Effect of upper airway obstruction in acute stroke on functional outcome at 6 months

P M Turkington, V Allgar, J Bamford, P Wanklyn, M W Elliott

Background: The aim of this study was to determine whether upper airway obstruction occurring within the first 24 hours of stroke onset has an effect on outcome following stroke at 6 months. Traditional definitions used for obstructive sleep apnoea (OSA) are arbitrary and may not apply in the acute stroke setting, so a further aim of the study was to redefine respiratory events and to assess their impact on outcome.

Methods: 120 patients with acute stroke underwent a sleep study within 24 hours of onset to determine the severity of upper airway obstruction (respiratory disturbance index, RDI-total study). Stroke severity (Scandinavian Stroke Scale, SSS) and disability (Barthel score) were also recorded. Each patient was subsequently followed up at 6 months to determine morbidity and mortality.

Results: Death was independently associated with SSS (OR (95% CI) 0.92 (0.88 to 0.95), p<0.00001) and RDI-total study (OR (95% CI) 1.07 (1.03 to 1.12), p<0.01). The Barthel index was independently predicted by SSS (p=0.0001; r=0.259; 95% CI 0.191 to 0.327) and minimum oxygen saturation during the night (p=0.037; r=0.16; 95% CI 0.006 to 0.184). The mean length of the respiratory event most significantly associated with death at 6 months was 15 seconds (sensitivity 0.625, specificity 0.525) using ROC curve analysis.

Conclusion: The severity of upper airway obstruction appears to be associated with a worse functional outcome following stroke, increasing the likelihood of death and dependency. Longer respiratory events appear to have a greater effect. These data suggest that long term outcome might be improved by reducing upper airway obstruction in acute stroke.

METHODS

Subjects
One hundred and twenty patients admitted to one of three wards in the Leeds Teaching Hospitals NHS trust who had suffered a stroke in the previous 24 hours were invited to participate. Although stroke patients were admitted to other wards, patients refused participation. Although stroke patients were admitted to other wards, patients refused participation.

METHODS

Subjects
One hundred and twenty patients admitted to one of three wards in the Leeds Teaching Hospitals NHS trust who had suffered a stroke in the previous 24 hours were invited to participate. Although stroke patients were admitted to other wards, patients refused participation.

Abbreviations:
CPAP, continuous positive airway pressure; GCS, Glasgow Coma Scale; OSA, obstructive sleep apnoea; RDI, respiratory disturbance index; SDB, sleep disordered breathing; SSS, Scandinavian Stroke Scale; UAO, upper airway obstruction
wards during the recruitment period, they were excluded because stroke admissions to these wards were not frequent enough to ensure that nursing staff maintained their familiarity with the monitoring equipment used. Written consent was obtained from either the patient or their next of kin. Consent was sought as soon as possible after admission to the ward and the studies started directly thereafter. All patients admitted to the Leeds Teaching Hospitals NHS trust with stroke are registered on a database. We were therefore able to determine whether the sample studied was representative. The study was approved by the local ethics committee.

Baseline and follow up assessments

Strokes were classified into the four Oxford Community Stroke Project (OCSP) clinical subtypes. Stroke severity was graded using the Scandinavian Stroke Scale (SSS). The Glasgow Coma Scale (GCS) and limb weakness (Motricity index) were documented on admission, and disability was assessed using the Barthel index. A CT brain scan was performed in each patient in the first 72 hours to confirm the diagnosis and pathological type of stroke. Previous history of stroke was documented (if patients or their relatives recalled a prior event or a previous admission with stroke had been documented in the medical notes). The patients were followed up at 6 months by a researcher blinded to their initial sleep study to prevent observer bias. The length of hospital admission (defined as date of admission to date of discharge to permanent place of residence so any time spent in a rehabilitation ward or hospital was included as part of their stay) was recorded. A standard questionnaire was sent to each patient to be completed either by them or by their carer. If the questionnaire was not returned by 14 days a further questionnaire and letter were sent. If the questionnaire was still not returned 14 days later a telephone call was made to their place of residence and, if possible, the questionnaire completed over the telephone. Data from the questionnaire were used to calculate residual disability (Barthel index), place of residence (nursing home, residential home or own home), whether the patients described themselves as independent or dependent on other people’s help to carry out their daily tasks (dependency), and death.

