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Original Article

Hyperviscosity as a possible cause of positive acoustic evoked potential findings in patients with sleep apnea: A dual electrophysiological and hemorheological study

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Abstract

Objective: To test the hypothesis that blood hyperviscosity could account for the controversial results observed during electrophysiological evaluation of the brain stem in sleep apnea syndrome.
Methods: This was a prospective study of a sample of patients with sleep apnea who were participating in a stroke prevention evaluation. Participants were 610 male patients with obstructive sleep apnea, aged 30–55 years, without large vessel disease on Magnetic Resonance Angiography and neck Doppler sonography, and an infratentorial lesion on head magnetic resonance imaging. Brainstem auditory-evoked potential and hemorheological investigations were carried out.
Results: Forty-six percent ($N = 282$) of the patients evidenced hyperviscosity and 53% ($N = 328$) had normal rheological findings. Evoked potential changes appeared only in the hyperviscosity positive subgroup. Of these, 84% ($N = 239$) evidenced BAEP changes with 24% ($N = 57$) demonstrating sensorineuronal and 76% ($N = 182$) demonstrating brain stem type abnormalities. After six months of CPAP therapy, hyperviscosity was normalized in 66% ($N = 159$) of patients. BAEP wave III latency values were normalized in 70% ($N = 112$) of these patients.
Conclusions: Viscosity changes play an important role in the brainstem electrophysiological abnormalities in apnea patients. These abnormalities can be normalized after six months of CPAP therapy.

Keywords: Blood hyperviscosity; Brain stem auditory evoked potential; Obstructive sleep apnea

1. Introduction

Obstructive sleep apnea (OSA) syndrome is often associated with substantial vascular morbidity and mortality, but why that is the case remains controversial.

A recent study concluded that OSA significantly increases the risk of stroke and death from any cause [1]. In this study, risk association was independent of major factors for stroke such as hypertension, suggesting that additional pathogenetic mechanisms may play a contributory role. OSA induced hyperviscosity [2–3] leading to altered cerebral blood flow and hypercoagulability could be one of these possible mechanisms. Based on our prior observation [4] of an association among OSA, hyperviscosity and changes in normal patterns of brain stem auditory evoked potentials (BAEPs) in OSA patients with hyperviscosity, we sought to study BAEPs changes in OSA patients with and without hyperviscosity in an effort

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to more carefully document specific BAEPs changes that are reliably associated with hyperviscosity in OSA patients. BAEP is an inexpensive, reproducible method used in a variety of clinical settings.

A small number of studies have investigated BAEP functions in OSA patients, but these studies were plagued by small sample sizes, lack of control groups and inconsistent findings across laboratories [5–9]. While several studies have reported symmetric wave prolongations in OSA patients of varying severities, a few studies reported normal BAEP functions in OSA [10–12].

In at least one study of severe OSA patients, BAEP abnormalities have been linked with lesions localized to the middle brain stem regions, and BAEP abnormalities increased with the duration of the disease [13].

Interestingly, although OSA is often characterized by altered hemorheological state, the lack or presence of hyperviscosity was not considered in these previous BAEP studies. In this study we studied a large sample of OSA patients with hyperviscosity of varying severity and compared them with control patients without hyperviscosity. We also studied BAEP functions before and after CPAP therapy. This experimental design allowed us to definitively test the effect of hyperviscosity on BAEP functions in OSA patients.

2. Methods

2.1. Patients

We recruited a convenience sample of 800 newly diagnosed patients with OSA to carry out hemorheological and BAEP studies both at baseline and after CPAP therapy. Those patients with abnormal rheology and/or BAEP evaluation at six months had an additional hemorheological and BAEP study following hemodilution.

