MASTER OF MEDICINE (OPHTHALMOLOGY)

EVALUATION OF VISUAL ELECTROPHYSIOLOGICAL TEST IN OBSTRUCTIVE SLEEP APNOEA

BY

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for quotations and summaries which have been duly acknowledged.

Dated: 25th May 2017 …..……..……

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ABSTRAK

Pengenalan

"Obstructive sleep apnea (OSA) " atau Apnea tidur adalah masalah gangguan pernafasan ketika tidur yang boleh membahayakan nyawa. OSA merangkumi gangguan pernafasan separa (hypopnea) dan gangguan pernafasan total (berhenti bernafas atau apnoe) berlanjutan sekurang-kurangnya 10 saat ketika seseorang tidur. Ia mengakibatkan kekurangan oksigen dalam darah. OSA seringkali menyebabkan masalah gangguan saraf ("NAION", "bengkak saraf optik", Glaukoma) dan juga masalah salur darah tersumbat (CRVO) Pemeriksaan elektrofisiologi penglihatan (VEP) ke atas pesakit OSA seperti ujian potensi (PVEP) dan elektroretinogram (PERG) boleh membantu mengesan sebarang masalah pada saraf retina dan di sepanjang laluan saraf yang bersambung ke otak.

Objektif

Kajian ini dilakukan adalah bertujuan untuk membandingkan perubahan pada ujian potensi penglihatan berpola (PVEP) dengan ujian elektroretinogram berpola (PERG) di kalangan pesakit OSA dan kumpulan kontrol. Analisa hubungkait di antara ujian elektroretinogram dengan tahap keterukan penyakit OSA juga turut dilakukan.

Bahan dan kaedah

Satu perbandingan kajian "cross-sectional" telah dijalankan di Hospital Universiti Sains Malaysia yang melibatkan seramai 40 orang pesakit OSA dan 31 kumpulan kontrol. Pemeriksaan mata secara menyeluruh dilakukan. Seorang juruteknik khas ditugaskan untuk mengendalikan ujian PERG (0.8' saiz kotak) dan PVEP (0.25' saiz kotak).Untuk analisa statistik, kaedah "Independant t-test, Mann Whitney, Kruskal-Wallis, Pearson and Spearman’s test telah digunakan.

Keputusan

Terdapat penurunan ketara amplitud juga kelambatan kemunculan "P100 wave" dan N75 latency ($P<0.001$) pada ujian PVEP di dalam kumpulan pesakit OSA. Di kalangan pesakit OSA ini juga, kami dapati penurunan ketara amplitude "P50 wave" ($P<0.001$) pada ujian PERG berbanding dengan kumpulan kontrol. Analisa mendapati tidak wujud hubungan yang kuat di antara PVEP dan PERG dalam AHI di kalangan pesakit OSA. Tiada perbezaan ketara "PERG latency" dalam kedua-dua kumpulan kajian. Tiada hubungan ketara dalam PVEP atau PERG di kalangan pesakit OSA dengen tahap keseriusan penyakit mereka kecuali latency N75 pada PVEP yang mana ada menunjukkan hubungan statistic yang ketara tetapi hubungan negatif yang biasa.

Kesimpulan

Pesakit OSA menunjukkan bacaan tidak normal yang sangat ketara pada "amplitude" dan "latency" VEP dan juga "latency" ERG yang mana membuktikan kekurangan oksigen kemungkinan adalah punca terjadinya keadaan tersebut.

Kata kunci: Obstructive Sleep Apnea (OSA), Apnea-Hypopnea Index (AHI), Pattern Visual Evoked Potential (PVEP), Pattern Electroretinogram (PERG).

ABSTRACT

Introduction

Obstructive sleep apnea (OSA) is a life-threatening, sleep-related breathing disorder characterized by partial (hypopneas) and complete pauses (apneas) in breathing that last at least 10 seconds during sleep. As a consequence, the blood oxygen saturation may fall, with resulting in a hypoxia state. OSA has been associated with ocular conditions such as non-arteritic anterior ischemic optic neuropathy (NAION), papilloedema, glaucoma and central retinal vein occlusion. Visual electrophysiological tests like pattern visual evoked potential (PVEP) and pattern electroretinogram (PERG) may be able to detect functional impairment of the retina and visual pathway in OSA patients.

Objective

To compare the PVEP & PERG changes in patients with OSA and control group. We also analyzed the relationship between visual electrophysiological tests with the severity of OSA.

