Influence of Continuous Positive Airway Pressure on Outcomes of Rehabilitation in Stroke Patients With Obstructive Sleep Apnea

Clodagh M. Ryan, MD; Mark Bayley, MD; Robin Green, PhD; Brian J. Murray, MD; T. Douglas Bradley, MD

Background and Purpose—In stroke patients, obstructive sleep apnea (OSA) is associated with poorer functional outcomes than in those without OSA. We hypothesized that treatment of OSA by continuous positive airway pressure (CPAP) in stroke patients would enhance motor, functional, and neurocognitive recovery.

Methods—This was a randomized, open label, parallel group trial with blind assessment of outcomes performed in stroke patients with OSA in a stroke rehabilitation unit. Patients were assigned to standard rehabilitation alone (control group) or to CPAP (CPAP group). The primary outcomes were the Canadian Neurological scale, the 6-minute walk test distance, sustained attention response test, and the digit or spatial span-backward. Secondary outcomes included Epworth Sleepiness scale, Stanford Sleepiness scale, Functional Independence measure, Chedoke McMaster Stroke assessment, neurocognitive function, and Beck depression inventory. Tests were performed at baseline and 1 month later.

Results—Patients assigned to CPAP (n=22) experienced no adverse events. Regarding primary outcomes, compared to the control group (n=22), the CPAP group experienced improvement in stroke-related impairment (Canadian Neurological scale score, P<0.001) but not in 6-minute walk test distance, sustained attention response test, or digit or spatial span-backward. Regarding secondary outcomes, the CPAP group experienced improvements in the Epworth Sleepiness scale (P<0.001), motor component of the Functional Independence measure (P=0.05), Chedoke-McMaster Stroke assessment of upper and lower limb motor recovery test of the leg (P=0.001), and the affective component of depression (P=0.006), but not neurocognitive function.

Conclusions—Treatment of OSA by CPAP in stroke patients undergoing rehabilitation improved functional and motor, but not neurocognitive outcomes.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00221065. (Stoke. 2011;42:1062-1067.)

Key Words: continuous positive airway pressure ■ functional outcomes ■ neurocognitive outcomes ■ obstructive sleep apnea ■ stroke

The incidence of stroke and its consequent burden of morbidity and mortality remain unacceptably high. If outcomes from stroke are to improve, then the underlying mechanisms of functional impairment will need to be addressed. One contributing factor may be obstructive sleep apnea (OSA).

Cross-sectional and prospective epidemiological data indicate that OSA is associated with increased risk of having a stroke independently of other risk factors.1-3 Compared to the general population,4 stroke patients have a 4- to 6-fold higher prevalence of OSA.5,6 In the poststroke period, patients with OSA have greater functional impairment and higher mortality than patients without OSA.6,7 These data suggest that OSA both increases the risk of stroke and, in the poststroke period, exacerbates the degree of disability as well as the risk of death. It is therefore possible that treatment of coexisting OSA might improve recovery from stroke. Accordingly, we performed a randomized controlled trial in stroke patients with OSA during their inpatient stroke rehabilitation to determine if treatment with continuous positive airway pressure (CPAP) would improve functional, motor, and neuropsychological outcomes over a 4-week period.

Subjects and Methods

Study Design
This was a randomized, open label, parallel group trial with blind assessment of outcomes performed at the stroke rehabilitation unit of the Toronto Rehabilitation Institute.

Received August 12, 2010; accepted November 23, 2010.
From the Toronto Rehabilitation Institute (C.M.R., M.B., R.G., B.J.M., T.D.B.) and the Centre for Sleep Medicine and Circadian Biology (C.M.R., B.J.M., T.D.B.), University of Toronto, Ontario, Canada; the Department of Medicine (C.M.R., T.D.B.), Toronto General Hospital of the University Health Network and Sunnybrook Health Sciences Centre (B.J.M.), Toronto, Ontario, Canada.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.597468/DC1.

Correspondence to Clodagh M. Ryan, MD, 9N-967, Toronto General Hospital, 585 University Avenue, Toronto, Ontario, M5G 2N2. E-mail clodagh.ryan@uhn.on.ca

© 2011 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.110.597468
Subjects
Eligible patients were those admitted from acute care facilities to the stroke rehabilitation unit within 3 weeks of stroke onset with the following inclusion criteria: (1) 18 to 89 years of age; (2) completed ischemic or hemorrhagic stroke confirmed by a neurologist based on history of sudden onset of a neurological deficit lasting ≥24 hours, neurological deficit on physical examination, and brain lesion compatible with the neurological deficit on computerized tomography or MRI; (3) ability to follow simple commands in English; (4) competency to provide informed consent; and (5) OSA on an overnight attended polysomnogram (PSG) as described. Exclusion criteria were: (1) brain stem strokes that could increase aspiration risk while using CPAP; (2) previously diagnosed OSA on therapy; (3) concomitant central nervous system diseases such as dementia; (4) history of psychosis; (5) traumatic brain injury; and (6) anosagnosia, global, or Wernicke aphasia.

