Safety and Tolerability of Early Noninvasive Ventilatory Correction Using Bilevel Positive Airway Pressure in Acute Ischemic Stroke

Georgios Tsivgoulis, MD*; Yi Zhang, MD*; Anne W. Alexandrov, PhD; Mark R. Harrigan, MD; April Sisson, RN; Limin Zhao, MD; Mary Brethour, RN, NP; Luis Cava, MD; Clotilde Balucani, MD; Kristian Barlinn, MD; Damon E. Patterson, MD; Sotirios Giannopoulos, MD; Jennifer DeWolfe, DO; Andrei V. Alexandrov, MD

Background and Purpose—Hypercapnia can induce intracranial blood-flow steal from ischemic brain tissues, and early initiation of noninvasive ventilator correction (NIVC) may improve cerebral hemodynamics in acute ischemic stroke. We sought to determine safety and tolerability of NIVC initiated on hospital admission without polysomnography study.

Subjects and Methods—Consecutive acute ischemic stroke patients were evaluated for the presence of a proximal arterial occlusion, daytime sleepiness, or history of obstructive sleep apnea, and acceptable pulse oximetry readings while awake (96%–100% on 2 to 4 L supplemental oxygen delivered by nasal cannula). NIVC was started on hospital admission as standard of care when considered necessary by treating physicians. NIVC was initiated using bilevel positive airway pressure at 10 cmH2O inspiratory positive airway pressure and 5 cmH2O expiratory positive airway pressure in combination with 40% fraction of inspired oxygen. All potential adverse events were prospectively documented.

Results—Among 356 acute ischemic stroke patients (median NIHSS score, 5; interquartile range, 2–13), 64 cases (18%) received NIVC (median NIHSS score, 12; interquartile range, 6–17). Baseline stroke severity was higher and proximal arterial occlusions were more frequent in NIVC patients compared to the rest ($P<0.001$). NIVC was not tolerated by 4 patients (7%). Adverse events in NIVC included vomiting ($n=1$), aspiration pneumonia ($n=1$), respiratory failure/intubation ($n=1$), hypotension requiring pressors ($n=1$), and facial skin breakdown ($n=3$). The in-hospital mortality rate was 13% in NIVC patients and 8% in the rest ($P=0.195$). Neurological improvement during hospitalization tended to be greater in the NIVC group (median NIHSS score decrease, 2 points; interquartile range, 0–4) compared to the rest (median NIHSS score decrease, 1; interquartile range, 0–2; $P=0.078$).

Conclusions—In acute ischemic stroke patients with proximal arterial occlusion and excessive sleepiness or obstructive sleep apnea, NIVC can be initiated early with good tolerability and a relatively small risk of serious complications. (Stroke. 2011; 42:1030-1034.)

Key Words: arterial occlusion ■ hemodynamics ■ hypercapnia ■ hypoxia ■ noninvasive ventilatory correction ■ sleep apnea ■ stroke

Sleep-related breathing disorders appear to contribute to the risk of stroke through hemodynamic and hematologic changes.$^1$ Cerebrovascular reactivity and ventilation are tightly linked, so that any potential for fluctuation of partial pressure of carbon dioxide levels mandates the need for stabilization of breathing to ensure adequacy of cerebral blood flow.$^1$ Vasodilator responses to chemical stimuli in the cerebral circulation are impaired in many patients with obstructive sleep apnea (OSA). Some of these impairments have been corrected by continuous positive airway pressure,$^2$ but this method is often poorly tolerated because of difficulty exhaling against elevated airway pressures. More recently, bilevel positive airway pressure devices that incorporate both inspiratory positive airway pressure to support inspiration and expiratory positive airway pressure to ease expiration have become popular. These devices are generally better-tolerated and commonly are used in both inpatient and outpatient settings; additionally, because bilevel positive airway pressure does not exacerbate muscular fatigue, these devices have become popular for use in patients with neurological dysfunction.

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From the Comprehensive Stroke Center (G.T., Y.Z., A.W.A., A.S., L.Z., M.B., L.C., C.B., K.B., D.E.P., A.V.A.), University of Alabama at Birmingham Hospital, Birmingham, AL; Department of Neurology (G.T.), Democritus University of Thrace, School of Medicine, Alexandroupolis, Greece; Division of Neurosurgery (M.R.H.), University of Alabama at Birmingham Hospital, Birmingham, AL; Department of Neurology (S.G.) University of Ioannina School of Medicine, Ioannina, Greece; and Sleep Medicine and Neurology (J.D.), University of Alabama at Birmingham Hospital, Birmingham, AL.