Sleep studies

Studies were carried out using the Alice 4 sleep system (Respironics, Paris, France) and were started as soon as possible after admission and continued up to a total of 24 hours or until patients requested that the equipment be removed (each patient had at least 6 hours of data recorded during the night). Oronasal airflow (thermistor), heart rate (electrocardiogram), oxygen saturation (finger probe), abdominal and respiratory effort (strain gauge), snoring (microphone), body position (sensor detecting eight points of compass on thoracic strain gauge), and light intensity (light meter) were recorded. Each patient was studied in his or her own hospital bed and was not transported to the sleep laboratory. Usual nursing and physiotherapy practices were not altered during the study; in particular, the patient was positioned according to the usual ward protocol. Each study was individually scored by the same physician (PT) using standard criteria. An apnoea was defined as a 10 second cessation in airflow and a hypopnoea as a 50% reduction in airflow for 10 seconds associated with a 4% oxygen desaturation. Baseline oxygenation was defined as the oxygen saturation in the first minute of the study. Respiratory disturbance index was expressed in three different ways (1) per hour of study (RDI-total study), (2) during the night only (RDI-lights out), and (3) during the hour when UAO was at its most severe (RDI-worst hour).

Analysis of data

Statistical analysis of all data was performed with SPSS version 9.0 for Windows. Logistic and linear regression analyses were used to assess the factors independently associated with outcome. Several variables were entered into the equation including stroke characteristics, patient demographic data, and sleep study variables. This was then repeated for RDI-lights out and RDI-worst hour. ROC curves using mean length of apnoea were used to calculate the mean length of apnoea which best predicted the outcome following stroke.

RESULTS

Of the 120 patients who underwent the initial sleep study analysis (data from whom have already been published in a previous report and are summarised in table 1), full follow up data were obtained in all but six patients (two refused to fill in the questionnaire and four could not be traced, at least one of whom had moved out of the region). There were no significant differences in the age and sex of the study population and all of the patients admitted with stroke in Leeds during the study period. Frequent UAO was found in the study population (61% had RDI-total study >10 events/h; analysis of the night time only and worst hour data increased this further (81% had RDI-lights out >10 events/h and 92% had RDI-worst hour >10 events/h). The mean delay from estimated time of onset of symptoms of stroke until the start of the sleep study was 10 hours 50 minutes. (For patients who awoke with their stroke, estimated time of onset of symptoms was taken as 05.00 hours.) Initial sleep study data of the patients followed up at 6 months are shown in table 2. Most of the respiratory events were obstructive in nature; only 9% of patients had predominantly central apnoea. Baseline oxygen saturation (defined as mean oxygen saturation in the first 5 minutes of each study) was not significantly different in the patients who were alive (mean (SD) 94.4 (2.1)%) and those who had died (mean (SD) 94.3 (2.5)%) at 6 months. Table 3 illustrates the results of the 6 month follow up data and a comparison between patients with an RDI >10 and those with an RDI <10. Patients with frequent UAO (RDI >10) had a higher mortality rate and the survivors spent a longer time in hospital than those with RDI <10 (fig 1). Patients with an RDI <10 survived longer than those with an RDI >10.

Logistic regression analysis was used to predict mortality, dependency, and place of residence at 6 months. Linear regression was used to predict disability (Barthel index). Confounders such as stroke characteristics (SSS, subtype, GCS, limb weakness, and whether or not this was the first stroke), basic demographic data (age, body mass index, neck circumference, hypertension, diabetes), and oxygen saturation data (desaturation index, minimum oxygen saturation, and baseline oxygen saturation) were entered into the equation. Sleep study data were entered as a continuous

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**Table 1** Basic demographic data of study subjects

| All patients |%
|--------------|---
| Age (years)* |79.3 (10.6)
| Sex (% male)  |41.7%
| Glasgow Coma Scale† |15 (12–15)
| Limb weakness (Motricity index)† |104 (43.5–151)
| Barthel index on admission† |3 (0–9)
| First stroke (%) |73.3%
| Hypertensive (%) |35.8%
| Diabetic (%) |16.7%

*Mean (SD)
†Median (interquartile range)
Sleep disordered breathing and stroke

At 6 months. Furthermore, stroke patients with frequent UAO occurring within the first 24 hours after stroke is associated with a worse functional outcome, increasing the likelihood of death and dependency. The study has shown that UAO occurring within the first 24 hours after stroke is associated with death was 15 seconds (sensitivity 0.625, specificity 0.525).

