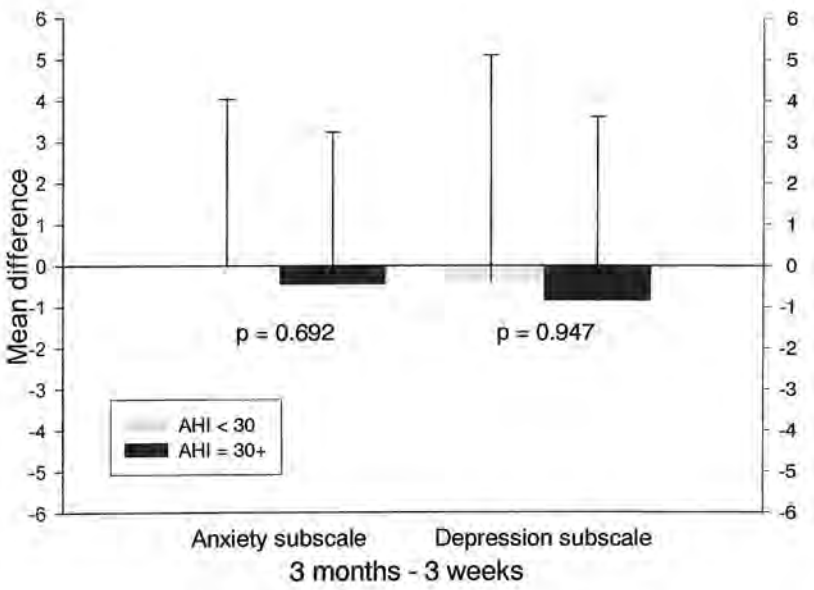


Figure 6.9 Time course of Modified Rankin Scale between patients with AHI ≥ 30 and < 30

