Obstructive Sleep Apnea Is Frequent in Patients with Hypertensive Intracerebral Hemorrhage and Is Related to Perihematoma Edema

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Background

Sleep breathing disorders are highly prevalent in patients with established cardiovascular and cerebrovascular diseases [1]. Among the sleep breathing disorders, obstructive sleep apnea (OSA) has been proposed as an independent risk factor for the development of essential hypertension [2]. OSA has also been found in up to 77% of patients with an acute ischemic stroke, and has been related to early neurological deterioration and to increased long-term mortality in this population [3–5]. Possible mechanisms include increased cardiovascular variability, activation of the coagulation cascade, increased oxidative stress and systemic inflammation [6–8].

Intracerebral hemorrhage (ICH) is the most deadly subtype of stroke, as approximately 65% of its victims are dead after 1 year [9]. Hematoma expansion and the development of perihematoma edema are 2 of the major factors that may contribute to the high morbidity and mortality of ICH [10–12]. Animal studies demonstrate that brain edema peaks around the fourth day after ICH [13]. In humans, the edema volume could exceed that of the original hematoma, and lead to elevated in-
tracranial pressure or shift in the midline structures with subsequent neurological deterioration or death [11, 12].

The frequency and the clinical impact of OSA in acute phase of ICH are still unknown. We hypothesize that OSA is frequent in patients with ICH, and may be related to increased development of perihematoma edema.

Subjects and Methods

We prospectively assessed 132 consecutive patients between with a first-ever ICH admitted to the Emergency Department of our University Hospital from January 2006 to January 2008. All patients had a baseline computerized axial tomography (CT) scan on admission. According to the exclusion criteria, 66 patients with stupor or coma that demanded orotracheal intubation in the first 24 h of stroke onset for airway protection were excluded from the study. Additionally, 34 patients were also excluded from the study because they were admitted 24 h after stroke onset, were <18 or >80 years old, had baseline oxyhemoglobin saturation <92% or had secondary causes of ICH (anticoagulant use, underlying aneurysm or vascular malformation, tumor, head trauma, or hemorrhagic transformation of ischemic infarcts). Finally, 32 patients with a primary ICH were included in this analysis. They underwent a full polysomnography (PSG) in the first night after admission and had 2 follow-up CT scans 24 h after admission and at day 4/5. This study was approved by the ethics committee at our institution, and written informed consent was obtained from each patient or their relatives.

Data Collection

We collected demographic, clinical, laboratory, polysomnographic and radiological data. On admission, information about the patients was collected from themselves or their relatives using a comprehensive questionnaire that included demographic data, the frequency of risk factors for stroke, sleep habits, sleep disturbances that were noticed before the stroke (snoring, daytime sleepiness, non-restorative sleep) and hemorrhage onset-to-imaging time. Additionally, patients were assessed with physical and neurologic examinations that included auxiliary temperature, mean arterial blood pressure (MAP; calculated as 1/3 systolic + 2/3 diastolic blood pressure), pulse oximetry, Glasgow coma scale and National Institute of Health Stroke Scale (NIHSS) scores (on admission and daily until discharge) [14]. Early neurologic deterioration was defined as an increase of 4 points in the NIHSS in the first 48 h [15]. Body mass index and cervical perimeter were measured during admission. Laboratory data collected on admission included electrocardiogram, chest radiography, and standard blood tests (serum glucose and complete blood counts – hemoglobin, hematocrit and white cell count) at presentation. We also registered the hospital morbidity and mortality. The NIHSS and the modified Rankin Scale (mRS) scores were collected on follow-up visits in the outpatient clinic at approximately 6 months after discharge to assess mortality and the degree of neurological and functional recovery after ICH [14].

Polysomnographic Assessment

PSG was performed at the hospital ward from 11:00 PM to 7:00 AM, by using a full digital PSG system (BioLogic Sleepscan IT™; Mundelein, Ill., USA), without interfering with conventional care of the patient. System variables included 6 EEG channels (F3-A1, F4-A2, C3-A1, C4-A2, O1-A1, O2-A2), electro-oculogram, chin and left and right anterior tibial surface electromyogram, electrocardiogram, nasal and oral airflow, thoracic and abdominal movements, and oxyhemoglobin saturation. Sleep stages were scored according to standard criteria [16]. Apnea was defined as the absence of airflow for at least 10 s. In obstructive apnea, respiratory effort was maintained, whereas in central apnea, breathing movements were absent. Mixed apnea was defined as a combination of central and obstructive apnea. Hypopnea was defined as a thoracoabdominal amplitude decrease >50% for at least 10 s with either an arousal or an oxygen desaturation >3%. Cheyne-Stokes respiration was defined as a periodic crescendo and decrescendo breathing pattern with central apnea or hypopnea. The apnea-hypopnea index (AHI) was defined as the average number of apnea and hypopnea episodes per hour of sleep, and sleep apnea was defined by an AHI ≥10 and further classified as obstructive or central according to type of event that predominates [3, 5].