Out of 800 consecutive male patients (aged between 30–55 years) newly diagnosed with OSA (apnea/hypopnea index > 5/h) by a polysomnographic study, 763 were candidates for CPAP therapy (apnea/hypopnea index > 30/h). An additional brain MRI and MR angiography and neck Doppler sonography excluded 73 patients due to preexisting infratentorial lesion or large vessel disease. Stenoses exceeding 50% of one or more arterial branches and/or plaque ulceration were the criteria of large vessel involvement. Patients with a supratentorial MRI lesion were not excluded. These anomalies were lacunar lesions either in the centrum semiovale or in the basal ganglia not exceeding 1 cm in diameter. Baseline cardiac evaluation excluded another 68 patients due to chronic atrial fibrillation, sick sinus syndrome, left ventricular enlargement and prior myocardial infarction. The diagnosis of diabetes mellitus was diagnosed according to clinical history and use of specific medication if the serum level was in normal range. We recorded a lipid disorder as present if the patient was taking lipid lowering medication at recruitment and if serum lipids (cholesterol or cholesterol and triglyceride) were not higher than the upper limit. Patients with abnormal serum levels at recruitment (n:12) were excluded. Patients with high lipid levels and diabetes were previously diagnosed under medication treatment, and laboratory results showed that their condition was compensated. For drinking and smoking habits see Table 1 and 2. Patients tagged as alcohol users had two or more hard drinks per day. Current smokers had more than 20 cigarettes per day. We found no significant background clinical differences between groups one to six (Table 2). The mean data values for CPAP compliance, arousal index, alcohol consumption, tobacco, diabetes, lipid and hypertonia did not differ significantly across groups. High blood pressure was commonly reported among the groups of patients.

Table 1
OSA patient characteristics

	Subgroup of patients					
	I. $N = 328$	II. $N = 112$	III. $N = 47$	IV. $N = 61$	V. $N = 19$	VI. $N = 49$
Mean age (years)	48	42	40	49	41	44
Mean (±SD) BMI (kg/m^2)	29.98 (2,17)	28.15 (2,08)	27.23 (2,14)	30.31 (2,06)	27.05 (1,95)	31.21 (2,18)
Reported mean length of observed apnea (years)	6.81 (3,06)	7.44 (4,34)	6.38 (5,65)	7.26 (5,31)	6.63 (5,65)	7.22 (6,25)
Number of patients treated for hypertension (percentage of group)	261 (79.6%)	102 (91%)	41 (87.2%)	54 (88.5%)	14 (73.6%)	34 (79%)
Number of patients with supratentorial MRI white matter lesion	21 (6.4%)	8 (7.1%)	5 (10.6%)	7 (11.4%)	3 (15.8%)	5 (11.6%)
Number of patients with diabetes (percentage of group)	9 (2,70%)	3 (2,60%)	2 (4,20%)	3 (4,90%)	1 (5,20%)	4 (9,30%)
Number of patients with lipid disorders	29 (8,80%)	8 (7,10%)	3 (6,30%)	4 (6,50%)	0	4 (9,30%)
Number of current smoker	92 (28%)	43 (38,30%)	12 (25,50%)	22 (36%)	8 (42,10%)	14 (32,5%)
Number of alcohol user	31 (9,45%)	14 (12,50%)	3 (6,30%)	6 (9,80%)	2 (10,50%)	4 (9,30%)

I: OSA patients with normoviscosity and negative BAEP.
II: Six months of CPAP treatment normalizing viscosity and BAEP.
III: CPAP treatment normalizing viscosity but not BAEP.
IV: Hemodilution needed to normalize viscosity and BAEP.
V: Hemodilution normalizing viscosity but not BAEP.
VI: OSA patients with hyperviscosity and negative BAEP.

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Table 2
Results of the sleep study and effectiveness of CPAP therapy

