ORIGINAL ARTICLE

Effect of transnasal insufflation on sleep disordered breathing in acute stroke: a preliminary study

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Abstract

Background and Purpose Sleep disordered breathing (SDB) is frequent in acute stroke patients and is associated with early neurologic worsening and poor outcome. Although continuous positive airway pressure (CPAP) effectively treats SDB, compliance is low. The objective of the present study was to assess the tolerance and the efficacy of a continuous high-flow-rate air administered through an open nasal cannula (transnasal insufflation, TNI), a less-intrusive method, to treat SDB in acute stroke patients.

Methods Ten patients (age, 56.8±10.7 years), with SDB ranging from moderate to severe (apnea–hypopnea index, AHI, >15/h of sleep) and on a standard sleep study at a mean of 4.8±3.7 days after ischemic stroke (range, 1–15 days), were selected. The night after, they underwent a second sleep study while receiving TNI (18 L/min).

Results TNI was well tolerated by all patients. For the entire group, TNI decreased the AHI from 40.4±25.7 to 30.8± 25.7/h ($p=0.001$) and the oxygen desaturation index >3% from 40.7±28.4 to 31±22.5/h ($p=0.02$). All participants except one showed a decrease in AHI. The percentage of slow-wave sleep significantly increased with TNI from 16.7± 8.2% to 22.3±7.4% ($p=0.01$). There was also a trend toward a reduction in markers of sleep disruption (number of awakenings, arousal index).

Conclusions TNI improves SDB indices, and possibly sleep parameters, in stroke patients. Although these changes are modest, our findings suggest that TNI is a viable treatment alternative to CPAP in patients with SDB in the acute phase of ischemic stroke.

Keywords Transnasal insufflation · Stroke · Sleep disordered breathing

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Abbreviations

SDB	Sleep disordered breathing
CPAP	Continuous positive airway pressure
TNI	Transnasal insufflation
AHI	Apnea–hypopnea index
CBFV	Cerebral blood flow velocity
PSG	Polysomnography
BL	Baseline diagnostic night
RERAs	Respiratory effort-related arousals
RDI	Respiratory disturbance index
ODI	Oxygen desaturation indexes
NIHSS	National Institutes of Health Stroke Scale
OAI	Obstructive Apnea Index
CAI	Central Apnea Index
MAI	Mixed Apnea Index
HI	Hypopnea Index

Background

A recent meta-analysis found that sleep disordered breathing (SDB) is present in up to 72% of stroke patients [1]. SDB was primarily obstructive in nature, only 7% of patients having primarily central apneas. SDB is known to increase the risk of stroke and stroke risk factors (as hypertension) [2]. In the acute phase of stroke, when ischemic penumbra is still present [3], the consequences of recurrent apneas may have the most deleterious effect on critically ischemic, but viable, brain tissue. It has been shown that, in the acute stroke phase, sleep apnea is associated with early neurologic worsening [4]. The presence of SDB in stroke patients is also associated with worse functional outcomes, daily living dependence, a longer period of hospitalization and rehabilitation [5], and more psychiatric and behavioral symptoms [6]. Despite the absence of scientific proof, it is reasonable to assume that treatment of poststroke SDB may favorably influence stroke outcome [7]. Furthermore, it may be reasonably assumed that early treatment may be more effective than late intervention.

Continuous positive airway pressure (CPAP) is the most effective and widely used therapy for SDB. However, 25–50% of patients with SDB will refuse or not tolerate the use of CPAP therapy [8, 9]. The adherence to CPAP treatment seems even lower in stroke patients with SDB. With the exception of some studies performed in the rehabilitation poststroke setting and in selected patients showing higher adherence rates [10–12], reported CPAP compliance in the acute [13–16] and sub-acute stroke phase [12, 17–19] is around 25–50%. Most patients had stroke-related problems that caused non-compliance, including facial palsy inducing CPAP mask leaks [20]. Reasons for discontinuation treatment also include mask discomfort, difficulty tolerating pressure, claustrophobia, skin breakdown, inability to apply headgear, mask, and hose, and to readjust equipment. In addition, little is known on the effects of CPAP on cerebral hemodynamics. Data about the effects of CPAP upon cerebral perfusion are conflicting [21–23], but studies, performed in healthy volunteers [24] and in acute stroke patients [16], have shown that CPAP could lead to a decrease in cerebral blood flow velocity (CBFV). Thus, there is a clear need for alternative treatments in these patients.