*G.T. and Y.Z. contributed equally to this work.

Correspondence to Andrei V. Alexandrov, RWUH M226, 619 19th St South, Birmingham, AL 35249-3280. E-mail avalexandrov@att.net

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1030
The concept of blood-flow steal with arterial occlusions is well-known. In brain, hemodynamic steal and shunts also have been documented in patients with angiomas or arteriovenous malformations. Moreover, neurological symptoms have been linked to cerebral blood flow reduction with arteriovenous malformations or rare cases of the subclavian steal syndrome. Furthermore, the findings of a recent structured, critically appraised topic provide strong evidence supporting that OSA is an independent risk factor for stroke or death. After stroke, both in the acute and chronic stages, patients have a high prevalence of OSA that reduces the potential for rehabilitation, further increasing the risk of stroke recurrence and early as well as long-term mortality. Successful correction of sleep apnea with noninvasive positive airway pressure ventilation lowers mean blood pressure and indirectly lowers the risk of stroke. However, the safety and the tolerability of early noninvasive ventilatory correction (NIVC) in acute stroke patients never has been studied. We sought to determine safety and tolerability of NIVC initiated on the first day of admission without polysomnography study.

Subjects and Methods
Consecutive patients with symptoms of both posterior and anterior acute cerebral ischemia admitted within 48 hours from symptom onset to our tertiary hospital stroke service were prospectively evaluated. Patients who met inclusion criteria were adults 19 years of age or older, had an ischemic stroke or TIA, had temporal windows for transcranial Doppler examination, and consented to participation in the study. According to the Trial of Org 10172 in acute stroke treatment criteria, ischemic strokes were classified based on etiopathogenetic mechanisms into the following groups: large artery atherosclerotic stroke, cardioembolic stroke, small artery occlusion or lacunar stroke, and infarct of unknown cause. Demographic and common risk factors were documented from routine stroke work-up as previously described. Neurological deficits were measured by serial NIHSS scores obtained by certified stroke team members. Neurological improvement during hospitalization was evaluated as the decrease in NIHSS score at hospital discharge from the baseline NIHSS score at hospital admission. The attending physicians of our stroke team evaluated all patients for sleep apnea or the history of OSA or the history of daytime sleepiness using either room air or no more than 2 to 4 L of supplemental oxygen delivered by nasal cannula. Treatment with intravenous thrombolysis or intra-arterial reperfusion procedures (intra-arterial thrombolysis, thrombectomy, thrombus aspiration) was documented in all cases. Patients requiring airway intubation and mechanical ventilation were not considered candidates for NIVC. Additionally, patients deemed eligible for NIVC were monitored using pulse oximetry to ensure a baseline oxygen saturation level ranging from 96% to 100% during periods of wakefulness using either room air or no more than 2 to 4 L of oxygen delivered by nasal cannula.

NIVC was started on the first day of admission (at night or sooner if daytime sleepiness was present) as standard of care at our institution when thought necessary by treating physicians on the basis of the following indications: history of OSA, suspected OSA, or persisting proximal arterial occlusions with neurological worsening during sleep. NIVC was initiated using bilevel positive airway pressure at 10 cmH₂O inspiratory positive airway pressure and 5 cmH₂O expiratory positive airway pressure in combination with 40% fraction of inspired oxygen. Once initiated, inspiratory positive airway pressure was titrated upward to ensure a tidal volume of between 5 and 7 mL/kg. In the case of patients with preexisting home use of NIVC, initial settings mirrored prescribed home settings but were adjusted if necessary to ensure adequate tidal volume and prevent hypercapnia. All potential adverse events were prospectively documented. NIHSS score at hospital discharge was recorded and neurological improvement during hospitalization was considered as the difference in NIHSS score between hospital admission and hospital discharge. The causes of death of all patients were documented in all cases. The members of the stroke team documenting serial NIHSS scores and causes of death were blinded to whether patients received treatment with NIVC. The project evaluating intracranial steal and its correction with noninvasive ventilatory correction was approved by our Institutional Review Board.