Material and methods

A comparative cross-sectional study was conducted in Hospital Universiti Sains Malaysia involving 40 samples of OSA patients and 31 control subjects. A complete ocular examination was performed which include visual acuity, anterior and posterior segment. PERG (0.8º checks size) and PVEP (0.25º checks size) were conducted by

a single technician. Independent t-test, Mann-Whitney, Kruskal-Wallis Test, Pearson and Spearman's correlation test were used in statistical analysis.

Results

There were statistically significant reduction of the PVEP P100 wave amplitude (P<0.001) and delay in PVEP P100 and N75 latency (P<0.001) in the OSA group. Among OSA patients, we also observed a significant reduction of the P50 wave amplitude (P<0.001) in PERG, compared to the control group. However, there is no finding on association of PVEP and PERG according to severity of OSA . There was no significant differences of PERG latency were observed in either group. There was no significant correlation in PVEP or PERG between OSA patients with different disease severity except PVEP latency N75 which is statistically significant but fair negative correlation

Conclusion

OSA patients have significant abnormalities in VEP amplitude and latency, and ERG amplitude, suggesting that hypoxia may be a pathophysiology in these conditions. There were no significant relationships between PVEP and PERG in AHI of OSA patients

KEYWORDS: Obstructive Sleep Apnea (OSA), Apnea-Hypopnea Index (AHI), Pattern Visual Evoked Potential (PVEP), Pattern Electroretinogram (PERG).

Chapter 1

Introduction

1.1 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a life-threatening, sleep-related breathing disorder. OSA occurs when the throat muscles relax during sleep, causing soft tissue in the throat to collapse and block the upper airway. This leads to partial (hypopneas) and complete pauses (apnea) in breathing that last at least 10 seconds during sleep. As a consequence, the blood oxygen saturation may fall, with oxygen levels decreasing by as much as 40 percent or more in severe cases (Medicine, 2014).

Chronic oxygen deprivation results in activation of the sympathetic pathway, vascular endothelial dysfunction, increased oxidative stress, inflammation, increased platelet aggregatability, and metabolic dysregulation, which could contribute to the initiation and progression of vascular diseases (Glacet-Bernard *et al.*, 2010). OSA has been shown to be associated with increased risk of coronary artery disease, heart failure, stroke, hypertension and arrhythmia.

1.2 OSA and ocular diseases

OSA is associated with various adverse effects not only systemically but also in the eye,. It has been associated with ocular conditions like non-arteritic anterior ischemic optic neuropathy (NAION), papilloedema, glaucoma and central retinal vein occlusion (Purvin *et al.*, 2000; Glacet-Bernard *et al.*, 2010; Archer and Pepin, 2013). A recent study among patients with NAION found that the vast majority of them had OSA (Bandi *et al.*, 2015) (Aptel *et al.*, 2015). The postulated mechanisms include direct exposure of optic nerve to OSA- induced hypoxia , intermittent sympathetic

surges secondary to repetitive apnoeic episodes leads to cardiovascular functioning changes result in arteriosclerosis and altered vascular autoregulation of optic nerve, hypoxia induced oxidative stress leads to vascular endothelial damage and result in autoregulatory dysfunction, hypoxia-induced cerebral vasodilatation may further impair autoregulation of optic nerve due to decreased cerebral perfusion pressure, increased intracranial pressure during apnoeic episodes may contribute to optic nerve damage directly, or by circulatory compression, increased concentration of VEGF and endothelin-1 among OSA patients (Archer and Pepin, 2013). Florent et al (2015) also observed that patients with OSAS also had a higher risk of second eye involvement in NAION. As a result, these authors have suggested that polysomnography should be considered in patients with NAION. Therapeutic measures for OSA should be undertaken if polysomnography is diagnostic of OSA (Aptel *et al.*, 2015).

The potential association between OSA and papilledema has also been studied (Fraser, 2014). This association is thought to be related to hypoxia and hypercapnia secondary to the nocturnal apnoeic episodes, leading to secondary cerebral vasodilatation with elevated intracranial pressure and consecutive papilloedema (Peter *et al.*, 2007) (Reeve *et al.*, 1985) .