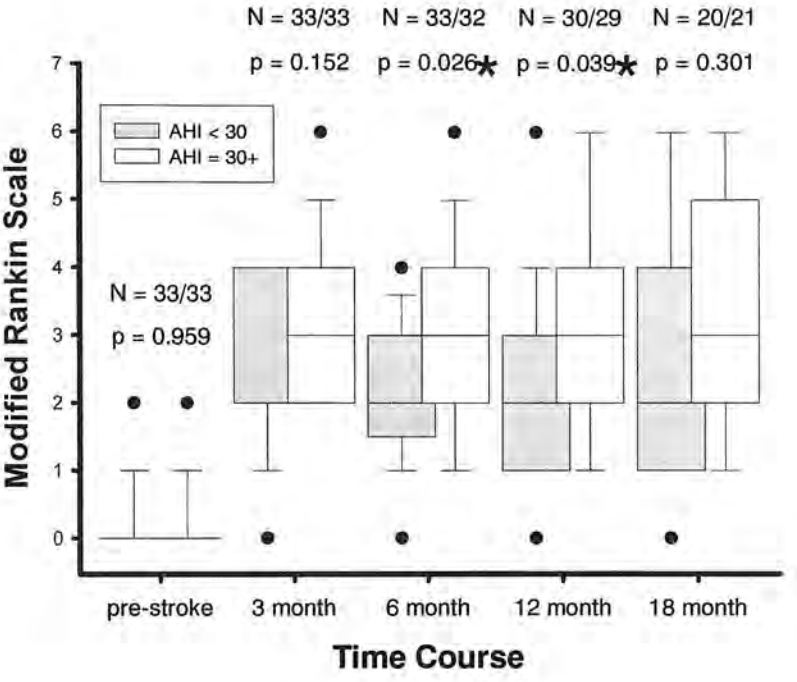
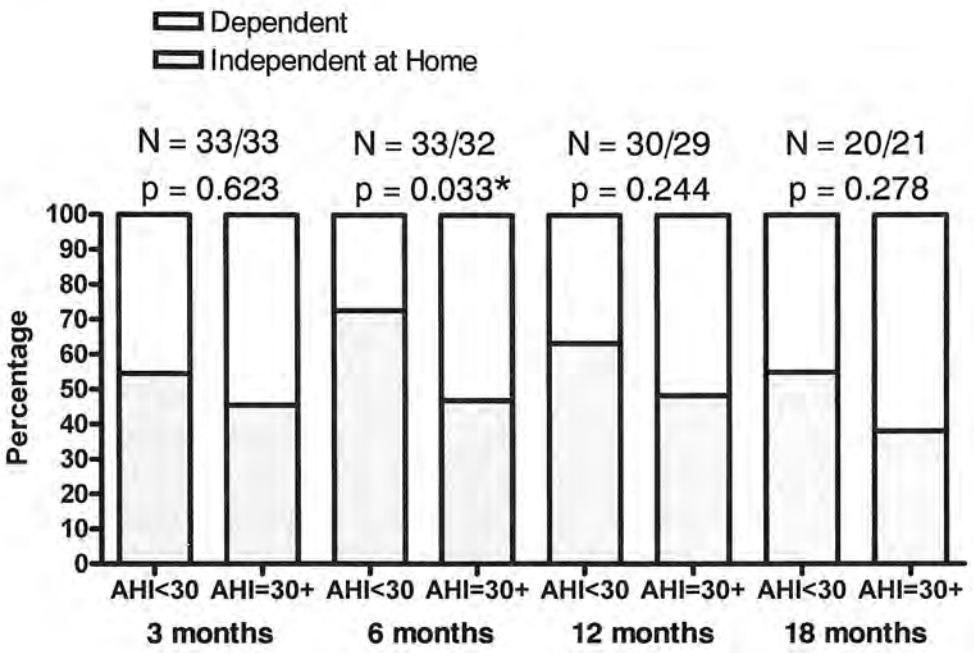
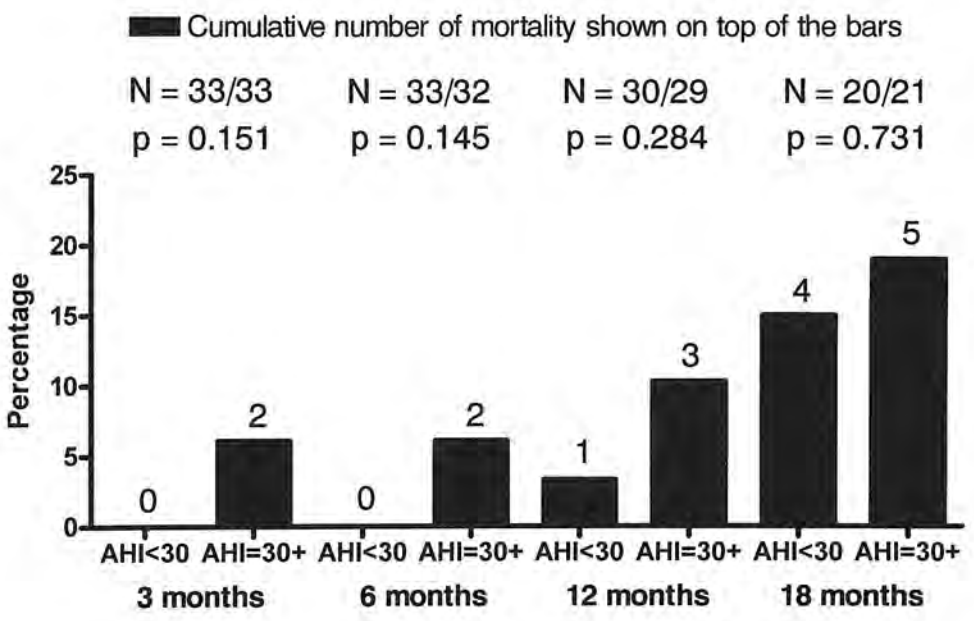


Figure 6.10 Cumulative mortality rate (a) and time course of "independent at home (home with MRS ≤ 2)" (b) between patients with AHI ≥ 30 and < 30





Chapter 7 Concluding Remark and Future Work

7.1 Concluding remark

Stroke is one of the most devastating cardiovascular diseases. Only half of cardiovascular diseases can be explained by conventional risk factors. Some new risk factors have been proposed and sleep-disordered breathing (SDB) is one of those which are treatable [Diaz and Sempere 2004]. Stroke usually happens in the elderly. Similarly, SDB is more common with increasing age [Ancoli-Israel *et al.* 1991]. The total cost of road traffic accidents is about £5 million per 500 untreated patients with SDB in every 5 years [Douglas and George 2002] and the total cost of acute and long-term care of stroke is about the double per 500 patients [Dewey *et al.* 2001]. Many previously published and ongoing studies have been trying to clarify the link of SDB to stroke, treatment effect of continuous positive airway pressure (CPAP) and impact of SDB on stroke outcomes. The contributions in our study are:

The data supports the high prevalence of SDB in stroke. A portable limited sleep study is a feasible and reliable tool to confirm the diagnosis of SDB. SDB seems to be a consequence of stroke rather than directly causing stroke during sleep.