Transnasal insufflation (TNI) is a less-invasive method to treat apneas/hypopneas. It delivers warm and humidified air at a continuous high flow rate through an open nasal cannula. Treatment with TNI has been shown, in previous studies, to significantly reduce the apnea–hypopnea index (AHI) in adults [25, 26] and children [27]. The primary mechanism of action of TNI appears to be related to small increases in end-expiratory pharyngeal pressure. The present study was designed to determine if TNI is well tolerated in acute stroke patients and whether treatment with TNI alleviates SDB in these patients.

Materials and methods

Recruitment and demographic characteristics

Participants were recruited from patients admitted for acute ischemic stroke at the stroke unit of the CHUV (Lausanne, Switzerland). The study received institutional review board approval, and after receiving a detailed explanation of the protocol, each subject signed a written informed consent to take part in the study. Patients unable to consent due to the severity of the stroke were excluded. We calculated that we needed to include ten subjects to have an 80% power to detect a 5 ± 5-event-per-hour difference on AHI using a paired t test with an alpha of 0.05.

Study protocol

Patients underwent two consecutive polysomnographies (PSG) as soon as circumstances allowed it. Night 1 was used to diagnose the presence of SDB (baseline diagnostic night: BL). PSG was performed in the hospital room with titanium recorders and Somnologica biosignal analysis software (Embla, Broomfield, CO). Signals included electroencephalograms (F3-A2, F4-A1, C3-A2, C4-A1), left and right electrooculograms, submental electromyogram, electrocardiogram, oxyhemoglobin saturation, body position, nasal pressure, and thoracic and abdominal respiratory movements.

If AHI was >15/h, a second polysomnography with TNI was performed on the following night (TNI treatment night: TNI). As previously described [25], TNI consists of an air compressor (Seleon, Freiburg, Germany) delivering a constant airflow up to 20 L/min through a nasal cannula. We chose to apply a flow of 18 L/min for comfort reasons. A heater and humidifier included in the TNI device regulated the temperature and humidity. A heated wire was incorporated into the lumen of the nasal cannula tubing to achieve a temperature of 30–33°C and relative humidity of approximately 80% at the nasal outlet.

Analysis

Standard PSG scoring techniques were used to stage sleep and arousals [28]. Respiratory events were scored according to the "Chicago criteria" [29]. An apnea was defined as complete cessation of airflow for more than 10 s. We differentiate apneas into obstructive, mixed, or central, according to the presence or absence of discernable

excursions of either the chest or abdomen. A hypopnea was defined as a decrease >50% of airflow from baseline or a clear amplitude reduction (>30% but <50%) associated with either an oxygen desaturation of >3% or an arousal. Respiratory effort-related arousals (RERAs) were identified as a series of flow-limited breaths that was terminated by an arousal. An AHI for each individual was calculated, as well as a respiratory disturbance index (RDI), consisting of the number of apnea + hypopnea + RERA per hour of sleep. We also determined an AHI in REM and NREM sleep.

We calculated oxygen desaturation indexes (ODI): ODI3 was defined as the number of 3% desaturation per hour of sleep, and the ODI4 was defined as the number of 4% desaturation per hour of sleep. Sleep studies were scored by a unique, experienced, and registered polysomnographic technician (DA) and independently reviewed by one of the authors (JHR).