Radiological Measurements

We measured the hematoma and edema volumes on admission and follow-up CT scans, done after 24 h and between 4 and 5 days after admission. A single evaluator (O.M.P.N), experienced in the interpretation of CT and blinded to patients’ clinical and polysomnographic data, analyzed all CT scans to conduct volumetric measurements of ICH and edema lesion volumes. All images were processed offline using ImageJ 1.38 (NIH, public domain). The ICH and edema volumes were calculated using a semi-automated process. The examiner manually drew regions of interest (ROI) by tracing the perimeter of appropriate high- and low-attenuation zones in each slice throughout the lesion (fig. 1). Automated threshold values, based on Hounsfield unit measurements, were then applied to differentiate hematoma from skull and brain parenchyma from perihematoma edema. Using the threshold values to differentiate hematoma from edema, contiguous voxels were automatically summed to yield a hematoma volume and absolute edema volume (the volume of the hematoma and surrounding edema). Relative edema was then calculated dividing the absolute edema by hematoma volume. In order to facilitate data calculation, relative edema volume was also multiplied by 100 to express perihematoma edema volume as a percentage of the associated hematoma volume.

The blinded observer drew the ROI on an initial subset of 10 patients twice, at an interval of 2 weeks apart. The test/retest agreement was r = 0.98 for edema and hematoma volume measurements. Another investigator (G.S.) independently drew the ROI on the same subset of 10 patients. The interobserver agreement was r = 0.90 for edema and hematoma volume measurements. Because the intra- and interobserver reliability was extremely high, only 1 measurement by 1 observer (O.M.P.N.) was used for the remainder of the ROIs.

Statistical Analysis

In univariate analyses, Fisher’s exact test was used for categorical data and Wilcoxon rank-sum test for quantitative data. For-
ward stepwise logistic regression analyses were used to identify the independent predictors of AHI $\geq 10$ and AHI $\geq 30$. The independent contribution of variables with a $p$ value $< 0.05$ on univariate analyses was assessed. Results are expressed as mean $\pm$ SD, median $\pm$ interquartile range (IQ), adjusted odds ratios, and corresponding 95% CI. The Spearman correlation coefficient ($r_s$) was used to determine the presence or absence of a correlation between quantitative variables, including AHI and relative edema volume on admission, after 24 h and on days 4–5. Statistical significance was corrected for multiple comparisons by Bonferroni correction ($p < 0.01$). We used the following limits for the interpretation of the correlation coefficient value: weak ($r_s$ between 0.2 and 0.5); moderate ($r_s$ between 0.5 and 0.8); strong ($r_s$ between 0.8 and 1); perfect ($r_s = 1$) [17]. All statistical analyses were done with the SPSS package (version 15.0 for Windows; Chicago, Ill., USA).

**Results**

A total of 132 patients were admitted to our Emergency Department with ICH during the study period. One hundred subjects were excluded from the present analysis: 66 were comatose and underwent subsequent orotracheal intubation in the first 24 h, 12 had a secondary cause of ICH, 7 had stroke onset more than 48 h before admission, 7 had previous ischemic stroke, 3 had a previous ICH, for 3 patients it was impossible to obtain informed consent, and 2 underwent urgent surgery in the first 24 h. Data from the remaining 32 subjects were included in this analysis.

There were 23 men and 9 women with a mean age of 57 $\pm$ 11.8 years. The mean MAP on admission was 144.3 $\pm$ 28.4 mm Hg. The mean BMI was 26.5 $\pm$ 4.9, the mean cervical perimeter was 39.92 $\pm$ 3.28 cm. The most frequent ICH risk factors reported were: arterial hypertension in 32 (100%), chronic alcohol abuse in 21 (65.6%), smoking in 18 (56.3%), obesity in 12 (37.5%), sedentary lifestyle in 10 (31.3%), diabetes in 9 (28.1%), and aspirin use in 7 (21.9%). History of habitual snoring was retrieved from 14 (43.8%) patients, history of witnessed respiratory pauses during sleep reported by bed partner in 4 (12.5%), and excessive daytime sleepiness in 3 (9.4%) patients. No patient received medications, such as hypnotics, that could have induced OSA or worsened the AHI.