The study was approved by the Research Ethics Board of the Toronto Rehabilitation Institute and all subjects provided written consent before participation.

Baseline Assessments
Clinical classification of strokes was performed according to the Oxfordshire Community Stroke Project criteria.8 Eligible patients underwent a clinical assessment followed by an overnight PSG. PSG were performed using standard techniques and scoring criteria for sleep stages and arousals from sleep.9,10

The frequency of apneas and hypopneas per hour of sleep was expressed as the apnea–hypopnea index. Patients with an apnea–hypopnea index of ≥15 were classified as having sleep apnea for the purpose of this study. OSA was diagnosed when at least 80% of the respiratory events were obstructive.

Subjects with OSA then completed the functional, motor, and neuropsychological assessments between 2:00 and 5:00 pm administered by individuals blinded to subject randomization. To take the heterogeneity of stroke-related impairment into account, we evaluated several domains as our primary outcomes, including stroke severity by the Canadian Neurological scale, motor function by the 6-minute walk test, neurocognitive function by sustained attention to response test (a measure of vigilance), and the digit or spatial span-backward (a measure of executive function). Secondary outcomes included the Functional Independence measure (FIM), Chedoke-McMaster Stroke assessment of upper and lower limb motor recovery test, hand-grip strength, Berg Balance scale, Epworth Sleepiness scale (ESS), Stanford Sleepiness scale (SSS), the Purdue Pegboard test and the Beck depression inventory-1 (BDI). Please see http://stroke.ahajournals.org for additional information.

Randomization
Eligible patients were randomly assigned by a computer-generated randomization schedule in random blocks of 2 and 4, with allocation concealment by opaque, sequentially numbered, sealed envelopes to alternate groups for the primary outcomes at a 2-tailed α of 0.05. Outcomes were analyzed by the original assigned groups. Differences in the outcome variables, from baseline to follow-up, were compared within and between groups by analysis of covariance with post hoc analyses as appropriate. Test scores on psychometric data were transformed to a common metric (z scores) and aggregate scores were created.11 P<0.05 was considered statistically significant. Continuous data are expressed as means±SD unless otherwise indicated.

Results

Characteristics of the Subjects
Progress of subjects through the trial is illustrated in Figure 1. Between June 2005 and March 2008, 466 patients with strokes admitted to the stroke rehabilitation unit were screened. Exclusions were mainly attributable to language barriers. One-hundred ninety-four met initial inclusion criteria, and 103 agreed to PSG. Of these, 48 (47%) had OSA with an apnea–hypopnea index ≥15. One patient in the control group and 3 in the CPAP group left the study before trial completion; thus, outcome data were available for 22 patients in each group for analysis by originally assigned group. Stroke location and type (Table 1) and time from occurrence of the stroke to entry into the study were similar in the control and CPAP groups (19.7±16.8 days versus 21.5±8.7 days; P=0.41).

Baseline data were similar in the control and CPAP groups, except more subjects in the control group had a history of smoking (Table 1). The Canadian Neurological scale and FIM scores were also similar in the 2 groups, indicating comparable functional impairment (Table 3). The ESS and SSS were similar in the 2 groups and were within normal limits, indicating a lack of subjective sleepiness (Table 2).
Table 1. Baseline Characteristics of the Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (n=22)</th>
<th>CPAP (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60.7±10.3</td>
<td>62.8±12.8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>19/3</td>
<td>16/6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.3±5.8</td>
<td>28.8±5.3</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>11 (50)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (68.2)</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>17 (77.3)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (31.8)</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>2 (9.1)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>1 (4.6)</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>4 (18.2)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Total ischemic strokes, n</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total hemorrhagic strokes, n</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>PACI</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>LACI</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>TACI</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>POCl</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Right/ left brain, n</td>
<td>6/16</td>
<td>9/13</td>
</tr>
<tr>
<td>Right/ left handedness, n</td>
<td>18/4</td>
<td>22/0</td>
</tr>
</tbody>
</table>

Values are mean±SD or % as indicated.

CPAP indicates continuous positive airway pressure; LACI, lacunar infarction; PACI, partial anterior circulation infarct; POCl, posterior circulation infarct; TACI, total anterior circulation infarct.

Sleep variables were similar in both groups. No adverse events were recorded during the study.