Statistical analysis

Data are shown as mean and standard deviation, if not otherwise specified. A paired Student's t test was performed to compare differences in polysomnographic indices between BL diagnostic and TNI treatment night. A p value <0.05 was considered statistically significant. Statistical analyses were performed with a software program (IBM SPSS Statistics 18, SPSS Inc., Chicago, IL).

Results

Subject demographics

For this study, we approached 15 patients admitted for acute ischemic stroke. Five were excluded for analysis after the BL night: one for technical problems with the PSG recording, two refused the second PSG, and two had an AHI <15/h at BL. The remaining ten patients who completed the study were all men, with a mean age of 56.8±10.7 years. Their median score on the National Institutes of Health Stroke Scale at admission was 4±4.3 (range 1–13). According to the Oxford Community Stroke Project classification [30], 3 had partial anterior circulation infarct, 2 had posterior circulation infarct, and 5 had lacunar infarct. PSG was performed 4.8±3.7 days after the stroke symptom onset (range 1–15 days). No patient included in the study was previously diagnosed for sleep apnea syndrome, and none of them had ever been treated by CPAP.

Effect of TNI on SDB indices and on sleep variables

TNI was well tolerated by patients with acute stroke: there were no reports of significant discomfort or side

effects after a full night of treatment with TNI. Overall, TNI led to a 23.8% reduction in the AHI (40.4±25.7 to 30.8±25.7/h, $p=0.001$) (Fig. 1). The RDI was also significantly decreased (41±25.4 vs. 31.4±25.4/h, $p=0.001$) (Table 1). TNI decreased the AHI both in REM (39.8±16.8 vs. 28.7±21.4/h, $p=0.048$) and NREM sleep (40.5±28.9 vs. 31±28.9/h, $p=0.003$).

The ODI3 and the ODI4 both significantly improved with TNI: 40.7±28.4 vs. 31±22.5/h, $p=0.02$, and 32.1±27.7 vs. 22.8±19/h, $p=0.04$, respectively. No significant change was observed in the mean oxygen saturation (92.8±1.6% vs. 93.1±1.8%, $p=0.1$).

TNI induced heterogeneous response rates among participants. Noticeable reductions in the AHI were observed for eight patients, in particular in patients with moderate SDB. In one of them, the AHI normalized (<5/h). In one patient with severe SDB, the AHI fell only minimally from 87.3 to 86.2/h. In one subject, the AHI was greater with TNI (17.5 vs. 21.4/h).

Sleep structure also improved with TNI. The percentage of slow-wave sleep (SWS) significantly increased with TNI (16.7±8.2% vs. 22.3±7.4% of total sleep time, $p=0.01$). No changes were noted in the distribution of other sleep stages. TNI showed a tendency to decrease markers of sleep disruption, with fewer awakenings (24.5±9.3 vs. 17.9±8.3, $p=0.05$), a decreased arousal index (28.9±24.1 vs. 22.4±22.4/h, $p=0.06$), and a decreased respiratory arousal index (23.9±27.6 vs. 17.3±24.5/h, $p=0.06$). The sleep time spent in the supine position was similar in both nights (336.4±41.8 vs. 326.6±89 min, $p=0.7$).

Discussion

This study was designed to examine the tolerability and the effect of treatment with TNI on SDB in a series of patients with acute stroke. TNI was well accepted, and no significant side effects were reported. Globally, TNI
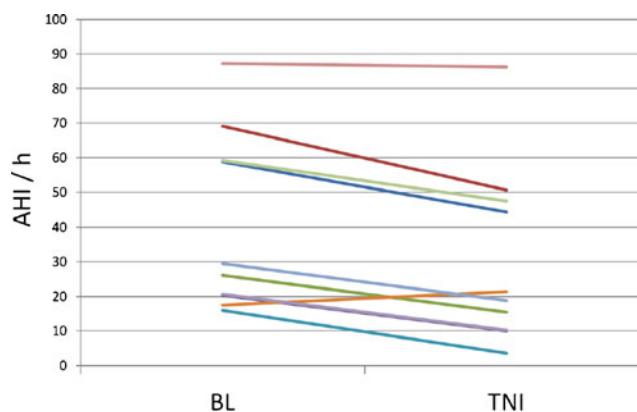