	Subgroup of patients					
	I. $N = 328$	II. $N = 112$	III. $N = 47$	IV. $N = 61$	V. $N = 19$	VI. $N = 49$
AH/I before CPAP treatment	45.21 (6,09)	45.04 (8,17)	51.53 (7,16)	45.98 (7,8)	46.78 (8,03)	47.32 (8,2)
AH/I at 6 month control	2.24 (1,18)	2.76 (1,31)	2.65 (1,16)	3.21 (1,12)	2.63 (1,46)	2.58 (1,19)
Arousal index before CPAP treatment	45.17 (6,11)	44.76 (6,88)	51.7 (7,46)	45.67 (7,25)	47.68 (8,45)	52.31 (8,22)
Arousal index at 6 month control	5.2 (1,20)	5.67 (1,28)	5.44 (1,19)	5.09 (1,19)	5.31 (1,05)	5.23 (1,11)
ST02 < 90%*	62.22 (1,27)	61.12 (2,11)	61.44 (1,87)	63.75 (2,01)	60.32 (1,87)	64.12 (1,88)
CPAP compliance (hours per all days)	5.67 (0,81)	5.78 (0,82)	5.88 (0,84)	5.89 (0,83)	5.75 (0,81)	5.45 (0,88)

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IV: Hemodilution needed to normalize viscosity and BAEP.
V: Hemodilution normalizing viscosity but not BAEP.
VI: OSA patients with hyperviscosity and negative BAEP.
* Percent of total sleep time spent with oxygen level less than 90%.

Participants gave either written or oral informed consent and the study was approved by the Human Investigation Committee at Hungarian Home Defense Force.

2.2. BAEP investigations

BAEP was recorded following sound clicks 75 dB above the hearing threshold determined previously. Clicks were generated by a stimulator and delivered through headphones. The amplifier's band pass was 150–3000 Hz. Waves were recorded by gold cup electrodes with the active electrode placed at the vertex (Cz) and the difference electrode placed at the mastoid ipsilateral to the ear of stimulation and the ground at the contralateral mastoid (inter-electrode impedance <5 kΩ). Each test consisted of a minimum of 2000 stimulus presentations, and at least two tests demonstrating reproducibility were obtained for each ear. Before BAEP testing, all patients had normal audiometry results. Reference values based on our laboratory's normal values (which were previously tested and matched for age and gender) were used to evaluate BAEP findings. Abolition of one or more waves or significant prolongation of one or more peak latencies was considered to be an abnormal finding. Based on the reference values, latency of wave I exceeding 2 ms, latency of wave III exceeding 4 ms and latency of waves IV–V exceeding 6 ms were considered a positive result. Concerning interpeak latencies (IPL), I–V exceeding 4.5 ms, I–III exceeding 2.4 ms, and III–V exceeding 2.5 ms were considered abnormal. V/I amplitude ratio less than 1 was also considered abnormal.

2.3. Hemorheological evaluation

Blood samples were drawn at the same time in the morning. Whole blood viscosity was measured by a computer operated and shear rate gradient dependent capillary viscosimeter (Hevimet 40), which has the capacity to measure whole blood and plasma viscosity in the range of 10/s to 200/s shear rate. Out of the above interval, three different shear rates were evaluated: 10/s representing the low, 40/s representing the medium, and 90/s representing the high shear rate gradients. According to the results of a preliminary study at our laboratory, whole blood viscosity is considered normal when it is <6 mPa at 10/s and <5.5 mPa at 40/s or <4.5 mPa at 90/s. Plasma viscosity was measured with the same instrument at 90/s. It was considered normal when it was <1.35 mPa.

2.4. Haemodilution

Three hundred milliliters of blood was taken from a peripheral vein followed by administration of 500 ml 0.9% NaCl for three consecutive days. On day four and five 500 ml of hydroxyethyl starch solution (HES 6:1) was infused.

2.5. Sleep study

A complete overnight sleep study was performed on a polysomnographic system (Alice 4, Respironics Inc., USA) with the following montage: two-channel electroencephalogram, right and left electro-oculogram and a chin myogram (using standard method with Gold Cup electrodes), oronasal air flow (thermistor and nasal cannula-pressure transducer), thoracic and abdominal piezo electric respiratory effort belts, oxygen saturation (Healthdyne 930 pulseoximeter) and electrocardiogram using precordial leads. Sleep data were staged for 30-s intervals manually according to standard criteria [14]. Arousals were assessed according to ASDA criteria (ICSD-2): an arousal was defined as an abrupt shift in EEG frequency, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles. Ten seconds of continuous sleep must precede the arou-

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sal. The arousal must last three seconds and it must be accompanied by an increase in chin EMG if it occurs during rapid eye movement sleep.