Effects of CPAP on Sleep Variables

Among those randomized to CPAP who completed the trial, CPAP usage averaged 4.96±2.25 hours per day at a mean pressure of 8.1±0.5 cm H₂O. There were no adverse effects of CPAP. Compared to the control group, the CPAP-treated group showed significant improvements in the apnea–hypopnea index, as well as an increase in minimum sleep oxyhemoglobin saturation. Mean oxyhemoglobin saturation also improved within the CPAP group (Table 2). However, there were no improvements in sleep structure in either group.

Physiotherapy

Time per day spent in physiotherapy and participation scores did not differ between the control and CPAP groups (control: 45±13 versus 45±9 minutes per day and P=0.97; CPAP: 5.2±0.8 versus 5.4±0.7 and P=0.30).

Primary Outcomes

The CPAP group experienced significant improvements in the total Canadian Neurological scale score and its cognitive and motor components that were greater than in the control group (Table 3). There was a significant increase in the 6-minute walk distance (113 meters) in the CPAP group, but not in the control group (46 meters). However, the between-group difference was not significant. The CPAP group did not experience a significant improvement in sustained attention/vigilance on the sustained attention to response test but did show a significant improvement in digit span and visual spatial span-backward, not seen in the control group, although the between-group difference was not significant (Table 4).

Secondary Outcomes

There were significant reductions in the ESS and SSS in the CPAP compared to the control group (Table 2). There were also significant improvements in the FIM and Berg Balance scale within both groups; however, these did not differ significantly between them. Separate analysis of the motor and cognitive components of the FIM revealed a significantly greater improvement in the motor, but not the cognitive, component in the CPAP than in the control group. The Chedoke-McMaster Stroke Assessment scale demonstrated significant improvements in the arm, hand, leg, and foot function.

Table 2. Sleep Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>4.5±2.1</td>
<td>4.5±2.2</td>
<td>0.94</td>
<td>4.4±1.8</td>
<td>1.8±1.0</td>
<td>0.0001&lt;0.0001</td>
</tr>
<tr>
<td>SSS</td>
<td>2.5±1.3</td>
<td>2.0±1.0</td>
<td>0.06</td>
<td>2.2±1.1</td>
<td>1.3±0.6</td>
<td>0.005 0.05</td>
</tr>
<tr>
<td>AHI, n/hr</td>
<td>33.3±16.4</td>
<td>30.3±17.5</td>
<td>0.60</td>
<td>38.5±18.1</td>
<td>7.6±8.5</td>
<td>0.0001&lt;0.0001</td>
</tr>
<tr>
<td>TST, hr</td>
<td>6.30±0.90</td>
<td>5.82±1.77</td>
<td>0.27</td>
<td>5.66±1.15</td>
<td>5.83±1.01</td>
<td>0.63 0.89</td>
</tr>
<tr>
<td>S1, %</td>
<td>9.5±5.4</td>
<td>9.3±4.8</td>
<td>0.92</td>
<td>8.6±5.6</td>
<td>8.2±6.5</td>
<td>0.84 0.70</td>
</tr>
<tr>
<td>S2, %</td>
<td>61.3±9.1</td>
<td>54.4±12.4</td>
<td>0.06</td>
<td>60.3±8.7</td>
<td>59.7±9.9</td>
<td>0.84 0.17</td>
</tr>
<tr>
<td>SWS, %</td>
<td>12.2±6.6</td>
<td>17.1±13.0</td>
<td>0.13</td>
<td>14.1±9.5</td>
<td>14.8±7.6</td>
<td>0.80 0.36</td>
</tr>
<tr>
<td>REM, %</td>
<td>16.9±8.9</td>
<td>19.2±7.2</td>
<td>0.40</td>
<td>17.4±6.3</td>
<td>17.3±7.4</td>
<td>0.97 0.53</td>
</tr>
<tr>
<td>ArI, n/hr</td>
<td>25.5±12.8</td>
<td>26.2±14.4</td>
<td>0.87</td>
<td>28.6±22.0</td>
<td>18.8±13.4</td>
<td>0.09 0.10</td>
</tr>
<tr>
<td>Mean sleep SaO₂, %</td>
<td>95.5±1.8</td>
<td>95.5±1.4</td>
<td>0.94</td>
<td>94.4±1.6</td>
<td>96.0±1.6</td>
<td>0.003 0.26</td>
</tr>
<tr>
<td>Minimum sleep SaO₂, %</td>
<td>79.6±11.3</td>
<td>79.4±15.7</td>
<td>0.97</td>
<td>80.7±5.7</td>
<td>90.9±3.4</td>
<td>0.0001 0.005</td>
</tr>
</tbody>
</table>

Values are mean±SD.

AHI indicates apnea–hypopnea index; ArI, arousal index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness scale; REM, rapid eye movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; SaO₂, oxyhemoglobin saturation; SSS, Stanford Sleepiness scale; SWS, slow wave sleep; TST, total sleep time.