We did not show any benefit in treating patients with SDB post-stroke with continuous positive airway pressure (CPAP). We cannot exclude clinically significant benefit or harm from CPAP because of our small sample size, which was only adequate to identify large treatment effects. The other major problem was that compliance with CPAP was poor even in our highly selected stroke patients. Compliance was poor despite our expertise in this area, our exclusion of many patients in whom we thought CPAP would be difficult, our use of auto-titrating CPAP and the intensive input from a very experienced specialist nurse. Many of the patients were inpatients during the treatment phase. Compliance might be improved in future studies by focusing on less depressed and cognitively less impaired patients but this would further decrease recruitment and also reduce the generalizability of any result. We believe that CPAP should only be used post-stroke in those patients who satisfy the criteria for SDB plus major related symptoms, usually sleepiness. However in our patients there was no correlation between daytime sleepiness and

CPAP compliance although this may have been because our sample size was too small (n = 15).

We found that the influence of SDB on the long-term outcome of stroke, i.e. three to eighteen months following stroke, was small. SDB may compromise the recovery of functional capacity following stroke instead of emotion, cognition and health-related quality of life. The effect might be more prominent after three months of stroke when patients had gone beyond the highest risk of complication and mortality. At this stage patients with stroke may be more compliant with nasal CPAP and CPAP may reduce recurrence of stroke by lowering blood pressure. On the other hand, SDB could perhaps play a role in the functional recovery of stroke in patients with less severity, less depression and higher cognitive function.

The merits of methodology in our study are:

- We had a more homogenous cohort than most studies. The patients were recruited at 14-19 days following stroke and had less severe stroke according to our inclusion and exclusion criteria.
- We performed the second ever randomized controlled trial of nasal CPAP in stroke.
- We had larger sample size (n = 66) in longitudinal outcome study than most previous studies.
- We had data collection in diverse domains of outcome in comparison with other studies which focused on functional outcome and mortality only. As outcome of stroke has a multi-dimensional nature, several outcome measures are beneficial.
- Most outcome measures are self-reported questionnaires. These can decrease the bias of assessment in outcome studies.
- We had interview-based instead of telephone or postal-based follow-up. This can increase the rate and validity of responses so we have less missing data during follow-up period.

- We performed follow-up at set time: 3 months (12^{th} week) and 6, 12, 18 months (all are based on calendar month) instead of unclear definitions such as "outcome at discharge" reported in other studies.
- We adjusted for baseline data and confounders in data analysis. Most of the previous studies did not adjust for baseline cofounders so their results might be biased by imbalance at baseline.

7.2 Future work

The prevalence of SDB is high in both the fit elderly and in those with cerebrovascular disease. In a study conducted in our sleep centre, TIA patients did not have significantly higher frequencies of sleep apnoea and hypopnoea than age matched controls. It might be informative to conduct a further study with similar design recruiting: (1) only young TIA patients (i.e. those aged below 45) and young controls to find out whether SDB is more prevalent in young TIA patients in whom SDB and hypertension might play a more important role in the pathogenesis of cerebrovascular disease than older ones and in whom there would be a much lower "background" level of SDB in the normal controls; (2) only young stroke patients to see whether SDB is an independent predictor for mortality after stroke after subtracting old-aged patients who usually have higher mortality resulting from other clinical conditions.

We need to test the prediction model of SDB in stroke generated in our study. This can be done by applying both the screening questionnaire generated from the model and overnight sleep study for confirmation of SDB to another population of stroke with similar hospital-based background. The validation of the prediction model can be performed through either traditional regression analysis or a more modern computer-assisted neural network. Sensitivity, specificity, positive predictive value and negative predictive value and area under the curve (AUC) of Receiver Operating Characteristics (ROC) can be calculated. This model may be helpful to be used by the first line physicians who do not have much knowledge about SDB.