Fig. 1 AHI during the BL diagnostic and the TNI treatment nights

Table 1 Indices of SDB and sleep characteristics

	BL diagnostic night	TNI treatment night	p value
TST, min	419.4±43	410.3±95.1	0.77
TST in supine position, min	336.4±41.8	326.6±86.8	0.76
Sleep efficiency, %	81±8	77±13	0.31
Stage 1, %	19.6±12.1	14.4±4.8	0.13
Stage 2, %	43.8±6.2	42.3±7.7	0.63
SWS, %	16.7±8.2	22.3±7.4	0.01
REM, %	19.7±6	20.8±5.4	0.71
WASO, min	100.3±43.1	118.9±61.4	0.33
Awakenings, nr	24.5±9.3	17.9±8.3	0.05
Arousal index, nr/h	28.9±24.1	22.4±22.4	0.06
Respiratory arousal index, nr/h	23.9±27.1	17.3±24.5	0.06
AHI, nr/h	40.4±25.7	30.8±25.7	0.001
OAI, nr/h	8.6±8.6	4.9±4.9	0.08
CAI, nr/h	2±3.1	3.3±4	0.16
MAI, nr/h	8.2±13	3.5±5.7	0.1
HI, nr/h	23.8±16.2	19.2±18.2	0.26
RDI, nr/h	41±25.4	31.4±25.4	0.001
AHI NREM, nr/h	40.5±28.9	31±28.9	0.003
AHI REM, nr/h	39.8±16.8	28.7±21.4	0.04
Mean SpO_2, %	92.8±1.6	93.1±1.8	0.16
ODI >3%, nr/h	40.7±28.4	31±22.5	0.02
ODI >4%, nr/h	32.1±27.7	22.8±19	0.04

TST total sleep time, *SWS* slow-wave sleep, *REM* rapid eye movement, *WASO* wake after sleep onset, *AHI* apnea/hypopnea index, *OAI* obstructive apnea index, *CAI* central apnea index, *MAI* mixed apnea index, *HI* hypopnea index, *RDI* respiratory disturbance index, SpO_2 oxygen saturation index, *ODI* oxygen desaturation index

significantly lowered the AHI and the ODI and improved sleep stage distribution with an increase in slow-wave sleep, but the magnitude of the improvement was rather modest.

In a previous study, McGinley et al. assessed the efficacy of TNI in 11 selected subjects with mild to severe obstructive apnea–hypopnea syndrome [25]. TNI led to a mean reduction of 63.2% in the overall AHI (28±5 to 10± 3/h), and some improvement of the AHI was observed in each subject. Recently, in a larger study, Nilius et al. studied 56 patients with a wide spectrum of disease severity [26]. TNI decreased the RDI from 22.6±15.6 to 17.2±13.2 events/h, thus a 31% mean reduction of the RDI, which is closer to our results. Although TNI decreased RDI in the majority of patients, some demonstrated a marked increase in the RDI. In our study, we obtained a mean global reduction of 23.8% of the AHI. We also found heterogeneous response rates between patients. In one subject with moderate SDB, the AHI even increased in the night with TNI (17.5 vs. 21.4/h), and in one patient

with severe SDB, the AHI fell only minimally. Compared with the previous populations studied, our patients were older (57.1±11.3 years) and, overall, had a more severe SDB (AHI 44.5±25.3/h). We used a slightly lower flow rate of 18 L/min (vs. 20 L/min in previous studies) to guarantee a maximum of comfort.