2.6. Indicators of sleep-disordered breathing

For this analysis apnea and hypopnea index (AHI) was calculated. An apnea or hypopnea was defined as a respiratory event lasting at least 10 s that was associated with an oxyhaemoglobin desaturation of 4% or greater as compared with baseline and during which airflow completely ceased (apnea) or was 25% (hypopnea) of the baseline amplitude. AHI was defined as the total number of apneas and hypopneas per hour of electroencephalographic sleep. An indicator of hypoxaemia, the mean of the respiratory event oxygen minimum levels and the percent of total sleep time spent under 90% oxygen level (ST02 < 90%) was also examined. To quantify sleep fragmentation, arousal index was calculated (the number of arousals related to the total sleep time).

2.7. Follow-up

CPAP therapy was assessed by polygraphic study six months after initiation of therapy. At the same time, data of an Encore Pro system with a built-in counter—indicating the hours of usage of all days – were collected to monitor CPAP compliance. For compliance results see Table 2. In all cases repeated rheological investigation was performed six months after initiation of CPAP therapy. Two hundred and thirty-nine hyperviscosity patients with positive first BAEP findings had repeated BAEP at the six month follow-up. In some patients, where, in spite of CPAP treatment, rheological results remained positive, a course of hemodilution therapy was necessary ($n = 80$), and a third BAEP test was performed after hemodilution therapy.

2.8. Statistical analysis

A series of one-way ANOVAs were used to assess differences in clinical variables across groups. Paired Student's *t*-tests were conducted to check whether the patient group means were significantly different before and after the treatment. Bonferroni correction factor was used where appropriate to protect against false positives due to multiple tests.

3. Results

Forty-six percent ($N = 282$) of the patients evidenced hyperviscosity and 53% ($N = 328$) had normal rheological findings. Evoked potential changes appeared only in the hyperviscosity positive subgroup. Of these, 84% ($N = 239$) evidenced BAEP changes with 24% ($N = 57$) demonstrating sensorineuronal and 76% ($N = 182$) demonstrating brain stem type abnormalities. Abolition of all waves including wave I was evident in the sensorineuronal cases. This pattern indicates cochlear lesion. In all cases abnormalities appeared on both sides.

Significant delay in wave III peak latency occurred in the brain stem type lesion subgroup. Peak latency of wave IV/V complex was also slightly prolonged but these values remained beyond normal ranges. This pattern indicates that brain stem auditory pathways are affected at or caudal to the region of the superior olivary complex. Concerning interpeak latencies (IPL), the above finding resulted in significant I–III IPL delay while I–V and III–V IPL values remained in normal ranges. Since the salient feature of brainstem type BAEP abnormality was the significant prolongation of wave III peak latency its value before and after effective treatment will be detailed below.

IPL values are summarized in Table 5. All brain stem type abnormalities were symmetric, affecting both sides. Left/right peak latency differences were less than 0.2 ms (± 0.01). In all cases with brain stem type abnormality, the waves were well configurated and appeared with normal amplitudes.

After six months of CPAP therapy, hyperviscosity was normalized in 66% ($N = 159$) of patients. BAEP wave III latency values were normalized in 70% ($N = 112$) of these patients.

Table 2 depicts changes in apneic and arousal measures after six months of CPAP therapy. Compliance with the therapy was generally high with mean CPAP utilization rates of about 5.5 h per day. Group I. is OSA patients with normal viscosity and negative BAEP, *n*: 328, mean age 48 years. The mean AH/I values after CPAP therapy was 2.24 (1.18), a reduction of 43 points ($t(\mathrm{df}) = 288(654)$), $p < .001$). A similar reduction in the arousal index was noted for group I participants ($t(\mathrm{df}) = 267(654)$), $p < .001$).