The relationship – if any- between SDB and sleep-related stroke still needs to be clarified. Time and sleep-wake state upon stroke onset can be routinely recorded in the first instance when patients suffering from stroke are sent to emergency department. If neurological deficits are noted upon awakening, a detailed history should be taken to try to identify the time when the patient was last intact. The time interval between these two points should be as narrow as possible.

In my study, 24-hr ambulatory blood pressure (ABP) was only applied in randomized controlled trials (RCT) to stroke patients who had moderate to severe SDB. Further study could use 24-hr ABP monitoring in more stable stroke patients with or without SDB to clarify the association between SDB, surge or drop of blood pressure and circadian rhythm of stroke onset.

My study showed no benefit from CPAP and suggested some impairment of function on CPAP. It is questionable whether further RCTs in this area are justified given possible deterioration on CPAP but as other study showed some improvement in depression score and our sample size was low, further study might be justified. An RCT of stroke patients with features of pre-existing SDB is certainly justified.

The problem will be sample size. According to the results in this thesis, the effect size of difference in the primary outcome, Nottingham Extended Activity of Daily Living Scale, between untreated patients with $(A+H)\cdot h^{-1} \geq 30$ and < 30 at 6 months after stroke was 0.89. Based on a power calculation, a sample size of 64 in each limb may achieve 80% power to detect the difference of functional outcome of stroke between treated and untreated groups with a significance level (alpha) of 0.05. However, this is the minimum size if all the difference was due to sleep apnoeas and hypopnoeas and all of these were abolished by CPAP with 100% CPAP use. Thus any further study to attempt to demonstrate a benefit of CPAP in similar patients will probably need hundreds of patients in each limb.

Placebo instead of "conservative treatment of SDB" can be considered. A sham CPAP is more similar with true CPAP than oral placebo but may be less feasible. I would consider using an oral placebo in the next trial as it has been used in several RCTs conducted in the sleep centre of Edinburgh University. We did not use that on this occasion because we decided that would add to the complexity of these elderly patients' treatment for no good ethical reason. In fact, there was no benefit from CPAP in this study which could have been attributed to a placebo effect anyway. We also need to identify further ways of trying to improve compliance with CPAP in stroke patients. A group of stroke patients in a stable chronic phase, for example, beyond three months after stroke who have less depression and higher cognitive

function screened through pre-determined inclusion and exclusion criteria can be recruited for a further RCT of CPAP.

A cohort study with longitudinal follow-up for stroke patients with and without SDB can be designed with a priori hypothesis that SDB may play a significant role in the outcome of stroke patients with less severity, less depression and higher cognitive function to avoid data dredging through post-hoc subgroup analysis. The patients with severe stroke can be recruited in another independent study of hyper-acute or acute stroke which will focus on the association between SDB, stroke-in-evolution (progressive stroke) and mortality. The other studies can recruit patients with central sleep apnoea and Cheyne-Stokes respiration to see whether they play a more important role than SDB in the outcome of stroke.

These potential studies are all important, but the results of the studies carried out in this thesis and by others strongly suggest that CPAP will not be beneficial in most patients who have irregular breathing after stroke.

Appendix A National Institute of Health Stroke Scale

Please circle the most appropriate response for each section

1.a. Level of Consciousness:	0 Alert
	1 Not alert, but arousable with minimal stimulation
	2 Not alert, requires repeated stimulation to attend
	3 Coma
1.b. Ask patient the month and their age:	0 Answers both correctly
	1 Answers one correctly
	2 Both incorrect
1.c. Ask patient to open and close eyes and	0 Obeys both correctly
	1 Obeys one correctly
	2 Both incorrect
2. Best gaze (only horizontal eye movement):	0 Normal
	1 Partial gaze palsy
	2 Forced deviation
3. Visual Field testing:	0 No visual field loss
	1 Partial hemianopia
	2 Complete hemianopia
	3 Bilateral hemianopia (blind including cortical blindness)
4. Facial Paresis (Ask patient to show	0 Normal symmetrical movement
teeth or raise eyebrows and close eyes	1 Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
tightly):	2 Partial paralysis (total or near total paralysis of lower face)
	3 Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)
5. Motor Function - Arm (right and left):	0 Normal (extends arms 90 (or 45) degrees for 10 seconds without drift)
	1 Drift
Right arm ____	2 Some effort against gravity
Left arm ____	3 No effort against gravity