The prevalence of glaucoma in OSA varies between studies, from 5.7% to 27% (Mojon *et al.*, 2000; Mojon *et al.*, 2002; Bendel *et al.*, 2008). OSA may cause glaucomatous optic neuropathy by creating transient hypoxemia and increasing vascular resistance, thus resulting in compromised optic nerve head perfusion and

oxygenation. This mechanism has been substantiated by the finding that OSA is relatively common in patients with normal tension glaucoma. Sergi et al.(2007) reported that the prevalence of NTG was higher in OSA patients compared with a control (Sergi *et al.*, 2007). While another study documented a relative risk for OSA of 3.34 in normal tension glaucoma patients (Bilgin, 2014). Tsang et al (2006) reported that moderate to severe OSA was associated with a higher incidence of visual field defects and glaucomatous changes in the optic nerve (Tsang *et al.*, 2006). Moghimi S, et al (2013) reported that OSA patients had a higher prevalence of glaucoma with reduced retinal nerve fiber thickness (Moghimi *et al.*, 2013) .

OSA-related hypoxia has also been associated with microvascular disease in the retina. OSA potential role as a player in the pathogenesis of diabetic retinopathy was highlighted in a recent Oxford study (West *et al.*, 2010), which found a high prevalence of sleep apnea in patients with diabetic clinically significant macular oedema (CSME). By causing autoregulatory dysfunction in the central retinal artery, OSA may also increase the risk of retinal vein occlusions.

1.3 Ocular electrophysiology

The visual evoked potential (VEP), or visual evoked response (VER), is a measurement of the electrical signal recorded at the scalp over the occipital cortex in response to light stimulus. It evaluate the integrity of the afferent visual pathway. Damage anywhere along the path may reduce the signal.

Pattern VEP response provides a more quantifiable and reliable waveform. The pattern is studied by the number of cycles per second or the size of the checkerboard pattern. Smaller sizes allow detection of smaller changes in function. The most commonly studied VEP waveform typically contains an initial negative peak (N1), followed by a positive peak (P1, also known as P100 for its usual location at 100 ms); second negative (N2) and second positive (P2) peaks follow (Figure 1). The latency of onset of a peak after light stimulus and (to a lesser degree) the amplitude of the peak are the most useful features analysed (Odom *et al.*, 2016). Abnormalities in the waveform result from impairment anywhere along the visual pathways. Demyelination of the optic nerve results in increased latency of the P100 waveform, without significant effect on amplitude; ischemic, compressive, and toxic damage reduce amplitude primarily, with less effect on latency (Fishman and Sokol, 1990) .