In group II (six months of CPAP treatment normalized viscosity and BAEP, *n*: 112, mean age 42 years). Mean reduction of apnea AH/I values was significant ($t(\mathrm{df}) = 145(222)$), $p < .001$, as were arousal episodes ($t(\mathrm{df}) = 144(222)$), $p < .001$).

In group III (CPAP treatment normalized viscosity but not BAEP, *n*: 47 mean age 40 years). Mean reduction of apnea AH/I values was significant ($t(\mathrm{df}) = 116(92)$), $p < .001$, as were arousal episodes ($t(\mathrm{df}) = 108(92)$, $p < .001$).

In group IV Hemodilution needed to normalize viscosity and BAEP, *n*: 61, mean age 49 years. Mean reduction of apnea AH/I values was significant ($t(\mathrm{df}) = 112(120)$), $p < .001$, as were arousal episodes ($t(\mathrm{df}) = 109(120)$), $p < .001$).

In group V Hemodilution normalized viscosity but not BAEP, *n*: 19 mean age 41 years. Mean reduction of apnea AH/I values was significant ($t(\mathrm{df}) = 62(36)$), $p < .001$, as was arousal episodes ($t(\mathrm{df}) = 60(36)$), $p < .001$).

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In group VI OSA patients with hyperviscosity and normal BAEP, *n*: 49 mean age 44 years. Mean reduction of apnea AH/I values was significant ($t(\mathrm{df}) = 96(84)$), $p < .001$, as was arousal episodes ($t(\mathrm{df}) = 101(84)$), $p < .001$).

Results of the rheological testing before and after CPAP and CPAP plus hemodilution therapy are summarized in Tables 3 and 4. At the low shear rate gradient (10/s) in the hyperviscosity subgroups the viscosity parameters were between 8.21 and 8.91 mPa, while in the normal viscosity subgroup these values were below 6 mPa. At the medium shear rate gradient (40/s) in the hyperviscosity subgroups viscosity was in the range of 6.23 and 7.11 mPa. In cases of normal viscosity these values were below 5.5 mPa.

At high shear rate gradients (90/s) in the hyperviscosity subgroups the viscosity parameters were 5.6 to 5.88 mPa. In cases of normal viscosity these values were below 4.5 mPa. All rheologically positive cases had whole blood hyperviscosity with abnormal values at low, medium and high shear rate gradients. In all cases CPAP or CPAP and hemodilution therapy had the capacity to achieve normal viscosity. The profile of viscosity findings were similar in the hyperviscosity subgroups with (II–III–IV–V) or without (VI) BAEP abnormalities. Since measurement of erythrocyte adhesion and aggregation profile, platelet activation and fibrinogen level were not included in the protocol, isolated plasma hyperviscosity could have given rise to

Table 5
BAEP findings

Parameters	Patients with abnormal BAEP $N = 239$	Patients with normal BAEP $N = 371$	Therapy normalising BAEP $N = 173$
Latency (ms) (±SD)			
I	1.62 (0.15)	1.63 (0.17)	1.61 (0.16)
III	4.42 (0.13)	3.71 (0.12)	3.76 (0.18)
V	5.82 (0.14)	5.69 (0.18)	5.71 (0.17)
Interpeak latency (ms) (±SD)			
I–III	2.84 (0.34)	2.08 (0.29)	2.11 (0.19)
I–V	4.2 (0.28)	4.06 (0.35)	4.18 (0.29)
V/I amplitude ratio	3.2 (2.21)	2.95 (2.29)	3.1 (2.26)