	4 No movement
	9 Untestable (Joint fused or limb amputated)
6. Motor Function - Leg (right and left):	0 Normal (hold leg 30 degrees position for 5 seconds)
	1 Drift
Right leg ____	2 Some effort against gravity
Left leg ____	3 No effort against gravity
	4 No movement
	9 Untestable (Joint fused or limb amputated)
7. Limb Ataxia:	0 No ataxia
	1 Present in one limb
	2 Present in two limbs
8. Sensory (Use pinprick to test arms, legs,	0 Normal
trunk and face -- compare side to side):	1 Mild to moderate decrease in sensation
	2 Severe to total sensory loss
9. Best Language (describe picture, name items,	0 No aphasia
read sentences)	1 Mild to moderate aphasia
	2 Severe aphasia
	3 Mute
10. Dysarthria (read several words):	0 Normal articulation
	1 Mild to moderate slurring of words
	2 Near unintelligible or unable to speak
	9 Intubated or other physical barrier
11. Extinction and inattention:	0 Normal
	1 Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities
	2 Severe hemi-inattention or hemi-inattention to more than one modality

Appendix B Modified Rankin Scale

With respect to your functional ability, do you have (circle one):

0 = No symptoms at all

1 = No significant disability despite symptoms; able to carry out all usual duties and activities

2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 = Moderate disability; requiring some help, but able to walk without assistance

4 = Moderate severe disability; unable to walk without assistance, and unable attend to own bodily needs without assistance

5 = Severe disability; bedridden, incontinent, and requiring constant nursing care and attention

6 = Dead

7 = Not known

Appendix C Barthel ADL Index

I want to ask some questions about how you are getting on performing everyday. This information is important so we can determine whether people are getting the treatment that they need.

Feeding

0 = unable

1 = Needs help but can do about half unaided (e.g. help with buttons or zip, but can put some garments on unaided)

2 = independent

Bathing

0 = dependent

1 = Independent in bathing or showering (must get in and out unsupervised, and wash self; or shower unsupervised or unaided)

Grooming

0 = needs to help with personal care

1 = independent face/hair/teeth/shaving (implements provided)

Dressing

0 = dependent

1 = needs help but can do about half unaided

2 = independent (including buttons, zips, laces, etc.)

Bowels

0 = incontinent (or needs to be given enemas)

1 = occasional accident

2 = continent

Bladder

0 = incontinent, or catheterized and unable to manage alone

1 = occasional accident

2 = continent

Toilet Use

0 = dependent

1 = needs some help, but can do something alone

2 = independent (on and off, dressing, wiping)

Transfers (bed to chair, and back))

0 = unable, no sitting balance

1 = major help (one or two people, physical), can sit

2 = minor help (verbal or physical)

3 = independent

Mobility (on level surfaces)

0 = immobile

1 = wheelchair independent, including corners

2 = walks with help of one person (verbal or physical)

3 = independent (but may use any aid; for example, stick)

Stairs

0 = unable

1 = needs help (verbal, physical, carrying aid)

2 = independent

Appendix D Nottingham Extended ADL Index

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the last few weeks. DID YOU.....

- Not at all; with help; on your own with difficulty; own your own.

1. Walk around outside?
2. Climb stairs?
3. Get in and out of a car?
4. Walk over uneven ground?
5. Cross roads?
6. Travel on public transport?
7. Manage to feed yourself?
8. Manage to make yourself a hot drink?
9. Take hot drinks from one room to another?
10. Do the washing up?
11. Make yourself a hot snack?
12. Manage your own money when out?
13. Wash small items of clothing?
14. Do your own housework?
15. Do your own shopping?
16. Do a full clothes wash?
17. Read newspaper or books?
18. Use the telephone?
19. Write letters?
20. Go out socially?
21. Manage your own garden?
22. Drive a car?

Appendix E Sleep and Stroke Questionnaire

Please try to answer all questions. If you cannot give an exact answer then give a "best guess" as your answer (for some questions it will be difficult to give an exact answer) or if you definitely don't know put "not known" as your answer. Answer question by placing a circle around the correct/best answer and provide further information, if necessary, on the line provided.

1) What time did your current stroke happen?

2) At that time you were:

- Awake; asleep.

3) Have you ever been diagnosed with stroke, TIA, angina or leg claudication previously?