DISCUSSION

The study has shown that UAO occurring within the first 24 hours after stroke is associated with a worse functional outcome, increasing the likelihood of death and dependency at 6 months. Furthermore, stroke patients with frequent UAO appeared to die sooner than those without UAO, and the surviving patients spent longer in hospital if they experienced UAO. We have previously shown that there is no correlation between stroke severity and severity of UAO, which would suggest that UAO is not just a marker of severe stroke. In addition, in this previous study other stroke characteristics (such as subtype and pharyngeal function), demographic factors (such as age and sex), and co-morbid medical conditions (such as hypertension and diabetes) also had no association with the presence of OSA following stroke.

The results would suggest that it is longer apnoeas and hypopnoeas that have the most deleterious effect. UAO occurring persistently throughout the night was a better predictor of outcome than short bursts of severe UAO.

The fact that UAO occurring within 24 hours of stroke affects the prognosis is not surprising, given the haemodynamic oscillations and fluctuations in oxygen saturation that accompany it. Blood pressure, pulse rate, cardiac output, and cerebral blood flow all decrease during obstructive apnoeas and hypopnoeas. At apnoea termination sudden increases in blood pressure, cardiac output, and pulse rate occur and are usually associated with a decrease in oxygen saturation. Neurological deterioration has been reported to occur in up to 43% of patients with stroke, 87% of which occurs within 48 hours. Iranzo et al have recently reported a link between this early neurological deterioration and SDB occurring within 24 hours of stroke onset, but were unable to demonstrate any association between the SDB and functional outcome 6 months after the stroke. However, their study differed from ours in several ways: their population was younger (mean (SD) age 66.8 (9.5) years), the severity of stroke appeared less (mean (SD) SSS 40 (13.5)), and they used full polysomnography. Two other studies have, however,

Table 2  Basic sleep study data

<table>
<thead>
<tr>
<th>All patients</th>
<th>RDI-total study (events/h)</th>
<th>RDI-lights out (events/h)*</th>
<th>RDI-worst hour (events/h)*</th>
<th>4% DI (desaturations per hour)</th>
<th>Time saturation (90% min)</th>
<th>Baseline oxygen saturation (%)</th>
<th>Snorers per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14.5 (7–25.3)</td>
<td>29.7 (13.5–40)*</td>
<td>42.5 (21.3–55.8)*</td>
<td>33 (10–70)</td>
<td>13.5 (4–55)</td>
<td>94.3 (2.2)</td>
<td>33 (8.2–54)</td>
</tr>
</tbody>
</table>

All values are expressed as median (IQR) except *mean (SD).

*Significant difference from RDI-total study assessed by Mann-Whitney tests.

RDI-total study = respiratory disturbance index per hour of study; RDI-lights out = respiratory disturbance index during the night only; RDI-worst hour = respiratory disturbance index during the hour when UAO was at its most severe; DI = desaturation index per hour of study.

Figure 1 Kaplan-Meier survival plot. Stroke patients with a respiratory disturbance index (RDI) of <10 had significantly longer survival times than those with an RDI of >10 (p<0.04).

Table 3  Results of 6 month follow up

<table>
<thead>
<tr>
<th>All patients</th>
<th>RDI &lt;10</th>
<th>RDI &gt;10</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in hospital in survivors (days)*</td>
<td>25 (10–64)</td>
<td>24 (10–39)</td>
<td>43 (15–71)</td>
</tr>
<tr>
<td>Stroke severity (SSS)</td>
<td>30 (16–42)</td>
<td>30 (16–43)</td>
<td>30 (18–41)</td>
</tr>
<tr>
<td>Barthel index*</td>
<td>1.5 (0–13.5)</td>
<td>1.5 (0–14.25)</td>
<td>2 (0–11.75)</td>
</tr>
<tr>
<td>Mortality (% dead)</td>
<td>36.7</td>
<td>25</td>
<td>45.2</td>
</tr>
<tr>
<td>Dependency (% “independent”)</td>
<td>16.7</td>
<td>18.1</td>
<td>16.3</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing home (%)</td>
<td>15.8</td>
<td>14.9</td>
<td>16.4</td>
</tr>
<tr>
<td>Own home (%)</td>
<td>29.2</td>
<td>32.9</td>
<td>23.4</td>
</tr>
</tbody>
</table>

*Median (interquartile range, IQR).
†Significance tested by *y* tests except those marked with an asterisk which are tested by Mann-Whitney U tests.
RDI = respiratory disturbance index, SSS = Scandinavian Stroke Scale.

