Brief Report

Endothelial Dysfunction and Arterial Stiffness in Ischemic Stroke
The Role of Sleep-Disordered Breathing

Carlo W. Cereda, MD; Renaud Tamisier, MD; Mauro Manconi, MD; Jennifer Andreotti, MSC; Jane Frangi, NP; Valeria Pifferini, NP; Claudio L. Bassetti, MD

Background and Purpose—Sleep-disordered breathing (SDB) represents a risk factor for cardiovascular morbidity after a cerebral ischemic event (acute ischemic event, ischemic stroke, or transient ischemic attack). In the present study, endothelial function and arterial stiffness were analyzed in patients who experienced a postacute ischemic event with relation to SDB, sleep disruption, and nocturnal oxygenation parameters.

Methods—SDB was assessed by full polysomnography in patients with acute ischemic event 3 months after the admission at our stroke unit. Moderate-severe SDB was defined according to the apnea-hypopnea index as apnea-hypopnea index ≥20. Endothelial function and arterial stiffness were assessed by peripheral arterial tonometry using Endo-PAT 2000.

Results—Thirty-seven patients were included. The augmentation index was significantly different between patients with apnea-hypopnea index <20 and apnea-hypopnea index ≥20 (22.4±15.6% versus 34.6±21.6%; P=0.042), whereas reactive hyperemia index level was not (2.02±0.65 versus 2.31±0.61; P=0.127). Patients with apnea-hypopnea index ≥20 showed an increased risk for arterial stiffness (odds ratio, 5.98 [95% CI, 1.11–41.72]) even when controlling for age, sex, body mass index, hypertension, and diabetes mellitus. The augmentation index was correlated with the arousal index (P=0.010) and with mean O2 saturation (P=0.043).

Conclusions—Poststroke patients with moderate-severe SDB were more prone to have increased arterial stiffness, although we did not find significant differences in endothelial function. Arterial stiffness also correlated with sleep disruption (arousal index) and mean O2 saturation. (Stroke. 2013;44:XXX-XXX.)

Key Words: sleep-disordered breathing • stroke

Sleep-disordered breathing (SDB) is observed in 50% to 70% of patients with acute ischemic events (AIEs).1 In the chronic phase of stroke, mostly central apneas tend to improve.1 At the same time, SDB is an independent risk factor for vascular damage,2 but the exact mechanisms are still unclear. SDB may be associated with endothelial dysfunction, possibly mediated by intermittent hypoxia and sleep disruption.3 Increased arterial stiffness (AS) is widely recognized as a determinant of cardiovascular risk and has also been related to SDB.4

Patients and Methods
This investigation is part of the prospective multicenter study (SAS-CARE 2; URL: http://www.clinicaltrials.gov. Unique identifier: NCT01097967).4 The protocol was approved by the local ethics committee, and written informed consent was obtained from the patients. Patients between 35 and <75 years old, with a clinical diagnosis of AIE in the previous 60 to 90 days, fulfilled the inclusion criteria. Patients with unstable clinical situation (cardiorespiratory or life-threatening medical conditions) currently or during the last 3 months on continuous positive airway pressure were excluded. All of the data were prospectively collected.

Clinical Evaluation
Stroke workup included assessment of cardiovascular risk factors, time of stroke onset, and estimation of stroke severity at admission (National Institutes of Health Stroke Scale). Cerebral magnetic resonance imaging was performed in all of the patients at admission to the stroke unit to confirm the diagnosis. Stroke outcome at 3 months was assessed using the modified Rankin Disability Scale.

Polysomnography
Nocturnal video polysomnography was performed with Embla titanium 3 months after stroke. The apnea-hypopnea index indicates the mean number of apneas and hypopneas per hour of sleep. Moderate-severe SDB was defined as apnea-hypopnea index ≥20. The time spent with oxygen saturation <90% and the number of desaturations per hour of sleep (oxygen desaturation index) were obtained from the recording. Manual scoring of sleep and respiration was performed by fully trained, experienced scorers who were blinded to the identity of the patients.

Endothelial Function and AS
Endothelial function (EF) an AS were assessed by pulse wave analysis with peripheral arterial tonometry, using Endo-PAT 2000, a validated...
noninvasive method.\textsuperscript{6} Peripheral arterial tonometry was performed 3 months after stroke in the morning after video polysomnography and overnight fasting.

Statistical Analysis
Data were checked for normal distribution using the Kolmogorov-Smirnov test. Natural logarithmic transformations were applied when normality assumptions were not fulfilled. Differences between patients with and without apnea-hypopnea index $ \geq 20$ were assessed with the Mann-Whitney U test (2 tailed). Associations were explored with Pearson and Spearman correlation coefficients, as appropriate. Logistic and linear regression analyses were used to explore the association of outcomes to multiple parameters. A $P$ value of $<0.05$ was considered significant. All of the data were analyzed with SPSS (IBM Inc), version 17.0.

Results
Clinical Data
Thirty-seven subjects were included (Table 1).

EF, AS, and SDB
The augmentation index (AIX) was statistically significantly higher in patients with SDB compared with those without SDB, whereas EF expressed as reactive hyperemia index did not differ between the 2 groups (Table 1 and the Figure, A and B). The apnea-hypopnea index did not correlate with AIX or the reactive hyperemia index (Table 2).

Determinants of EF and AS
No significant correlations were found between EF and National Institutes of Health Stroke Scale scores or modified Rankin scores. Reactive hyperemia index but not AIX correlated with the age of the participants. AIX was positively associated with the arousal index (Pearson coefficient, 0.42; $P=0.010$) and negatively associated with the mean $O_2$ saturation (Pearson coefficient, –0.34; $P=0.043$; Table 2).