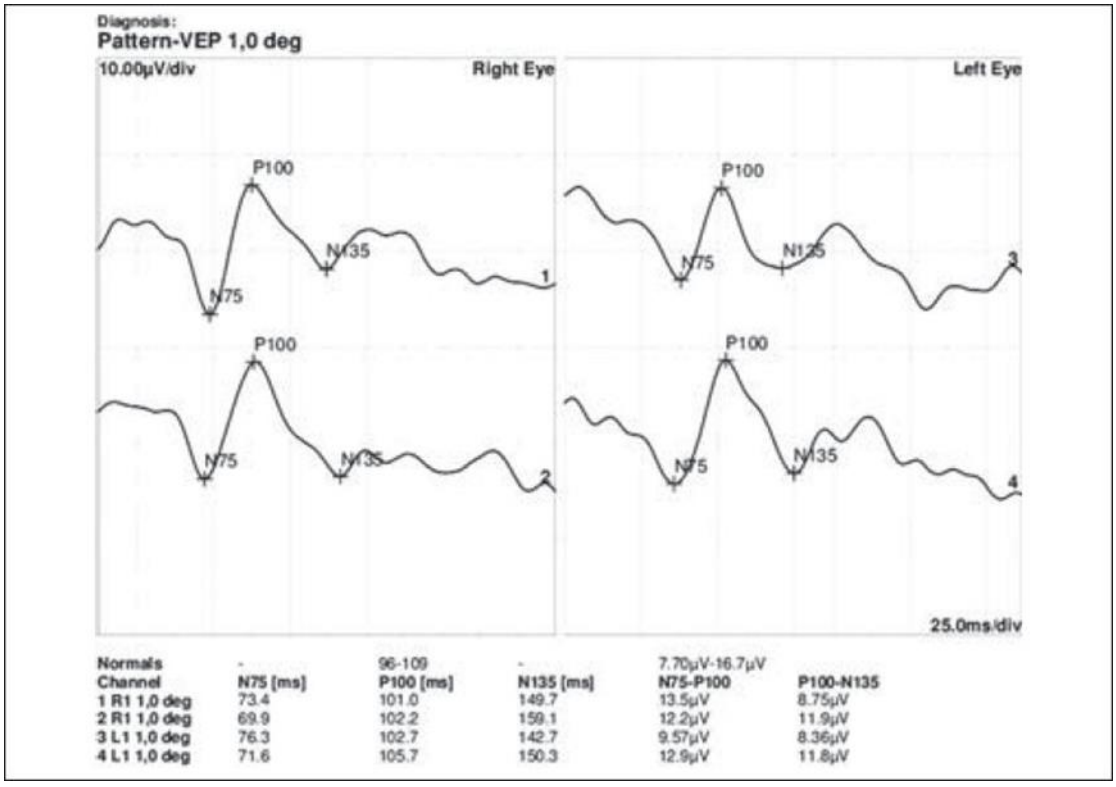

Figure 1 : A typical pattern VEP

The pattern electroretinogram (PERG) is a retinal biopotential evoked by a patterned stimulus (e.g. checkerboard or grating) of constant mean luminance. The standard PERG is recorded to abrupt contrast reversal of a black and white checkerboard pattern with central fixation. The PERG arises largely in the ganglion cells, driven by the photoreceptors and corresponding retinal cells. Since the PERG (in contrast to the flash ERG) is a local response from the area covered by the retinal stimulus image, it can be used as a sensitive indicator of dysfunction within the macular region and it reflects the integrity of the photoreceptors, bipolar cells and retinal ganglion cells (Bach *et al.*, 2013) .

The PERG waveform in normal subjects usually consists of a small initial negative component with a peak time of approximately 35 ms (N35), followed at 45–60 ms by a much larger positive component (P50). This positive component is followed by a large negative component at 90–100 ms (N95) (Figure 2) (Bach *et al.*, 2013) .