Statistical Analyses
Statistical analyses were performed with the SPSS 15.0 software (SPSS). The 2-tailed Fisher exact test or Pearson χ² test for categorical variables and Student t test or Mann-Whitney U test for continuous variables were used to assess intergroup differences. Correlations between continuous variables were assessed by the Spearman correlation coefficient. Initially, univariable logistic regression analyses of potential predictors of in-hospital mortality (demographic characteristics, stroke risk factors, admission NIHSS score, presence of proximal arterial occlusion, NIVC, history of OSA) were performed. To maximize sensitivity, those variables with a univariable association of P<0.2 were included as candidates into a multivariable logistic regression model and then removed by the backward stepwise selection procedure. To confirm the robustness of multivariable models, we repeated all multivariable analyses using a forward selection procedure. Predictor variables that were significant at P<0.05 were retained in the multivariable model. A level of P<0.05 was accepted as statistically significant.

Results
A total of 356 consecutive patients with acute cerebral ischemia (mean age, 62±15 years; 54% men) were evaluated during the study period (August 2008–August 2009). The median NIHSS score was 5 points, with an interquartile range (IQR) of 2 to 13. Nearly one-fifth of our study population received NIVC (n=64; 18%). Baseline characteristics in patients receiving NIVC and in the remaining study population are shown in Table 1. Male gender, atrial fibrillation, and

<table>
<thead>
<tr>
<th>Variable</th>
<th>NIVC (+)</th>
<th>NIVC (−)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>63±13</td>
<td>62±15</td>
<td>0.729</td>
</tr>
<tr>
<td>Male, %</td>
<td>72</td>
<td>50</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>80</td>
<td>78</td>
<td>0.823</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36</td>
<td>30</td>
<td>0.335</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>86</td>
<td>77</td>
<td>0.116</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>23</td>
<td>13</td>
<td>0.034</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>33</td>
<td>24</td>
<td>0.142</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>48</td>
<td>39</td>
<td>0.166</td>
</tr>
<tr>
<td>Proximal arterial occlusion, %</td>
<td>88</td>
<td>64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructive sleep apnea syndrome, %</td>
<td>36</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission NIHSS score, median (interquartile range)</td>
<td>4 (2–12)</td>
<td>12 (6–17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intravenous thrombolysis, %</td>
<td>28</td>
<td>18</td>
<td>0.051</td>
</tr>
<tr>
<td>Intra-arterial reperfusion procedures, %</td>
<td>17</td>
<td>11</td>
<td>0.140</td>
</tr>
</tbody>
</table>

NIVC indicates noninvasive ventilatory correction.
OSAS were more prevalent in patients who received NIVC. Baseline stroke severity was higher in patients with NIVC (median NIHSS score, 12 points; IQR, 6–17) compared to the rest (median NIHSS score, 4 points; IQR, 2–12; P<0.001 by Mann-Whitney U test). The NIVC group had a higher rate of proximal arterial occlusions (88% versus 64%; P<0.001). Patients treated with NIVC tended to receive more frequently intravenous thrombolysis (28%) compared to the rest (18%; P=0.001). The NIVC group had a higher average admission NIHSS† score (17.5 points; IQR, 11–23) compared to the rest (13.0 points; IQR, 9–17; P=0.001). Among the adverse events, the events that, in the opinion of the investigators, were serious and may have contributed to unfavorable stroke outcomes occurred in 7% (95% CI, 2%–16%). Overall in-hospital mortality was 8% (n=30). The rate of in-hospital mortality was 13% in patients treated with NIVC and 8% in the remaining subjects (P=0.195). Among stroke survivors, neurological improvement during hospitalization tended to be greater in the NIVC group (median NIHSS score decrease, 2 points; IQR, 0–4) compared to the rest (median NIHSS score decrease, 1 point; IQR, 0–2; P=0.078 by Mann-Whitney U test).

Table 2 shows the univariate and multivariate associations of baseline characteristics, stroke risk factors, and NIVC with in-hospital mortality. In the initial univariate analyses, the following variables were selected for inclusion in the multivariable model (using a cut-off of P<0.2): admission NIHSS score (P<0.001); hypercholesterolemia (P<0.001); proximal arterial occlusion (P=0.008); intra-arterial reperfusion procedures (P=0.012); hypertension (P=0.012); atrial fibrillation (P=0.019); age (P=0.079); diabetes mellitus (P=0.086); and NIVC (P=0.198). In the final multivariable model, the following 3 variables emerged as independent predictors of in-hospital mortality: admission NIHSS (OR per 1-point increase, 1.16; 95% CI, 1.10–1.22; P<0.001); hypercholesterolemia (OR, 0.09; 95% CI, 0.03–0.24; P<0.001); and atrial fibrillation (OR, 4.96; 95% CI, 1.66–14.84; P=0.004). No association between NIVC and in-hospital mortality was identified in the multivariate models (OR, 1.12; 95% CI, 0.34–3.69; P=0.848).