- Yes; no (please go to Q4)

4) Do you snore during sleep?

- Yes; no (please go to Q8)

5) How many years have you snored?

6) How often do you snore?

- Occasionally (less than 3 nights per week); often (3-6 nights per week); nearly every day.

7) How loudly you snore?

- Quietly; moderately loud (heard in bedroom only); loudly (heard outside the bedroom).

8) Do you have a regular bed-partner or room-mate?

- Yes; no (please go to Q10)

9) Has your bed-partner/room-mate ever noticed that you stop breathing when asleep?

- Yes; no.

10) Do you need to go to toilet at night?

- Never or hardly ever; occasionally; 1-2 times per night; more than 2 times per night.

11) Have you woken in the night with choking episodes or suffocating?

- Never or hardly ever; 1-2 times; 3-6 times; more than 6 times.

12) Have you woken up in the morning with headache?

- Never or hardly ever; 1-2 times; 3-6 times; more than 6 times

13) In the morning do you feel that your nights sleep was refreshing/satisfactory?

- Never or hardly ever; 1-3 times per week; 4-6 times per week; always.

14) Do you have periods of the day when you feel sleepy or have trouble staying awake?

- Never or hardly ever; 1-3 times per week; 4-6 times per week; always

15) Do you drive?

- Yes; no (end)

16) Have you ever had, or nearly had an accident because of falling asleep while driving?

- No; yes (give details):

Appendix F Stanford Sleepiness Scale

Circle the statement that best describes your alertness or sleepiness right now.

1. Feeling active and vital; alert; wide-awake.
2. Functioning at a high level, but not at peak; able to concentrate
3. Relaxed; awake; not at full alertness; responsive.
4. A little foggy; not at peak; let down.
5. Fogginess; beginning to lose interest in remaining awake; slowed down.
6. Sleepiness; prefer to be lying down; fighting sleep; woozy.
7. Almost in reverie; sleep onset soon; lost the struggle to stay awake.

Appendix G Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

1. Sitting and Reading
2. Watching TV
3. Sitting, inactive in a public place (e.g. a theater or a meeting)
4. As a passenger in a car for an hour without a break
5. Lying down to rest in the afternoon when circumstances permit
6. Sitting and talking to someone
7. Sitting quietly after lunch without alcohol
8. In a car, while stopped for a few minutes in traffic

Appendix H Addenbrooke's Cognitive Examination

All instructions to the tester are in italics. All instructions to be said aloud to the patient are in bold non-italic print.

ORIENTATION

Ask the subject the following question:

Q1a) What is the year? season? month? date? day?

Q1b) Where are we? Country; town; hospital/building; floor/level.

ATTENTION/CONCENTRATION

Q2) Tell the subject I am going to ask you to recall the names of three things.

Say aloud. Then ask the subject to repeat them:

- Lemon, key, ball.

Q3) Ask the subject to take away 7 from 100.

If score<5 then ask the subject to Spell 'WORLD' backwards.

MEMORY

Q4) Ask the subject to recall the names of the 3 things learned earlier in question 2.

Q5) Anterograde Memory: Tell the subject I will read a name and address and ask you to repeat it when I have finished. Now read aloud the following name and address. 1st trial; 2nd trial; 3rd trial; 5 min delay.

- Peter Marshall
- 42 Market Street
- Chelmsford; Essex

Q6) Retrograde Memory: Tell me the full name of:

- The prime minister; the last prime minister; the Leader of the Opposition; the President of the United States of America.

VERBAL FLUENCY

Q7) Letter: Ask the subject to:

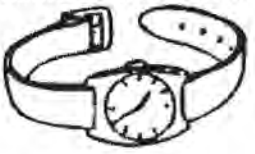
- Tell me all the words you can think of, but not people and places, beginning with the letter P.

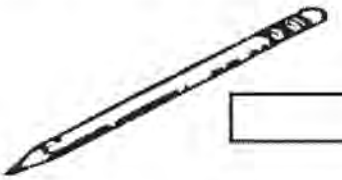
Q8) Category: Say:

- Now tell me the names of as many animals as you can, beginning with any letter of the alphabet.