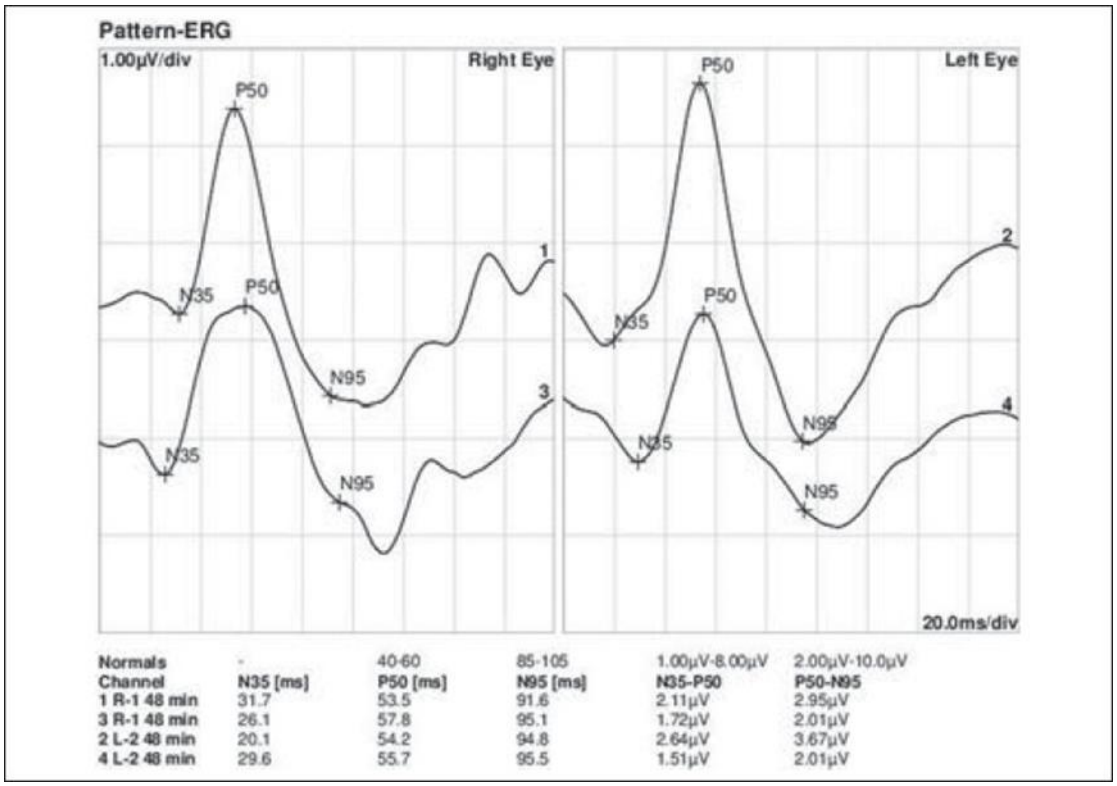

Figure 2: A typical PERG

The pattern ERG (PERG) uses pattern-reversal stimuli similar to VEP testing and captures retinal ganglion cell activity predominantly in the N95 waveform component. The PERG is used to detect subtle optic neuropathies. In demyelinating optic neuropathy, the PERG is relatively normal, while it may be abnormal in ischemic optic neuropathies.

Therefore, the aim of this study was to evaluate the changes of VEP & ERG in patients with OSA, which reflects the functional integrity of visual pathway. This difference was thought to be due to hypoxemia caused by OSA.

1.4 Rationale of study

OSA patients have been shown to be at risk of chronic hypoxia. The optic nerve is particularly susceptible to hypoxia. Electrophysiological tests like PVEP and PERG may be able to detect subtle optic nerve dysfunction in asymptomatic patients with OSA. Early identification and management of these patients may thus prevent on-going optic nerve damage and reduce ocular morbidity.

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Chapter 2

Objectives

2.1 General objectives:

To evaluate the ERG and VEP changes in OSA patients.

2.2 Specific objectives:

2.2.1 To compare ERG changes between OSA patients and control group

2.2.2 To compare VEP changes between OSA patients and control group

2.2.3 To examine the relationship between ERG changes and severity of OSA

2.2.4 To examine the relationship between VEP changes and severity of OSA

Chapter 3

Manuscript

Manuscript Title: .VISUAL ELECTROPHYSIOLOGICAL TESTS IN OBSTRUCTIVE SLEEP APNOEA

Running Title: Visual electrophysiological tests in OSA

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Abstract

The aim of this study was to compare the pattern visual evoked potential (PVEP) and the pattern electroretinogram (PERG) between obstructive sleep apnea (OSA) patients and controls. This was a prospective cross-sectional study involving 40 OSA patients and 31 control subjects in Hospital Universiti Sains Malaysia (USM). Convenience sampling was applied for patients with OSA to participate in the study. The apnea-hypopnea index (AHI) was obtained from their medical records and used for stratification of OSA severity. PVEP and PERG were performed. We observed a significant reduction of the PERG amplitude P50 ($P<0.001$) and the PVEP amplitude P100 ($P<0.001$) in OSA patients compared to the control group. OSA patients shown a significant increased in PVEP P100 latency ($p=0.003$) and N75 latency ($p=0.004$). However, there was no significant difference detected in PERG latency between OSA patients and controls. There was no significant difference in PVEP or PERG between OSA patients according to disease severity. There was no significant correlation in PVEP or PERG between OSA patients with different disease severity except PVEP latency N75 which is statistically significant but fair negative correlation OSA patients have significant abnormalities in PVEP amplitude and latency, and PERG amplitude. This may reflect subclinical optic nerve dysfunction in OSA. Further research is needed to determine the association between OSA severity and the degree of optic nerve dysfunction.

Introduction

Obstructive sleep apnea (OSA) is a life-threatening, sleep-related breathing disorder in which the throat muscles relax during sleep, causing soft tissue in the throat to collapse and block the upper airway. This leads to partial (hypopnea) and complete pauses (apnea) in breathing that last at least 10 seconds during sleep. As a consequence, the blood oxygen saturation may fall, with up to 40% decrease in oxygen levels in severe cases [1].Chronic oxygen deprivation results in activation of the sympathetic pathway, vascular endothelial dysfunction, increased oxidative stress, and inflammation, which may contribute to the initiation and progression of vascular diseases [2]. OSA has been shown to increase the risk of systemic diseases including heart failure [3], diabetes mellitus [4], sexual dysfunction [5], cognitive decline [6]. In the eye, OSA has also been associated with various conditions, particularly retinal and optic-nerve related disorders [7-9].