Table 3
Results and changing variables of the rheological study

	Subgroup of patients					
	I. $N = 328$	II. $N = 112$	III. $N = 47$	IV. $N = 61$	V. $N = 19$	VI. $N = 49$
Viscosity at 10/s shear rate (mPa) (±SD)	5.81 (0,11)	8.21 (0,13)	8.24 (0,11)	8.87 (0,24)	8.91 (0,25)	8.34 (0,18)
Viscosity at 10/s after CPAP therapy (mPa)	5.78 (0,12)	5.83 (0,12)	5.86 (0,12)	8.88 (0,26)	8.9 (0,25)	5.74 (0,14)
Viscosity at 10/s after hemodilution therapy (mPa)	–	–	–	5.77 (0,12)	5.78 (0,13)	–
Viscosity at 40/s shear rate (mPa)	5.42 (0,12)	6.23 (0,11)	6.44 (0,13)	6.81 (0,20)	7.11 (0,24)	6.32 (0,21)
Viscosity at 40/s after CPAP therapy (mPa)	5.41 (0,12)	5.39 (0,12)	5.37 (0,12)	6.82 (0,21)	6.99 (0,24)	5.38 (0,13)
Viscosity at 40/s after hemodilution therapy (mPa)	–	–	–	5.4 (0,12)	5.41 (0,12)	–
Pre-treatment plasma viscosity (mPa)	1.22 (0,10)	1.18 (0,12)	1.19 (0,11)	1.28 (0,14)	1.3 (0,13)	1.23 (0,11)

I: OSA patients with normoviscosity and negative BAEP.
II: Six months of CPAP treatment normalizing viscosity and BAEP.
III: CPAP treatment normalizing viscosity but not BAEP.
IV: Hemodilution needed to normalize viscosity and BAEP.
V: Hemodilution normalizing viscosity but not BAEP.
VI: OSA patients with hyperviscosity and negative BAEP.

Table 4
Changing rheological variables

	Subgroup of patients					
	I. $N = 328$	II. $N = 112$	III. $N = 47$	IV. $N = 61$	V. $N = 19$	VI. $N = 49$
Viscosity at 90/s shear rate (mPa) (±SD)	4,44 (0,10)	5,60 (0,17)	5,58 (0,17)	5,88 (0,34)	5,75 (0,29)	5,78 (0,18)
Viscosity at 90/s shear rate after CPAP therapy (mPa)	4,42 (0,10)	4,40 (0,11)	4,41 (0,12)	5,87 (0,30)	5,73 (0,27)	4,40 (0,12)
Viscosity at 90/s shear rate after hemodilution therapy (mPa)	–	–	–	4,45 (0,13)	4,49 (0,15)	–
Pre-treatment hematocrit (%) (±SD)	43,18 (0,98)	48,76 (1,31)	48,87 (1,37)	52,81 (2,51)	53,78 (2,57)	49,12 (1,12)
Hematocrit after CPAP therapy (%)	42,97 (0,97)	43,76 (1,31)	43,87 (1,37)	52,0 (2,55)	53,10 (2,58)	42,67 (1,36)
Hematocrit after hemodilution therapy (%)	–	–	–	40,03 (1,31)	40,63 (1,46)	–

I: OSA patients with normoviscosity and negative BAEP.
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false negative viscosity results. Normal baseline plasma viscosity results (<1.35 mPa) excluded this syndrome.

Taking the sleep, BAEP and rheological findings together, we can conclude that out of 610 OSA patients, 282 had hyperviscosity and 328 had negative rheological findings. Out of the 282 hyperviscosity positive patients, 239 presented BAEP alterations as well. Among the rheologically negative patients, none were positive on BAEP. When further analyzing the abnormal BAEP findings ($n = 239$) 57 patients had the pattern of bilateral sensorineuronal change (lack of any waveforms), and 182 patients had a brainstem type of lesion, appearing as a significant bilateral elongation of wave III latency – with the mean value of 4.42 ms (0.13). Unilateral changes did not occur.

After six months of follow-up, CPAP therapy normalized hyperviscosity in 159 patients. In 112 of 159 patients (all with brainstem lesion), the second BAEP showed normalization of wave III latency, with the mean value of 3.72 ms (0.11), while in 47 patients (with sensorineuronal lesion) even effective CPAP therapy and normal viscosity were unable to reverse BAEP findings to normal.

In 80 patients CPAP therapy was unable to normalize hyperviscosity, and the BAEP results were not different from the initial ones. These patients underwent hemodilution therapy. The third BAEP test performed after hemodilution, remained positive in 19 of 80 patients (10 with sensorinueronal lesion and 9 with brain stem lesion), where the mean value of wave III latency was 4.44 ms (0.11); in 61 patients (all with brain stem lesion), BAEP became negative with a mean value of wave III latency of 3.82 ms (0.12).