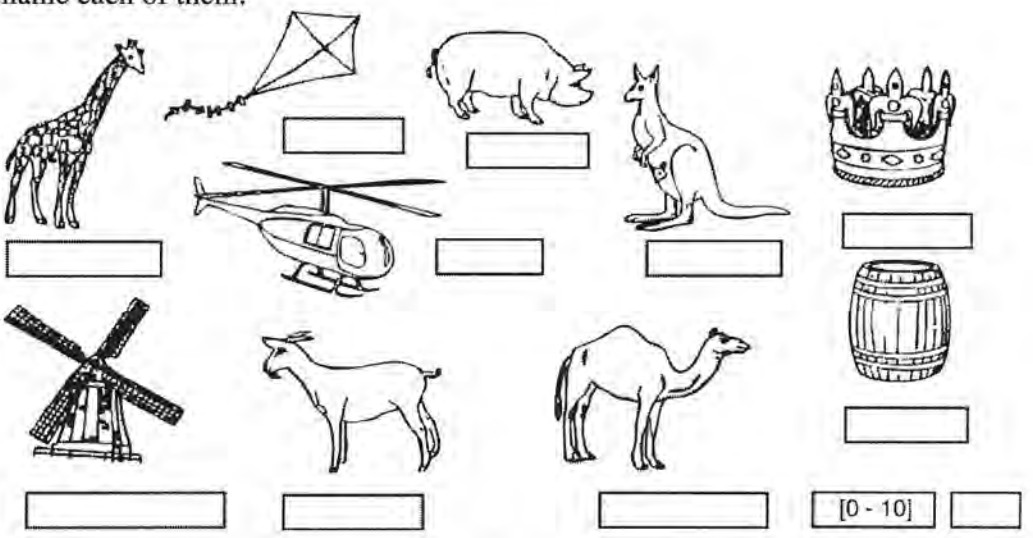
LANGUAGE

Q9) Naming: Show the subject the following two line-drawings and ask him/her to name each of them.





Q10) Naming: Show the subject the following ten line-drawings and ask him/her to name each of them.



Q11) Comprehension (one-stage): Ask the subject to please obey the following simple commands.

- Point to the door.
- Point to the ceiling.

Show the subject the following instruction and ask him/her to read this aloud and obey it.

- CLOSE YOUR EYES

Q12) Comprehension (3-stages): Give the subject a piece of paper and tell him to take this paper in your hands. Fold it in half. Then put the paper on the floor.

Q13) Comprehension (complex grammar): Ask the subject to please obey the following commands.

- Point to the ceiling then the door.

- Point to the door after touching the bed/desk.

Q14) Repetition (single words): Ask the subject to repeat each of these words after me:

- Brown; conversation; articulate.

Q15) Repetition (phrases): Ask the subject to repeat each of these phrases after me:

- No ifs, ands, or buts.
- The orchestra played and the audience applauded.

Q16) Reading (regular): Ask the subject to read each of these words aloud and show him/her the following five words. Shed; wipe; board; flame; bridge.

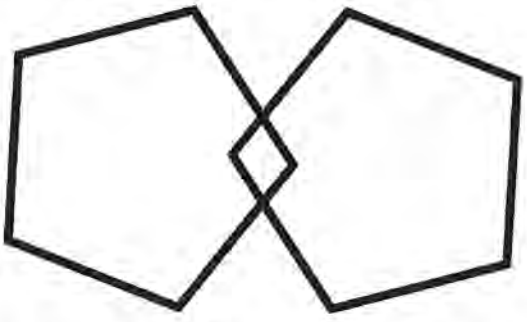
Q17) Reading (irregular): Ask the subject to read each of these words aloud and show him/her the following five words. Sew; pint; soot; dough; height.

Q18) Writing: Ask the subject to make up a sentence and write it down in the space below. If stuck suggest a topic e.g. weather, journey.

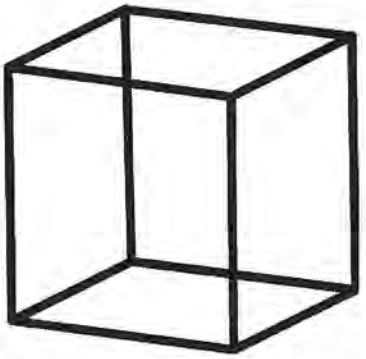
Q19) Now to check delayed recall ask the subject Can you tell me the name and address that I told you and that you practised at the beginning of the test.