The mean time between the onset of symptoms and admission was 13.0 $\pm$ 12 h. At presentation, the most frequent neurological signs were hemiparesis, present in 31 (96.8%) patients, dysarthria in 26 (81.3%), and aphasia in 20 (62.5%). Stroke was noticed on wakening in 8 patients (25%) and occurred during wakefulness in 24 (75%). At admission, the median NIHSS score was 15 (IQ: 10–20) and median GCS score was 14 (IQ: 12–15). The mean serum glucose was 128 $\pm$ 48.1 mg/dl, mean white blood cell count was 10,340 $\pm$ 3,972 cells/$\mu$l, and mean platelet count was 233,000 $\pm$ 71,219 platelets/$\mu$l. None of the patients studied showed signs of dehydration, and blood tests on admission showed no evidence of renal dysfunction or significant electrolyte disturbances. No patient received mannitol or other osmotic treatment for ICH.

Thirty patients (93.8%) had deep ICH and 2 (6.2%) had lobar ICH. The mean onset-to-imaging time was 14.6 $\pm$ 11.8 h for the admission CT scan, 41.3 $\pm$ 20.6 h for the 24 h follow-up CT scan, and 111.5 $\pm$ 39.7 h for the late follow-up scan. Table 1 lists the means $\pm$ SD of hematoma and perihematoma edema volumes at admission,

![Fig. 1. Depiction of the measurements of hematoma and perihematoma edema. ROIs drawn around the perimeters of the perihematoma edema (a) and hematoma (b) in all CT slices. Volumes from all slices were summed: $V_1$ (Veh) = edema + hematoma; $V_2$ (Vh) = hematoma; absolute edema = Vh – Veh; relative edema = absolute edema/Vh (relative edema volume was also multiplied by 100 to express perihematoma edema volume as a percentage of the associated hematoma volume).](image)
after 24 h and 4–5 days later. As shown, whereas the hematoma size increased by approximately 33% from baseline to day 4 to 5, the relative edema volume doubled during this time period. There was no significant correlation between the percent change in hematoma volumes and percent change in the corresponding relative perihematoma edema volume ($r_s = 0.27; p = 0.30$).

The median duration of hospitalization was 12 days (range: 2–42; mean ± SD: 16 ± 10.9). Eleven (34.4%) had early neurological deterioration. Seven (21.9%) patients died during hospitalization. The mortality rate was 18.5% in 30 days, 21.8% in 90 days, and 31.3% in 180 days. The median NIHSS score was 12.5 (IR:4–31) at 3 months. Six (18.8%) patients had mRS $^2$ at 3 months.

The mean latency between stroke onset and PSG was 20.2 ± 12.5 h (table 2). The mean AHI was 24.27 ± 24.0 (range 0–92). Twenty patients (62.5%) had an AHI ≥10. Of these, 9 had an AHI ≥30. Among the 20 patients with AHI ≥10, apneas were predominantly obstructive (95%) subjects, and central in only 1 (5%). Cheyne-Stokes respiration was detected in 3 (9.4%) patients, in whom clinical examination and history did not disclose signs or symptoms suggestive of heart failure. At echocardiography, all of them had concentric ventricular hypertrophy, but the ejection fraction was within normal values.

Compared to the patients with AHI <10, patients with AHI ≥10 had no differences in age, BMI, previous history of witnessed apneas or hypersomnia, risk factors for stroke, systolic and diastolic blood pressure, hematocrit, temperature on admission, fasting serum glucose, ICH location and volume, neurologic impairment, or functional outcome during the 6 months of follow-up. Nevertheless, in patients with AHI ≥10, a positive history of loud frequent snoring was far more frequent (60 vs. 16.7%, $p = 0.02$) than in patients with AHI <10. That was the only significant difference between patients with AHI <10 and AHI ≥10. In patients with AHI ≥30, a positive history of loud frequent snoring was also more frequent (66.7 vs. 16.7%, $p = 0.03$) when compared to patients with AHI <10. Additionally, patients with AHI ≥30 had more relative perihematoma edema (56.24 ± 26.6 vs. 37.8 ± 19.60; $p = 0.029$) than patients with AHI <10. We found no correlation between AHI ≥10, AHI ≥30, and outcome.

Table 3 shows the correlation coefficients of clinical and polysomnographic variables (including serum AHI on admission) with relative edema volume. After adjusting for multiple comparisons, there was a significant positive correlation between AHI and relative perihematoma edema volume that was weak at baseline ($r_s = 0.40; p = 0.030$), at 24 h ($r_s = 0.46; p = 0.011$) and increased to moderate at day 4–5 ($r_s = 0.59; p = 0.006$). The total white blood cell count on admission was the only other clinical or laboratorial variable that had a positive correlation with relative edema volume at day 4–5 ($r_s = 0.57; p = 0.008$).