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suggested that there is an association between SDB and snoring following stroke and a worse functional outcome. However, neither assessed the first 24 hour period following snoring following stroke and a worse functional outcome. SDB suggested that there is an association between SDB and predicting outcome than the traditional 10 second cut off. The traditional definitions of apnoeas and hypopnoeas as cut off for apnoeas or hypopnoeas would be better at ROC curve analysis in this study suggested that a 15 second decrease of at least 4% are arbitrary, as previously discussed. For example, chronic obstructive pulmonary disease or congestive heart failure may therefore be effective treatment and might be easier to implement than conventional CPAP aimed at abolishing all events in blood pressure, cerebral blood flow, and oxygen saturation. Non-invasive CPAP titration night continued to use CPAP after discharge from hospital. CPAP therapy just aimed at preventing more severe UAO (possibly with lower and therefore better tolerated pressures) and hence larger swings in blood pressure, cerebral blood flow, and oxygen saturation rather than conventional CPAP aimed at abolishing all events may therefore be effective treatment and might be easier to implement in acute stroke.

This study addresses two important issues. It has confirmed that persistent UAO throughout the night is the best predictor of outcome and that UAO occurring during the day has little additive effect is also interesting. Although this may have been biased by the fact that, in our study, 80% of patients were admitted in the evening and therefore their day has little additive effect is also interesting. Although this may have been biased by the fact that, in our study, 80% of patients were admitted in the evening and therefore their studies were started between 20.00 and 22.00 hours, suggesting that the night time UAO had more effect simply because it occurred earlier in the ischaemic penumbra. However, if this was a true effect, it would suggest that treatment should be targeted during the night and that using CPAP during daytime naps may not be essential.

This study addresses two important issues. It has confirmed that UAO—which is known to be common within the first 24 hours of stroke and to be associated with haemodynamic oscillation and oxygen saturation fluctuation—is associated with a worse functional outcome following stroke at 6 months, both in terms of morbidity and mortality. It has also shown that it is longer respiratory events and deeper oxygen desaturations occurring particularly at night that have the greatest detrimental effect. Several key issues now remain and need further investigation. Treatment of UAO in the acute stroke setting should be considered with the aim of determining whether it can improve functional outcome. CPAP is the “gold standard” treatment of OSA, but consideration should be given to how it is delivered (either

### Table 4 Logistic regression analysis results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Significance</th>
<th>Odds ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.0001</td>
<td>0.92</td>
<td>0.88</td>
<td>0.95</td>
</tr>
<tr>
<td>RDI-total study</td>
<td>0.001</td>
<td>1.07</td>
<td>1.03</td>
<td>1.12</td>
</tr>
<tr>
<td>Dependency</td>
<td>0.0001</td>
<td>0.9</td>
<td>0.86</td>
<td>0.95</td>
</tr>
<tr>
<td>RDI-total study</td>
<td>0.009</td>
<td>1.06</td>
<td>1.01</td>
<td>1.11</td>
</tr>
<tr>
<td>Nursing home</td>
<td>0.0001</td>
<td>0.9</td>
<td>0.88</td>
<td>0.94</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>1.06</td>
<td>1.01</td>
<td>1.11</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>0.04</td>
<td>1.02</td>
<td>1.001</td>
<td>1.03</td>
</tr>
</tbody>
</table>

Significant variables are shown after controlling for confounding variables such as stroke subtype, Glasgow Coma Score (GCS), limb weakness, whether or not this was the first stroke, age, body mass index, neck circumference, hypertension, and diabetes.

*OR for every 1 unit increase in variable (that is, estimated risk of death increases by 1.07 for every 1 unit increase in RDI or decreases by 0.92 for every 1 unit increase in SSS).*
fixed pressure or autotitration) and at what pressure. It may be that elderly patients with acute stroke will find CPAP difficult to tolerate, but this study suggests that, even if it is not possible to eliminate all obstructive respiratory events, then at least preventing longer events—and hence more severe haemodynamic oscillations and oxygen desaturations—may be effective in improving outcome.

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