4. Discussion

The present study was designed to explore the potential relationship between hyperviscosity and abnormal BAEP findings in OSA. Although not all OSA patients with hyperviscosity had abnormal BAEP findings, the fact that BAEP changes were restricted to the hyperviscosity positive OSA subgroup supported our hypothesis. Reversibility of brain stem type BAEP changes with the normalization of the viscosity – following effective CPAP or hemodilution therapy – provided further evidence for this hypothesis.

Our previous study [4] described hyperviscosity as the potential cause of BAEP alteration. Due to plasma volume dysregulation caused by the altered release of atrial natriuretic peptide [15–17], or to low nocturnal mean oxygen saturation [2–3], OSA frequently leads to sustained hyperviscosity [18–19]. In our previous study clinical hemorheological and brain stem auditory evoked potential (BAEP) investigations were performed [4]. Healthy age- and gender- matched controls, ischemic brain stem stroke cases with negative rheological parameters, ischemic brain stem stroke cases with concomitant hyperviscosity and patients with verified hyperviscosity but without neurological signs were examined. Focal unilateral BAEP alterations were found in brain stem stroke cases without hyperviscosity. Symmetric pathological BAEP patterns – either total lack of any waveforms, or bilateral prolongation of wave IV – were observed both in ischemic brain stem stroke patients with hyperviscosity and in hyperviscosity patients without neurological symptoms. During follow-up, normalization of the rheological profile after hemodilution therapy had a beneficial effect on BAEP in cases with wave III prolongation (brain stem lesion) but had no effect on cases with total lack of any waveforms (sensorineuronal lesion).

To our knowledge, this previous study was the first to confirm that blood hyperviscosity substantially influences BAEP morphology early in subclinical cases. The current study supports these conclusions and extends them. More specifically, the present study provides some detail on specific BAEP components that change in relation to hyperviscosity, namely sensorineural and brainstem wave components.

The significance of the two distinct subtypes of BAEP changes and the lack of response of the sensorineuronal lesions to clinically effective therapy remains obscure. Irreversible sensorineuronal BAEP changes in our series indicate cochlear dysfunction, possibly due to inadequate blood supply in the region of the internal auditory artery. Observed reversible brain stem type BAEP lesions may indicate brain stem dysfunction due to a border zone ischemia between the supply area of perforating branches of the short and long circumferential arteries. Hyperviscosity syndrome can represent the link between the two entities, where the brain stem watershed areas react more readily to altered rheological state than the cochlear region, thus giving way to reversible changes.

The fact that the internal auditory artery can have variable anastomoses, and the cochlear part is less involved due to the presence of both an extensive collateral circulation [20] and a lower intracochlear pressure [21], provides further evidence to this hypothesis. When we consider prior studies [22–26] where sudden sensorineuronal hearing loss presented as an initial sign of hyperviscosity syndrome, it seems reasonable to suggest that the same underlying condition can be a risk factor for a broad spectrum of lesions, ranging from reversible and irreversible subclinical electrophysiological changes to acute clinical events. At present we may speculate that in OSA patients without hyperviscosity, negative BAEP indicates the presence of effective compensatory mechanisms to balance hypoxemia, hypercapnia, acidosis and altered microcirculation developing during apnea. When hyperviscosity adds further to the impact of OSA, the above mechanisms may become insufficient, and a wide range of BAEP alterations may appear.

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At present, there are two major implications of our results. First, hyperviscosity (and consequently altered microcirculation) appears to be the main cause of bilateral BAEP alterations in OSA. Patients with abnormal BAEP may need hemorheological evaluation. Second, long term follow-up data is needed to evaluate whether pathological BAEP findings reveal a higher risk for cerebrovascular events. It is of particular interest because since previous studies investigating the relationship between OSA and stroke or death did not address the issue of OSA induced hyperviscosity with concomitant BAEP positivity.

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