VISUOSPATIAL ABILITIES

Q20) Overlapping pentagons: Show the subject the following figure and ask him/her to copy this diagram in the space provided next to it.



Q21) Wire cube: Show the subject the following figure and ask him/her to copy this diagram in the space provided next to it.



Q22) Clock: Ask the subject to draw a clock-face with numbers and the hands at ten past five.

Appendix I Hospital Anxiety and Depression Scale

Read each item and choose one response from the four given for each interview which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

1. I feel tense or "wound up."
   - Most of the time; a lot of the time; from time to time, occasionally; not at all.
2. I still enjoy the things I used to enjoy.
   - Definitely as much; not quite as much; only a little; hardly at all.
3. I get a sort of frightened feeling as if something awful is about to happen.
   - Very definitely and quite badly; yes, but not too badly; a little, but it doesn't worry me; not at all.
4. I can laugh and see the funny side of things.
   - As much as I always could; not quite so much now; definitely not so much now; not at all.
5. Worrying thoughts go through my mind.
   - A great deal of the time; a lot of the time; from time to time but not too often; only occasionally.
6. I feel cheerful.
   - Not at all; not often; sometimes; most of the time.
7. I can sit at ease and feel relaxed.
   - Definitely; usually; not often; not at all.
8. I feel as if I am slowed down.
   - Nearly all the time; very often; sometimes; not at all.
9. I get a sort of frightened feeling like "butterflies" in the stomach.
   - Not at all; occasionally; quite often; very often.
10. I have lost interest in my appearance.

- Definitely; I don't take so much care as I should; I may not take quite as much care; I take just as much care as ever.

11. I feel restless as if I have to be on the move.
    - Very much indeed; quite a lot; not very much; not at all.
12. I look forward with enjoyment to things.
    - As much as I ever did; rather less than I used to; definitely less than I used to; hardly at all.
13. I get sudden feelings of panic.
    - Very often indeed; quite often; not very often; not at all.
14. I can enjoy a good book or radio or TV program.
    - Often; sometimes; not often; very seldom.

Appendix J EuroQol

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

Self-Care

I have no problems with self-care

I have some problems washing or dressing myself

I am unable to wash or dress myself

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities

I have some problems with performing my usual activities

I am unable to perform my usual activities

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety/Depression

I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Appendix K SF-36

This questionnaire asks for your views about your health, how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is?
    - Excellent; very good; good; fair; poor.

2. Compared to one year ago, how would you rate your health in general now?
    - Much better now than one year ago.
    - Somewhat better now than one year ago.
    - About the same as one year ago.
    - Somewhat worse now than one year ago.
    - Much worse now than one year ago.

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
    - Yes limited a lot; yes limited a little; no not limited at all.

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

Lifting or carrying groceries

Climbing several flights of stairs

Climbing one flight of stairs

Bending, kneeling, or stooping

Waling more than a mile

Walking half a mile

Walking one hundred yards

Bathing or dressing yourself

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

- Yes; no.

Cut down on the amount of time you spent on work or other activities

Accomplished less than you would like

Were limited in the kind of work or other activities

Had difficulty performing the work or other activities (for example, it took extra effort)

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

- Yes; no.

Cut down on the amount of time you spent on work or other activities

Accomplished less than you would like

Didn't do work or other activities as carefully as usual

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

- Not at all; slightly; moderately; quite a bit; extremely.

4. How much bodily pain have you had during the past 4 weeks?

- No bodily pain; very mild; mild; moderate; severe.

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework?)

- Not at all; a little bit; moderately; quite a bit; extremely.

5. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

- All of the time; most of the time; a good bit of time; some of the time; a little of the time; none

Did you feel full of life?

Have you been a very nervous person?

Have you felt so down in the dumps that nothing could cheer you up?

Have you felt calm and peaceful?

Did you have a lot of energy?

Have you felt downhearted and low?

Did you feel worn out?

Have you been a happy person?

Did you feel tired?

10. During the past 4 weeks, how much of the time has you physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)

- All of the time; most of the time; a good bit of time; some of the time; a little of the time; none.

11. How TRUE or FALSE is each of the following statements for you?

- Definitely True; mostly true; don't know; mostly false; definitely false.

I seem to get ill more easily than other people

I am as healthy as anybody I know

I expect my health to get worse

My health is excellent

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