We observed that the effect of TNI on respiratory events was modest in most patients. Nasal CPAP is very likely to be more efficacious in reducing the AHI. However, CPAP is often not well tolerated, in particular in the acute phase of stroke. In addition, CPAP is known to increase intrathoracic pressure and therefore potentially could increase central venous and intracranial pressure and reduce cardiac output [31–33]. The anxiety induced by the sensation of breathing against a positive pressure could induce hyperventilation and hypocapnia and, in turn, increase cerebrovascular resistance. Moreover, studies performed in healthy volunteers [24] and in acute stroke patients [16] have shown that CPAP could lead to a decrease in CBFV, as measured by transcranial doppler. The negative consequences of a fall in CBFV may outweigh the therapeutic benefits of CPAP in the poststroke settings.

We thus believe that TNI offers a simplified nasal interface for delivering relatively low levels of pharyngeal pressure. Additionally, TNI does not require titration. TNI could be an alternative treatment of SDB when the use of CPAP is not feasible. The main question is whether the relatively modest AHI reduction with TNI will have a clinically significant effect on short- and long-term outcomes. In some clinical circumstances, even small decreases in SDB severity have had a profound clinical impact: Redline et al., analyzing data from a large prospective cohort of middle-aged and older adults, recently confirmed that OSA increases risk of first-time ischemic stroke, in particular in men [34]. In this population, the risk of stroke increased by 6% with every unit increase in baseline AHI from 5 to 25/h.

Moreover, the impact of treating SDB in the acute stroke phase, when cerebral tissue perfusion is seriously compromised, could be particularly important: apneas in the acute stroke phase have been associated with early neurologic worsening [4], and it has been shown that the presence of SDB in stroke patients is associated with worse functional outcomes [5, 6, 12]. Two studies have demonstrated reductions in cerebral tissue hemoglobin saturation levels with apneas [35, 36]. The severity of tissue deoxygenation correlated with the length of the respiratory disturbance events and the degree of related desaturation. Respiratory events also induce marked hemodynamic changes. At the onset of apnea, there is hypotension and progressive bradycardia, followed by abrupt tachycardia on resumption of breathing [37]. These changes are associated with large fluctuations in CBFV [38, 39]. The repeated hemodynamic

oscillations that accompany both occlusion of the upper airway and the post-apneic phase may have a deleterious effect in the penumbra zone. Reducing the AHI, even mildly, may have a positive effect on tissue survival after stroke.

There are several limitations to the current study. First of all, only a limited number of patients were included in this preliminary study and makes its generalizability to all stroke patients questionable. Also, only male patients were recruited. Because of the small number of patients studied, it is not possible to determine demographic or polysomno-graphic predictors for treatment responses. TNI was used for only one night, and further studies of TNI administered over several nights would be required to examine its long-term effects. We used a fixed relatively low flow rate of 18 L/min, determined empirically (no titration) to guarantee a maximum of comfort of TNI. We could speculate that a higher flow rate could yield better results. Since the order of baseline and TNI nights were not randomized, one could argue that the observed therapeutic effects of TNI may be attributed to the expected spontaneous decrease of apneas as stroke recovery progresses. The response rate to TNI was almost twofold as high as the expected night-to-night variability in sleep apnea severity of 13% [40]; however, randomizing TNI nights was beyond the scope of the current study. As patients were studied in the acute phase of stroke, they spent most of the night in the supine position (around 80% of the total sleep time, TST). This could be another factor responsible for the modest effects of the treatment: the supine position increases the severity of respiratory events, counteracting the expected improvement of treatment, if TNI does not act as a mechanical splint (as CPAP or oral devices) but by means of a functional increase of the expiratory pharyngeal pressure.

In summary, this preliminary study provides evidence that TNI is a viable alternative treatment, when CPAP is not tolerated or not indicated, in patients with SDB in the acute phase of ischemic stroke and induces a significant reduction in AHI in these patients. Further studies will be required to confirm these findings and to determine the effect of TNI in long-term outcome of stroke patients.

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