Given the fact that the NIVC group had a higher average admission NIHSS score and a higher atrial fibrillation prevalence compared to the rest (and both of these variables were independent predictors of in-hospital mortality), we decided to compare the rate of in-hospital mortality among NIVC and non-NIVC patients after matching them for admission NIHSS score and atrial fibrillation. The 2 groups matched for admission NIHSS score and atrial fibrillation consisted of 61 patients each. The median NIHSS score in each of the matched groups was 11 points (IQR, 6–15), whereas the prevalence of atrial fibrillation was 21% (n=13 in each group of 61 patients). Baseline characteristics in the 2 matched groups are shown in Table 3. The matched groups did not differ in terms of any baseline characteristic with the exception of OSAS (36% in NIVC group versus 5% in the rest; P<0.001). The rates of in-hospital mortality were 12% in patients treated with NIVC (n=7) and 18% in patients not treated with NIVC (n=11). For the given effect size (6% absolute reduction in in-hospital mortality), a sample size of 1120 patients (560 patients per group) would be needed in a

Table 2. Factors Independently Associated With In-Hospital Mortality on Multivariate Logistic Regression Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analyses</th>
<th>Multivariate Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age*</td>
<td>1.27 (0.97–1.65)</td>
<td>0.079</td>
</tr>
<tr>
<td>Male</td>
<td>1.31 (0.61–2.81)</td>
<td>0.487</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.37 (0.17–0.80)</td>
<td>0.012</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.42 (0.16–1.13)</td>
<td>0.086</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.75 (1.18–6.38)</td>
<td>0.019</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.60 (0.27–1.35)</td>
<td>0.215</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.09 (0.04–0.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>1.28 (0.56–2.90)</td>
<td>0.561</td>
</tr>
<tr>
<td>PAO</td>
<td>15.39 (2.07–114.42)</td>
<td>0.008</td>
</tr>
<tr>
<td>OSAS</td>
<td>0.90 (0.26–3.01)</td>
<td>0.861</td>
</tr>
<tr>
<td>IV thrombolysis</td>
<td>1.04 (0.41–2.66)</td>
<td>0.929</td>
</tr>
<tr>
<td>IA reperfusion procedures</td>
<td>3.12 (1.29–7.56)</td>
<td>0.012</td>
</tr>
<tr>
<td>NIVC</td>
<td>1.75 (0.74–4.14)</td>
<td>0.198</td>
</tr>
<tr>
<td>Baseline NIHSS†</td>
<td>1.17 (1.11–1.23)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Per 10-year increment.
†Per 1-point increment.

CAD indicates coronary artery disease; IA, intra-arterial; IV, intravenous; NIVC, noninvasive ventilatory correction; OSAS, obstructive sleep apnea syndrome; PAO, proximal arterial occlusions.
randomized controlled trial to test the hypothesis whether treatment with NIVC in patients with acute cerebral ischemia decreases in-hospital mortality with a power of 80.4% and a 2-tailed $\alpha$ value of 0.05.

**Discussion**

Our study showed that NIVC may be initiated early in acute ischemic stroke patients with good tolerability and a relatively small risk of serious complications. Moreover, NIVC treatment is not associated with higher in-hospital mortality, although we documented a trend toward greater neurological improvement with NIVC among stroke survivors. Finally, the present study provides preliminary data for estimation of the sample size needed to evaluate the hypothesis that NIVC may improve neurological outcome and functional outcomes. In conclusion, we documented that NIVC using bilevel positive airway pressure is safe in patients with acute cerebral ischemia and that it can be tolerated in the majority of patients (>90%). Consequently, our findings serve in generalizing the notion that if OSA is diagnosed in a timely manner in the acute stroke setting and the pertinent therapeutic actions are not taken, the potential injury that sleep apnea can cause during the first few days after an acute stroke may be affected.

**Disclosures**

None.
References

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