Multivariate Analysis
Logistic regression showed that patients with SDB had a significantly increased risk for AS (AIX $\geq 30\%$) compared with patients without SDB (odds ratio, 4.43 [95\% CI, 1.05–20.69]; $P=0.047$), and the effect remained when age, sex, body mass index, hypertension, and diabetes mellitus were controlled for (odds ratio, 5.98 [95\% CI, 1.11–41.72]; $P=0.047$). Similarly, in separate linear regression analyses the arousal index and the mean $O_2$ saturation significantly predicted AIX ($P=0.025$ and $P=0.033$, respectively) even when age and sex were controlled for. However, in the combined linear regression analyses, the effect failed to reach statistical significance ($P=0.073$ and $P=0.087$, respectively).

Discussion
The major findings of this prospective investigation are as described here. First, poststroke patients with moderate-severe SDB had a significantly increased AS, a signature of advanced vascular damage. However, secondly, peripheral EF was not different in patients with or without moderate-severe SDB. Finally, as postulated previously, AS was correlated with sleep fragmentation and oxygenation.

Only a few studies deal with peripheral arterial measurement of EF in stroke patients; mostly aiming at stroke subtype classification.\textsuperscript{8} To our knowledge, so far only 1 study has addressed EF in relation to SDB in acute stroke.\textsuperscript{9} We decided to investigate EF in poststroke patients because it probably reflects more adequately the baseline SDB severity in AIE patients\textsuperscript{1} and also to minimize the influence of possible confounders (ie, SDB acutely aggravated by stroke, comedications, or poor sleep quality). A recent article showed a difference of specific biomarkers of EF in stroke patients with sleep apnea,\textsuperscript{7} but this could be argued to be influenced by a significant difference in stroke severity between groups, which was not the case in our study. This reinforces the hypothesis of SDB being a supplemental “aggravating factor” for vascular damage in stroke patients rather than being secondary to stroke.

AS has emerged as a strong predictor for future cardiovascular events and all-cause mortality.\textsuperscript{10} The role of AS in stroke patients was mainly focused on stroke subtypes\textsuperscript{11,12} and did not control for the presence of SDB. Our preliminary study is the first to show that SDB influences AS in poststroke AIE patients. This should be considered in future studies that focus on the relationship between vascular morbidity and SDB in stroke patients.

The repetitive arousals associated with SDB are a known risk factor for cardiovascular diseases.\textsuperscript{13} Indeed, sleep restriction duration appears to increase the cardiovascular risk independent of upper airway obstruction.\textsuperscript{14} In sleep-deprived subjects, inflammatory markers are increased,\textsuperscript{15} pointing to effects on inflammation, sympathetic tone, and hypercoagulability, factors that are known to affect cardiovascular disease outcome. Our findings support the notion that sleep instability
is associated with higher vascular damage measured as AS and not as EF.14 This result underlines the impact of sleep quality evaluation in stroke patients and the importance of a proper sleep diagnosis in this high-risk population.

Our study has several limitations. We investigated only a small sample of SDB patients. Statistical comparisons and analyses of such a small sample are associated with considerably lower certainty and result in rather large CIs. In our population we found a dissociation of the results, documenting an influence of SDB on AS but not on EF. This is probably related to the limit of measuring interindividual differences on EF in vascular high-risk patients (mainly positive studies on EF difference included a healthy control group).15 EF testing may also be more sensible to confounding factors and external influences. Sympathetic hyperactivity in SDB patients may also contribute to a decreased sensitivity of the Endo-PAT 2000.

The results of this preliminary study add to our understanding of the complexity of vascular damage related to SDB in a poststroke population. Larger investigations of AS and endothelial dysfunction in patients with SDB in AIE are needed with the aim of proposing AS as a reliable vascular marker, which could prove to be useful in future large secondary stroke prevention studies addressing SDB.

Table 2. Correlations Between RHI and AIX With Sleep and Clinical Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>RHI Correlation Coefficient</th>
<th>RHI P Value</th>
<th>AIX Correlation Coefficient</th>
<th>AIX P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arousal index</td>
<td>−0.10</td>
<td>0.569</td>
<td>0.42</td>
<td>0.010**</td>
</tr>
<tr>
<td>Oxygenation, mean (O_2) saturation</td>
<td>0.11</td>
<td>0.531</td>
<td>−0.34</td>
<td>0.043*</td>
</tr>
<tr>
<td>Age</td>
<td>−0.35</td>
<td>0.032*</td>
<td>0.05</td>
<td>0.723</td>
</tr>
<tr>
<td>NIHSS (S)</td>
<td>0.10</td>
<td>0.548</td>
<td>0.12</td>
<td>0.476</td>
</tr>
<tr>
<td>Rankin (S)</td>
<td>−0.10</td>
<td>0.959</td>
<td>0.12</td>
<td>0.470</td>
</tr>
<tr>
<td>AHI</td>
<td>0.05</td>
<td>0.569</td>
<td>0.17</td>
<td>0.313</td>
</tr>
<tr>
<td>ODI</td>
<td>0.01</td>
<td>0.944</td>
<td>0.10</td>
<td>0.556</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.10</td>
<td>0.533</td>
<td>0.11</td>
<td>0.520</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.18</td>
<td>0.285</td>
<td>0.21</td>
<td>0.206</td>
</tr>
</tbody>
</table>

(S) indicates Spearman Rho coefficients, whereas for the other cases the Pearson correlation was used.

AHI indicates apnea-hypopnea index; AIX, augmentation index; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; ODI, oxygen desaturation index; RHI, reactive hyperemia index; and TIA, transient ischemic attack.

*P<0.05.

**P<0.01.
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Stroke. published online March 7, 2013;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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http://stroke.ahajournals.org/content/early/2013/03/07/STROKEAHA.111.000112

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