*Between-group differences by analysis of covariance adjusted for age and sex.
scores within both groups, and a significantly greater improvement in the leg score in the CPAP than in the control group. There was no within-group or between-group difference in the ratio of hand-grip strength between the affected and nonaffected hand in either group (Table 3). CPAP had no significant effect on visuo-motor speed and hand dexterity as assessed by the Purdue Pegboard score or in mental efficiency on the digit and visual spatial span-forward (Table 4). There was no significant reduction in the total BDI in either the control group (13.3±1.9 to 11.8±1.5; P=0.72) or in the CPAP group (12.6±1.9 to 11.8±1.5; P=0.7). The same result was true for the somatic component of the BDI. However, there was a significant reduction in the affective component of the BDI in the CPAP compared to the control group (7.4±1.9 to 7.2±1.5; P=0.001).

Discussion
This randomized trial involving stroke patients with OSA undergoing inpatient rehabilitation has demonstrated that, compared to the control group, CPAP usage was associated with improvement in the overall severity of stroke-related impairment manifest by a greater improvement in one of the primary outcomes, the Canadian Neurological Scale score. Although there were improvements in some of the other primary outcomes within the CPAP group, including mobility assessed by 6-minute walk test distance and neurocognitive capacity assessed by the digit/spatial span-backward, these were not statistically significant compared to the control group. There was no within-group or between-group improvement in vigilance assessed by the sustained attention response test score. CPAP usage was also associated with improvements in 5 of the secondary outcomes compared to the control group, including the motor component of the FIM, Chedoke-McMaster Stroke Assessment leg score, ESS, SSS, and the affective component of the BDI. Taken together, these results indicate a significant, although modest, beneficial effect of CPAP on stroke-related outcomes.

Table 3. Functional and Motor Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control (N=22)</th>
<th>CPAP (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Month</td>
</tr>
<tr>
<td>Canadian Neurological scale, total</td>
<td>7.7±1.9</td>
<td>8.4±1.5</td>
</tr>
<tr>
<td>Canadian Neurological scale, cognitive</td>
<td>4.6±0.2</td>
<td>4.6±0.2</td>
</tr>
<tr>
<td>Canadian Neurological scale, motor</td>
<td>3.1±1.9</td>
<td>3.8±1.5</td>
</tr>
<tr>
<td>Functional Independence measure, total</td>
<td>85.8±17.7</td>
<td>105.8±13.9</td>
</tr>
<tr>
<td>Functional Independence measure, cognitive</td>
<td>23.4±7.1</td>
<td>26.6±7.4</td>
</tr>
<tr>
<td>Functional Independence measure, motor</td>
<td>62.5±15.1</td>
<td>79.2±13.8</td>
</tr>
<tr>
<td>Chedoke-McMaster Stroke Assessment scale</td>
<td>Arm</td>
<td>4.3±1.9</td>
</tr>
<tr>
<td></td>
<td>4.0±1.7</td>
<td>4.7±1.6</td>
</tr>
<tr>
<td></td>
<td>4.1±1.0</td>
<td>4.5±1.1</td>
</tr>
<tr>
<td></td>
<td>3.8±1.3</td>
<td>4.3±1.3</td>
</tr>
<tr>
<td></td>
<td>28.2±17.5</td>
<td>44.3±11.3</td>
</tr>
<tr>
<td></td>
<td>270±236</td>
<td>316±178</td>
</tr>
<tr>
<td></td>
<td>0.48±0.46</td>
<td>0.61±0.58</td>
</tr>
</tbody>
</table>

Scale ranges: Canadian Neurological scale total, 1.5–11.5; Functional Independence measure total, 18–126; Chedoke-McMaster Stroke Assessment scale, 1–7; Berg Balance scale, 0–56.
CPAP indicates continuous positive airway pressure.
*Between-group differences by analysis of covariance.
†n=16 control and n=16 CPAP.

Table 4. Neuropsychological Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control (n=20)</th>
<th>CPAP (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>SART, total n of false-positive errors</td>
<td>12±7</td>
<td>11±7</td>
</tr>
<tr>
<td>SART, mean RT in the 4 trials just before a false press</td>
<td>484±121</td>
<td>433±141</td>
</tr>
<tr>
<td>Purdue Pegboard, dominant hand score</td>
<td>30±12</td>
<td>36±15</td>
</tr>
<tr>
<td>Purdue Pegboard, nondominant hand score</td>
<td>35±15</td>
<td>40±15</td>
</tr>
<tr>
<td>Purdue Pegboard, affected hand score</td>
<td>30±12</td>
<td>37±16</td>
</tr>
<tr>
<td>Digit+visual spatial span-forward</td>
<td>44±33</td>
<td>41±30</td>
</tr>
<tr>
<td>Digit+visual spatial span-backward</td>
<td>40±36</td>
<td>45±36</td>
</tr>
</tbody>
</table>