Discussion

Using a full PSG system, we evaluated 32 consecutive non-comatose patients with an acute hypertensive ICH and found a high percentage (59.4%) of OSA. To our knowledge, this is the first study that focused on the frequency and severity of OSA in patients with acute hypertensive ICH using a full PSG (the gold standard diagnos-
tic method). Moreover, we found a consistent relationship between the severity of OSA in the acute phase of ICH and the development of perihematoma edema, measured on serial CT scans done at admission, after 24 h and days 4–5.

At least 3 previous studies that searched for sleep breathing disorders in the acute phase of stroke have included ICH patients among their series [18–20]. In 2 of those studies, data from the few ICH patients included were analyzed together with ischemic stroke patients [18, 19]. In the third study, no distinction was possible between obstructive and central events because the authors only used pulse oximetry to screen for sleep apneas [20]. All of those studies have found high percentage (64–90%) of oxygen desaturations in the acute phase of ICH, which is in accordance with our results. We found a higher frequency (43.8%) of previous snoring in our study population of hypertensive ICH patients and history of snoring was associated with OSA at PSG, which may suggest that OSA was present before the ICH. Whether OSA independently contributed to the development of ICH is speculative, and should be addressed by future prospective studies that follow hypertensive patients with and without OSA.

Several mechanisms contribute to the development of brain edema after ICH. There is an early phase during the first few hours after the ictus involving hydrostatic pressure during hematoma formation and clot retraction, a second phase during the first 24 h resulting from thrombin production and activation of the coagulation cascade, and a delayed phase involving hemolysis of red blood cells and hemoglobin-mediated toxicity [21, 22]. The amount of perihematoma edema has also been related to several factors such as the serum ferritin level and increased activity of matrix metalloproteinase-9, an enzyme that is important for the remodeling of the blood brain barrier and appears to play a key role in the generation of perihematoma edema [23–26].

Patients with OSA experience repetitive episodes of hypoxia/reoxygenation during transient cessation of breathing that promote systemic oxidative stress, activation of the coagulation cascade, inflammation, and impaired repair capacity of the vascular endothelium [6]. Therefore, OSA may contribute in several pathways to the development of perihematoma edema. Most interestingly, OSA has also been recently related to increased activity of matrix metalloproteinase-9 [27]. These findings give biological plausibility for the association between OSA and perihematoma edema, but the role of matrix metalloproteinase-9 on this association needs to be addressed by additional studies in the future.

There are some limitations to our study, mainly related to a relatively small sample size. As expected, several ICH patients that were initially screened for this study were comatose and required early orotracheal intubation for airway protection. As orotracheal intubation and positive ventilation prevent OSA in the acute phase, screening with PSG is neither applicable nor necessary for those patients; therefore, they were excluded from the study. Exclusion of comatose patients has also been frequent in ICH trials because a severe pre-hospital neurologic deterioration might prevent the required prognosis for some therapeutic interventions [28, 29]. Although this might limit the direct extrapolation of our conclusions to the whole population of ICH patients, there are no clear reasons to believe that the correlation between AHI and edema would behave differently in patients with more severe ICH. Most notably, our findings apply to the impor-

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<th>Admission CT scan</th>
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<th>Day 4 to 5 CT scan</th>
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<td>0.24</td>
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<td>0.30</td>
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<tr>
<td>Mean arterial pressure</td>
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<td>0.90</td>
<td>–0.11</td>
<td>0.56</td>
<td>–0.27</td>
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<td>Baseline serum glucose</td>
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<td>0.04</td>
<td>0.80</td>
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<tr>
<td>AHI</td>
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<td>0.03*</td>
<td>0.46</td>
<td>0.01*</td>
<td>0.59</td>
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* p = 0.05.

^a Statistically significant correlation (p < 0.01) corrected for multiple comparisons.
tant subgroup of ICH patients with higher Glasgow coma scale scores at admission, i.e. those with a greater risk of inhospital neurologic deterioration [29]. These are also the patients most likely to benefit from potential treatment modalities intended to prevent deterioration, such as haemostatic treatment, early surgical intervention or non-invasive positive ventilation. Hence, our results are important at least for hypothesis generating at this point.

We found no association among AHI and outcome. Nevertheless, this study was not planned to detect a significant difference regarding mortality at this moment. Indeed, it is still controversial whether or not perihematoma edema formation contributes to ICH-induced neurological deficits [12, 21]. Subsequent studies might help to clarify the clinical impact of OSA in the evolution of ICH patients.

In conclusion, we found that OSA is highly frequent in non-comatose patients during the acute phase of hypertensive ICH, and its severity correlates to the development of perihematoma edema. Given the biological plausibility of this association, additional studies are necessary to confirm a causal relationship between sleep apnea and perihematoma edema, the clinical impact of OSA in the evolution of patients with acute ICH, and whether there is any prospect for non-invasive pressure ventilation to decrease edema in selected patients with ICH.

References