The visual evoked potential (VEP) is a measurement of the electrical signal recorded at the scalp over the occipital cortex in response to a stimulus, and reflects integrity of the afferent visual pathway. The electroretinogram (ERG) is a retinal bio-potential evoked by a stimulus of constant mean luminance. A stimulus can be used in the form of checkerboard, and the test is known as pattern VEP (PVEP). Similarly in ERG when stimulus is applied is known as pattern ERG (PERG). PERG is a local response from the area stimulated by the retinal image. It reflects the integrity of the photoreceptors, bipolar cells and retinal ganglion cells and can be a subtle indicator of optic nerve dysfunction [10]. Optic neuropathy may occur in OSA due to various mechanisms; increased intracranial pressure during apnoeic episodes, OSA- induced

hypoxia and increased levels of cytokines like endothelin-1 [11]. Our study thus aims to evaluate optic nerve function by comparing PVEP & PERG changes between patients with OSA and the control subjects.

Materials and Methods

This was a cross-sectional study involving 40 obstructive sleep apnea patients and 31 control subject. It was conducted in the Eye Clinic of Hospital Universiti Sains Malaysia (USM) between July 2015 and September 2016. This study received approval from the Human Research Ethics Committee USM (HREC), and was conducted according to the tenets of the Declaration of Helsinki for human research.

All patients who underwent overnight polysomnography with at least 5 apnea-hypopnea index (AHI) measurement were included in the OSA group. The diagnostic criteria for OSA was based on the international classification of sleep disorders by the American Academy of sleep medicine (2014) which included symptoms of loud snoring, excessive sleepiness, obstructed breathing during sleep and AHI [1]. The control group who volunteered to participate in this study, in whom OSA had been excluded by polysomnography. AHI represents the combined number of apneas and hypopneas that occur per hour of sleep. This was obtained from patients' medical record and used for stratification of the severity of OSA. The severity of OSA was divided into mild (AHI 5-15), moderate (16-30), and severe (>30). The inclusion criteria for both OSA and control subjects include best corrected visual acuity with normal anterior and posterior segment findings on thorough ocular examination. Informed written consent was obtained from all patients.

Ocular examination using slit lamp biomicroscopy (Topcon Corp, Japan) was performed to rule out ocular pathology, which would have precluded participation in the study. Intraocular pressure was assessed with Goldmann applanation tonometry (Haag-Streit Bern, Swiss). Electrophysiological tests (PVEP and PERG) were performed by a single technician in the electrophysiology laboratory, Department of Ophthalmology, Universiti Sains Malaysia. The results obtained were recorded as median values. PVEP was performed monocularly (right eye) while PERG was performed binocularly. Both tests were done in a quiet room under photopic conditions with ordinary room lighting. No pupil dilatation was necessary.

PVEP (RETIport 32, Roland Consult, Germany) measurement was performed as follows. A standard silver-silver chloride skin electrode was used. The skin was cleaned and an adequate amount of gel (Nu-Prep) was used to ensure good, stable electrical connection. The placement of electrode was based on the "10-20 International System". With the patient sitting 1.5 metres from the video monitor, wearing appropriate refractive correction, PVEP was elicited by checkerboard stimuli with large 1 degree and small 0.25 degree checks.

PERG (RETIport 32, Roland Consult, Germany) was conducted according to the International Society for Clinical Electrophysiology of Vision (ISCEGV) guideline 2012 [10]. A thin fibre electrode is used as recording electrode and place in the lower conjunctival fornix, near the nasal canthus. An electrode was placed at the ipsilateral skin near outer canthus of each eye was used as the reference electrode. The ground electrode was attached to the mid forehead. During the test, the impedance between

the ground and reference electrodes was kept at less than 5kΩ. Patient was seated 1.5 metres from the video monitor and wearing appropriate refractive correction. PERG was elicited by checkerboard stimuli with 0.8 degree checks.

All data was analysed using IBM SPSS Statistics version 21.0. Data which followed a normal distribution was analysed using independent t-test to compare mean values. In cases where the data was not normally distributed were analysed by non parametric Mann Whitney U test and Kruskal Wallis Test to compare the median values. Pearson and Spearman's correlation were used. Statistical significance was taken as $p<0.05$.

Results

A total of 71 age-matched subjects were included in this study. Of these, 40 had OSA (15 with mild, 9 with moderate and 16 with severe OSA) and 31 control subjects. There was slightly higher percentage of systemic disease among OSA compared to control (Table 1). However there was no significant different.