CPAP indicates continuous positive airway pressure; RT, reaction time; SART, sustained attention response time.
*Analysis of covariance adjusted for age and sex.
The most prominent beneficial effects of CPAP therapy involved motor and functional outcomes. These included improvements in the motor components of the Canadian Neurological scale, FIM, and the leg motor component of the Chedoke-McMaster Impairment scale. These improvements were greater than those observed in the control group and were accompanied by a significant increase in 6-minute walking distance within the CPAP group. Since impaired motor function of the leg is a major limitation to stroke recovery because it limits functional independence, these findings suggest that treatment of coexisting OSA by CPAP in stroke patients could improve functional independence and hasten return to community living.

ESS and SSS scores were within normal limits at baseline, indicating that patients were not hypersomnolent, consistent with the study by Arzt et al. Nevertheless, treatment of OSA by CPAP caused reductions in ESS and SSS scores, even though it did not improve sleep structure, vigilance as assessed by the sustained attention to response test, or participation in physiotherapy. Thus, CPAP-related improvements in functional and motor outcomes could not be attributed to a reduction in hypersomnolence, because subjects were not hypersomnolent at onset of rehabilitation, or to increased physiotherapy participation.

CPAP had marginal, if any, effects on the cognitive outcomes that were assessed. For example, although there was a significant improvement in digit and visual span-backward within the CPAP group, suggesting improvement in executive functioning, there were no improvements in sustained vigilance, attention span, and visuo-motor speed and dexterity, as tested by the sustained attention to response test, digit and visual span-forward, and Purdue Pegboard, respectively.

With respect to depression, compared to the control group, the CPAP group experienced a significant improvement in the affective, but not the somatic, component of the BDI. The former is a better index of mood after stroke, because the somatic component of the BDI is confounded by items that are also sensitive to the direct physiological effects of stroke (eg, loss of appetite). After a stroke, 25% to 40% of patients experience depression, which is associated with worse neurological recovery and increased mortality. Therefore, reductions in poststroke depression may contribute to neurological recovery.

An important aspect of our trial was that only 3 (12%) patients randomized to CPAP left the study. For the remaining 22 people who completed the trial, CPAP compliance was excellent, with average daily use of 4.96 hours (considering total sleep times were ~5.60 hours). This excellent compliance is most likely because our subjects were inpatients during the entire trial period, and because nurses were trained to administer CPAP to study subjects.

The mechanisms by which CPAP achieved beneficial effects on motor and functional, but not neurocognitive, outcomes are not clear. CPAP-induced abolition of intermittent hypoxia and negative intrathoracic pressure swings should increase cerebral blood flow and oxygen delivery. Accordingly, functional and motor improvements in the CPAP-treated group may have been attributable to alleviation of the adverse cerebrovascular effects of OSA, possibly through enhanced neuroplasticity.

Two other randomized trials evaluated the response of stroke patients with OSA to CPAP. Sandberg et al studied inpatients over a 1-month period. Subjects had good fixed-pressure CPAP compliance of 4.1 hours per night. However, the only improvement in the CPAP-treated group was a reduction in severity of depression. Several differences between that study and ours could account for apparent differences in outcomes. For instance, their patients were 18 years older, 50% had heart failure, sleep apnea was predominantly central, and there were no evaluations of sleep structure, alertness, or motor and neuropsychological functions.

The study by Hsu et al was similar to ours in that subjects predominantly had OSA and underwent assessments of subjective sleepiness, functional, and stroke severity outcomes. Their study differed from ours in that subjects were 14 years older, had more severe OSA, and did not undergo assessment of sleep structure by PSG or assessment of alertness, motor, or neuropsychological function. Subjects were studied over a longer period (6 months) and auto-titrating CPAP was used, with very poor compliance (1.4 hours per night). The negative results of that study therefore were likely attributable to poor CPAP compliance.

The heterogenous nature of neurological damage and stroke etiology makes evaluation of clinical interventions difficult. We took this into account by assessing the effects of treating OSA on various aspects of stroke outcome in different domains. Nevertheless, the present trial was subject to some limitations. Forty-two percent of patients were not eligible for the study, primarily because of lack of fluency in English. This, coupled with the small sample size, and inability to evaluate the effect of stroke subtype, affected vessel size, and lateralization make it difficult to know whether the results apply to the general stroke population. Recovery from stroke may evolve over several months and the 1-month follow-up may not have been sufficient to evaluate the extent and duration of stroke recovery while using CPAP or to assess its effects once subjects left the hospital.

Conclusions
In conclusion, this randomized trial demonstrated that treatment of OSA by CPAP in stroke patients undergoing rehabilitation was associated with significant improvements in functional and motor outcomes as well as mood. Functional and motor impairments are often the most disabling features of stroke because they limit mobility and activities of daily living. Although our findings suggest that treating OSA in stroke patients improves these outcomes, larger longer-term trials are needed to determine whether such improvements can persist or evolve further over longer periods.

Acknowledgments
The authors thank Dr William McIlroy for his expert opinion and access to facilities for the performance of motor tests.
Sources of Funding
Supported by an operating grant from the Physicians Service Incorporated Foundation, Ontario, Canada.

Disclosures
Tyco Health Care provided CPAP devices for the trial. Provision of ASV devices for investigator-initiated trial with Canadian Institutes of Health Research (to D.B. and C.R.).

References
Influence of Continuous Positive Airway Pressure on Outcomes of Rehabilitation in Stroke Patients With Obstructive Sleep Apnea

Clodagh M. Ryan, Mark Bayley, Robin Green, Brian J. Murray and T. Douglas Bradley

*Stroke*. 2011;42:1062-1067; originally published online March 3, 2011;
doi: 10.1161/STROKEAHA.110.597468

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/42/4/1062

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/03/11/STROKEAHA.110.597468.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/
Influence of Continuous Positive Airway Pressure on Outcomes of Rehabilitation in Stroke Patients with Obstructive Sleep Apnea.

SUPPLEMENTAL MATERIAL
Supplemental Methods:

Baseline Assessments

Upon enrollment, demographic characteristics, stroke risk factors (history of hypertension, coronary artery disease, heart failure, atrial fibrillation, diabetes mellitus, hypercholesterolemia, and cigarette smoking) handedness, height, weight and body mass index were determined for each patient. All medications used were recorded. The treating physicians prescribed appropriate secondary stroke prevention medications such as anticoagulants, antiplatelet agents, and antihypertensive agents, as per the accepted standard of care, to provide optimum therapy. Otherwise, medications were not altered during the study except as medically indicated. Eligible patients were those admitted from acute care facilities to the SRU within 3 weeks of stroke onset with the following inclusion criteria: 1) 18 to 89 years of age; 2) completed ischemic or hemorrhagic stroke confirmed by a neurologist based on: a) history of sudden onset of a neurological deficit lasting more than 24 hours, b) neurological deficit on physical examination, and c) brain lesion compatible with the neurological deficit on computerized tomography or magnetic resonance imaging of the brain; 3) able to follow simple commands in English based upon the speech therapist’s assessment, 4) competent to provide informed consent to participate in the study; and 5) OSA on an overnight attended PSG as described below. Exclusion criteria were: 1) brainstem strokes that could increase aspiration risk while on CPAP, 2) patients with previously diagnosed OSA on therapy, 3) concomitant central nervous system diseases such as dementia, Parkinson’s disease, multiple sclerosis or Huntington’s disease, 4) history of psychosis, 5) traumatic brain injury; and 6) anosagnosia, global aphasia or Wernicke’s aphasia.

Protocol

Subjects with OSA completed the functional, motor and neuropsychometric and outcome assessments. All these tests were performed in a quiet environment using standard protocols between 2 and 5 pm. All assessments were performed by individuals blinded to randomization of the subjects. Assessment of functional and motor outcomes was performed by occupational and physio-therapists, respectively. Neuropsychometric testing and subjective assessment of mood and sleepiness were administered by trained neuropsychometrists and a research assistant, respectively.

Sample Size Estimation

The study was based on 4 primary outcome measures which were SART, digit span/spatial span-backwards, 6-minute walk test and the Canadian Neurological Scale (CNS). For all of these tests we want to detect a difference between the control and CPAP treated groups equivalent to 1 SD around the mean of normative data, because in clinical terms, this represents the difference between normal function and mild impairment, or mild to moderate impairment, or moderate to severe impairment. We also assumed that because we are examining several primary outcomes, that the power of the test should be 90%, rather than the usual 80% to avoid the potential for type II errors.

For SART and digit span/spatial span backwards, at a 2-tailed alpha of 0.05 and power of 90%, a sample size of 22 subjects per group with complete data was estimated. For the 6-minute walk...
test, the sample size required to detect a clinically meaningful change of 52 meters with a two-tailed alpha of 0.05 and power of 90% was 16 per group. For the Canadian Neurological Scale, to detect a clinically important change at a 2-tailed alpha of 0.05 and power of 90%, a sample size of 13 subjects per group was estimated. Therefore, we required 22 subjects in each group to complete the trial. The trial was stopped upon reaching the prespecified group numbers.