TABLE 1: Demographic and systemic features of OSA and control group

	OSA patients, N = 40	Control group, N = 31	P-value
Mean age (SD)	45.4(12.2)	49.3(16.1)	0.250[a]
Gender, n (%)			
- Male	27(71.1)	11(28.9)	0.007[b]
Systemic disease (n,%)			
- Hypertension	12(0.3)	6(0.19)	0.306[b]
- Diabetes	5(0.13)	1(0.03)	0.222[c]
- Hyperlipidaemia	12(0.3)	6(0.19)	0.306[b]
Smoker (n,%)	2(0.05)	4(0.13)	0.393[c]

[a]Independent t-test

[b]Pearson Chi-square test

[c] Fisher's Exact Test

Among OSA patients, we observed a significant difference of the PERG P50 wave amplitude (P<0.001, Table 2) and the PVEP P100 amplitude (P<0.001, Table 3) compared to the control group. OSA patients also had a significant increase in PVEP

P100 latency (p=0.003) and N75 latency (p=0.004). However, no significant differences were detected in PERG latency between OSA patients and controls.

TABLE 2: Comparison of mean PERG and PVEP between OSA and controls

Electrophysiology	OSA (n=40) Mean (SD)	Control (n=31) Mean (SD)	Mean diff(95% CI)	t-statistics (df)	p-value*
PERG amplitude N35 P50	2.9(1.02)	5.6(0.82)	-2.69(-3.14,-2.24)	-11.96(69)	<0.001*
PERG amplitude N95 P50	4.7(1.86)	8.9(0.98)	-4.26(-4.94,-3.57)	-12.40(62)	<0.001*
PERG latency N35	37.0(4.96)	37.1(3.05)	-0.98(-2.00,1.81)	-0.10(66)	0.919
PVEP latency P100	118.6(4.01)	115.6(4.32)	3.02(1.04,5.00)	3.04(69)	0.003*

* Independent t-test

TABLE 3: Comparison of median values of PERG and PVEP between OSA and controls

Electrophysiology	Median (IQR)		Z statistic	p value
	OSA	Control		
PERG latency P50	64.37(4.50)	64.00(3.00)	-0.691	0.490
PERG latency N95	104.50(9.69)	101.00(9.00)	-1.073	0.283
PVEP amplitude N75 P100	10.22(6.41)	18.80(6.28)	-6.168	<0.001
PVEP amplitude N135 P100	7.96(6.63)	17.90(4.60)	-5.965	<0.001
PVEP latency N75	84.12(10.25)	79.00(5.00)	-2.849	<0.001
PVEP latency N135	146.25(6.88)	147.00(9.00)	-1.367	0.172

* Mann-Whitney test

* Mann-Whitney test was used because the distribution of data is skewed.

Among the disease severity of OSA were compared, the PVEP latency N75 was found to have slightly shorter in severe group of OSA, however which is statistically not significant (Table 4).

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TABLE 4: Comparison of median PERG & PVEP between OSA patients with different disease severity

Electrophysiology	OSA Severity by AHI	Median (IQR)	X^2(df)	p value*
PERG latency P50 [ms]	Mild	64.75 (3.75)	0.42(2)	0.979
	Moderate	64.50 (4.00)		
	Severe	62.63 (6.63)		
PERG latency N95 [ms]	Mild	104.50 (4.00)	0.72(2)	0.697
	Moderate	104.25 (19.75)		
	Severe	104.88 (15.13)		
PVEP latency N75 [ms]	Mild	87.00 (9.00)	6.620(2)	0.062
	Moderate	87.25 (8.38)		
	Severe	79.75 (15.81)		

*Kruskal Wallis Test

There was no significant correlation in PVEP or PERG according to severity of OSA except for PVEP latency N75 (p=0.007 , Table 5). There was a fair negative correlation between PVEP latency N75 with severity of OSA.

TABLE 5**:** Correlation of PERG & PVEP between OSA patients with different disease severity.

Electrophysiology	AHI(events/h)	
	r	p value
PERG latency N35	-0.014	0.934[a]
PERG amplitude N35 P50	-0.183	0.258[a]
PERG amplitude N95 P50	-0.288	0.071[a]
PVEP latency N135	0.016	0.920[a]
PVEP latency P100	0.158	0.330[a]
PVEP latency N75	-0.420	0.007[b]
PVEP amplitude N75 P100	-0.090	0.580[b]
PVEP amplitude N135 P100	-0.102	0.533[b]
PERG latency P50	0.111	0.494[b]
PERG latency N95	-0.024	0.882[b]

[a]Pearson correlation

[b]Spearman's rho correlation