**Randomization**

A computer-generated equal randomization schedule with a randomly varying block size of 2 to 4 was created to ensure equal numbers of subjects in each group. The statistician then enclosed the randomization codes in opaque sealed and stapled envelopes in sequence. These numbered envelopes were opened in sequence by a research assistant, once the subjects had completed all baseline assessments. The control group received standard stroke occupational and physiotherapy for the duration of the trial. The treatment group received standard stroke occupational and physiotherapy and in addition, received CPAP for their OSA. Personnel blind to the patients’ treatment allocation performed assessments and also analyzed and interpreted the data.

**CPAP**

CPAP was titrated during an overnight PSG to a pressure that reduced the AHI to < 5 or to the highest pressure tolerated. Patients were then provided with a CPAP machine (Tyco Healthcare, Goodnight 420G) and instructed to use it for at least 6 hours per night until the end of the trial. Night nursing staff were instructed how to apply CPAP to patients unable to apply it on their own, and assisted patients in reapplying it at night if they removed it for any reason. Compliance with CPAP was recorded automatically with a meter that records mask-on time.

**Details of Tests**

**PSG**

Routine PSGs were performed using standard techniques and scoring criteria for sleep stages and arousals from sleep {Iber C, 2007 #86; Rechtschaffen, 1968 #18}. Thoracoabdominal movements and their electronic sum were monitored by respiratory inductance plethysmograph (RIP) (Respitrace; Ambulatory Monitoring Inc., White Plains, NY) \(^1\). Arterial oxygen saturation (SaO\(_2\)) was continuously monitored by a pulse oximeter (Nellcor, Puritan Bennett, LLC). Apneas were defined as an absence of excursion of the RIP sum channel for at least 10 seconds and were classified as obstructive or central in the presence or absence of thoracoabdominal motion, respectively. Hypopneas were defined as a 50% or greater reduction in the RIP sum channel for at least 10 seconds and were classified as obstructive if there was out-of-phase thoracoabdominal motion on RIP, and as central if thoracoabdominal motion was in-phase. The frequency of apneas and hypopneas per hour of sleep was expressed as the apnea-hypopnea index (AHI). Patients with an AHI of \(\geq 15\) were classified as having sleep apnea for the purpose of this study. OSA was diagnosed when at least 80% of the respiratory events were obstructive.

**Stanford Sleepiness Scale (SSS)**

This is a Likert-type 7-point scale in which each point has a descriptive label, ranging from 1 – ‘feeling active and vital; alert; wide awake’, to 7 – ‘almost in reverie; sleep onset soon; lost struggle to remain awake.’ Subjects are asked to select the number that they feel most accurately
describes their level of alertness/sleepiness at that moment. The SSS has been found to be sensitive to changes in alertness due to both circadian variations and sleep loss. SSS scores were obtained after completion of the neuropsychological tests described below, as the SSS has been found to be more sensitive at the end of a performance test than before.

**Epworth Sleepiness Scale (ESS)**
The subjective Epworth Sleepiness Scale score is used to assess the general level of sleepiness under certain conditions. While imperfect, as it is not objective, it is widely validated and used in a number of populations for comparison. The ESS alone may not be sufficient for assessment of sleepiness over the course of a day due to sleep apnea, and therefore the SSS was also included. Scores greater than 10 on the ESS are indicative of excessive daytime sleepiness.

**Sustained Attention to Response Task (SART)**
The SART is a well-validated test of alertness and sustained attention in brain-damaged patients. Subjects were seated in a quiet environment in front of a computer screen. In this test numbers (each of the digits 0-9) are displayed briefly in random order, one at a time, on the screen. The subjects are instructed to press a key in response to each digit, unless the displayed digit is the number 3, in which case they are not to press the key. The number of errors (i.e. key presses in response to the number 3) is recorded. A complete test consists of 225 digits presented serially over a 4.3 minute period.

**Participation Assessment**
This included a daily documentation by the physiotherapists of actual time spent by the subjects performing physiotherapy. Furthermore, they also documented their perceived participation of each subject on a 7 point scale following each session. For participation 7 – ‘maximum’ 1- ‘no participation’ (Figure S1).

**Canadian Neurological Scale (CNS)**
This scale assesses the severity of the stroke according to the degree of neurologic impairment from brain damage. This test includes 8 items that measure level of consciousness, orientation, speech, motor function, and facial weakness.

**Functional Independence Measure (FIM)**
This tool measures functional capacity. It includes 18 items that measure self-care, sphincter control, mobility, locomotion, communication, and social cognition. It is used as an important determinant of fitness to be discharged from hospital.

**Berg Balance Scale**
This is an objective measure of balance abilities. The scale consists of 14 tasks common in everyday life. The items test the subject’s ability to maintain positions or movements of increasing difficulty by diminishing the base of support from sitting, standing, to single leg stance.

**Chedoke-McMaster Scale**
This scale measures the specific change in limb function among individuals who sustained cortical damage resulting in hemiplegia. This assessment tool stages the recovery from stroke based on Brunnstrom’s stages of recovery. A score ranging from 1 (flaccid paralysis) to 7 (full recovery) is used.
(normal movement patterns) provides an indication of the level of physical impairment resulting from the stroke.

**Walking Ability**
Walking ability was assessed with the 6-minute walk test. The 6-minute walk test assesses walking endurance. Subjects were instructed to walk from one end of the corridor to the other, covering as much distance as possible in a 6-minute period. At baseline, non-ambulant subjects were given a 6-minute walk test distance of 0.

**Upper Limb Strength**
Grip strength was assessed with a Baseline Hydraulic Hand dynamometer in both paretic and non-paretic hands. Subjects performed three repetitions and the highest value was taken as the measure of maximum grip strength. Grip strength has been used to provide a proxy measure of overall strength in healthy individuals, correlating well with lower limb strength. In stroke subjects, the ratio of strength between the paretic and non-paretic side was used to assess change over time.

**Neuropsychometric Assessment**

**Beck Depression Inventory I (BDI I)**
This is one of the most widely used instruments for measuring the severity of self-reported depression in adults, and its reliability and validity have been established across a broad spectrum of clinical populations including geriatric patients.

**Neuropsychological Test Battery**
The battery comprises tests of mental efficiency (attention, concentration, vigilance, speed of processing), executive function and memory (verbal and visuospatial). In addition, a test of premorbid verbal intellectual function is included in order to rule out an explanation of intellectual function for any group differences that are observed between the CPAP and no-CPAP group. Please see Table S1 for the test list, the area of cognitive function measured by each test, and the test references.

Tests with high test-retest reliability were selected because of the repeated measures design. The battery was brief in order to minimize patient burden and maximize reliability. Patients were offered breaks as needed. The test order was approximately counterbalanced in order to avert order effects.

The Purdue Pegboard test is a well-validated test of both fine motor (fingertip) and gross motor (arm and hand) dexterity. It has been used extensively as a test of the speed and accuracy of upper limb motor skills. In subjects with impaired motor function in the dominant hand/arm, whose performance on this test would be compromised, the non-dominant hand was used.
Supplemental Figure S1:

**Participation Assessment Form**

Please fill in all details on this form.

**Date:**

**Allotted Duration of Physiotherapy Session:** minutes

**Time spent by patient performing physiotherapy:** minutes

This is to assess an individual’s level of participation in physiotherapy as perceived by the physiotherapist. It is designed to assess the level of co-operation, willingness and enthusiasm of the individual for the physiotherapy. It is not designed to measure an individual’s functional outcome or exercise capacity. It is to be completed by the physiotherapist following the individual’s completion of the daily physiotherapy.

Please mark the relevant box

<table>
<thead>
<tr>
<th>LEVEL OF PARTICIPATION</th>
<th>SCALE RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum - individual participates fully &amp; is engaged throughout the activities</td>
<td>7</td>
</tr>
<tr>
<td>Very Good – individual participates extremely well</td>
<td>6</td>
</tr>
<tr>
<td>Good – individual participates well</td>
<td>5</td>
</tr>
<tr>
<td>Adequate – individual participates, but not to maximum of present capabilities</td>
<td>4</td>
</tr>
<tr>
<td>Poor – individual does not actively participate</td>
<td>3</td>
</tr>
<tr>
<td>Very Poor – little participation by the individual</td>
<td>2</td>
</tr>
<tr>
<td>None – individual refuses to participate</td>
<td>1</td>
</tr>
</tbody>
</table>
Supplemental Table S1:

Neuropsychological Tests

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>TEST</th>
<th>FUNCTION MEASURED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Efficiency</td>
<td>Digit Span, forwards&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Auditory verbal attention span</td>
</tr>
<tr>
<td></td>
<td>(Spatial Span, forwards, for patients with language production deficits;&lt;sup&gt;18&lt;/sup&gt;)</td>
<td>Visuospatial attention span</td>
</tr>
<tr>
<td></td>
<td>Sustained attention to response test&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Sustained attention / Vigilance</td>
</tr>
<tr>
<td>Executive</td>
<td>Digit Span, backwards&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Auditory working memory</td>
</tr>
<tr>
<td>functioning</td>
<td>Spatial Span, backwards; for patients with language production deficits;&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Visuospatial working memory</td>
</tr>
<tr>
<td>Manual Dexterity</td>
<td>Purdue Pegboard Test&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Motor speed &amp; dexterity</td>
</tr>
<tr>
<td></td>
<td>Subjects complete two 30sec trials with each hand</td>
<td></td>
</tr>
</tbody>
</table>
Supplemental References: