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Obstructive Sleep Apnea Screened by Overnight Pulse Oximetry and Higher Risk of Serious Cardiovascular Events: Prospective Cohort Study in the Primary Care

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Abstract: Introduction: Obstructive sleep apnea (OSA) is a condition characterized by sleep disordered breathing which results in health impairment and other related injuries. Cardiovascular and neurocognitive morbidities and increased risk of motor vehicle accidents have been demonstrated in patients with untreated OSA. Overnight pulse oximetry is a good screening tool for OSA. There is no study to examine the prospective outcome of patients with screening positive OSA in the primary care setting. Methodology: This is a prospective cohort study involving consecutive patients whom had performed OSA screening by overnight pulse oximetry in a primary care clinic of Hong Kong from year 2011 to year 2012. One hundred and eighty consecutive OSA screening positive patients were the cohort group while 180 consecutive OSA screening negative patients were the control group. The five year incidence of serious cardiovascular complications and associated predictive factors were examined. Results: Both of cohort and control group patients were followed prospectively for 5 years. There was higher proportion of male (68.3% versus 45.0%, $p<0.001$) and obesity (58.3% versus 41.1%, $p=0.001$) patients in the cohort group. There was no statistical difference in concomitant chronic disease or difference in mean blood pressure and Epworth Sleepiness Scale (ESS) score among two groups. At five year follow up, there was no cardiovascular related mortality among two groups. The five year relative risk (RR) of screening positive OSA versus screening negative for serious cardiovascular event is 3.03 (95% CI, 1.16-7.86; $p=0.018$). By stratification, the relative risk for stroke is 1.69 (95% CI, 0.40-7.16; $p=0.475$), while for coronary artery disease (CAD) is 4.24 (95%CI, 1.18-15.29; $p=0.017$). Conclusion: Overnight pulse oximetry screening positive obstructive sleep apnea is the independent risk factor for coronary artery disease.

Keywords: Obstructive Sleep Apnea, Overnight Pulse Oximetry, Stroke, Coronary Artery Disease

1. Introduction

Obstructive sleep apnea (OSA) is a condition characterized by sleep disordered breathing which results in health impairment and other related injuries. The prevalence of OSA is estimated at between 4 to 14% of the population. [1-3] There is some evidence that the prevalence of OSA in primary care setting is higher than in the community. [4-6] Cardiovascular [7-9] and neurocognitive morbidities [10] and increased risk of motor vehicle accidents [11, 12] have been demonstrated in patients with untreated OSA.

Long term follow up community-based cohort [13] and systematic review [14] have confirmed risk of OSA associated with stroke and cardiovascular mortality. Oximetry alone is often used as the first screening tool for OSA due to the universal availability of overnight recording pulse oximeters. [15] Nikolaus et al reviewed the

performance of pulse oximetry as a screening tool for sleep-disordered breathing, the value for sensitivity range from 31 to 98% while specificity range from 41 to 100%. [16] A study conducted in a primary care setting of Hong Kong concludes that overnight pulse oximetry is a good screening tool for OSA [17]. There is no study to examine the prospective outcome of patients with screening positive OSA in the primary care setting.

This study has followed the cohort patients with OSA screening performed in a primary care clinic of Hong Kong from year 2011 to 2012, and aims to investigate the five year incident of overnight pulse oximetry screening positive OSA related stroke and coronary artery disease; and secondly to examine the predictive correlation between overnight pulse oximetry screening positive OSA and serious cardiovascular events.

2. Methods

2.1. Study Population

Patients age 18 or above, and with one or more of the followings were eligible for OSA screening by overnight pulse oximetry: obese patients with body mass index (BMI) greater than 25 kg/m^2; patients with excess adipose tissue in the neck, i.e. neck circumference >16 inch for women, >17 inch for men; patients with a history of snoring; patients with excessive daytime sleepiness; patients who complain of chronic fatigue; patients with poor controlled hypertension (HT); patients with poor controlled diabetes mellitus (DM); or male patients with erectile dysfunction of undetermined etiology.

Patient with known anemia, i.e. hemoglobin less than 10 g/dl; uncooperative patient, such as dementia; patient with poor tissue perfusion, such as Raynaud's disease, nail vanish, fungal infection of nails; or patient with chronic obstructive pulmonary disease (COPD) were excluded from OSA screening with overnight pulse oximetry. Patients had known history of cardiovascular diseases, including stroke, coronary heart disease, transient ischemic attack, peripheral arterial disease, atrial fibrillation, congestion heart failure were excluded from current study.

Portable overnight pulse oximeter was used for OSA screening, which measured and stored pulse rate and peripheral capillary oxygen saturation (SpO_2) value continuously. Recorded data were then transferred to a computer for processing and analysis. The SpO_2 analysis, pulse rate analysis, oxygen desaturation index (ODI: number of oxygen desaturation events per hour of measurement time) and pulse disorder index (pulse rises events per hour of measurement time) will be generated in report. Oxygen desaturation was defined as a decrease of ≥4% from baseline SpO_2. Subjects who had sleep disordered breath events associated with 5 or more oxygen desaturation events of the peripheral capillary of 4% or greater per hour (ODI_4 ≥ 5 events/hr) was defined as screening positive. For screening positive patients, the severity of OSA was also determined by cut off as mild (ODI_4 = 5 to 14 events/hr), moderate (ODI_4 = 15 to 30 events/hr), and severe (ODI_4 > 30 events/hr). All overnight pulse oximetry screened patients were classified as screening positive for OSA (cohort group) and screening negative for OSA (control group) respectively. All patients were followed prospectively and observed for incidence of serious cardiovascular events.

2.2. Definition of Serious Cardiovascular Events

Incident events of cardiovascular related mortality;

Incident events of cerebrovascular disease, including diagnosis of stroke (cerebral infarction or haemorrhagic stroke), cerebrovascular accident (CVA) or transient ischaemic attack (TIA);

Incident events of coronary artery disease (CAD), including diagnosis of acute coronary syndrome, ischaemic heart disease, coronary heart disease, myocardial infarction, coronary artery bypass surgery (CABG), or percutaneous angioplasty (PTCA).

Patient clinical information and outcome events were retrieved and confirmed from electronic medical record in Computerized Medical System (CMS) of Hospital Authority Hong Kong.

2.3. Statistical Analysis

Descriptive statistics including mean, standard deviation, frequency and percentage will be used to summarize the characteristics of the variables. Univariate association between risk factors and CVD complications were investigated with Chi-square (X^2) tests. Logistic regression modelling was used to estimate the effect of OSA on the incidence of CVD events before and after adjustment for other risk factors. A p-value of less than 0.05 is considered as significant. Data analysis will be performed with the Statistical Package for the Social Sciences (SPSS, version 21.0, SPSS Inc, United States).

2.4. Ethical Approval

The study was approved by Hong Kong Hospital Authority Kowloon West Cluster Research Ethics Committee.

3. Results

180 cohort and 180 control patients had followed up prospectively for 5 years. Table 1 illustrated their demographics. There was higher proportion of male (68.3% versus 45.0%, p<0.001) and obese patients (58.3% versus 41.1%, p=0.001) in the cohort group. Also, the cohort group had higher mean age (55.6 versus 51.6, p=0.001) and higher mean diastolic BP (78.3 versus 75.9 mmHg, p=0.004). There was no statistical difference in proportion of smoking status, concomitant with hypertension, diabetes mellitus or hyperlipidaemia. Mean systolic BP and Epworth Sleepiness Scale (ESS) score were similar among two groups.

Table 1. *Patient demographics.*

	Cohort	%	Control	%	P value
Male	123	68.3	81	45.0	<0.001
Female	57	31.7	99	55.0	-
Mean Age (SD)	55.6 (11.9)	-	51.6 (14.2)	-	0.001
Current or Ex-smoker	41	22.8	27	15.0	0.088
Hypertension	99	55.0	90	50.0	0.342
Diabetes mellitus	35	19.4	23	12.8	0.085
Hyperlipidaemia	44	24.4	45	25.0	0.916
Chronic kidney disease	14	7.8	12	6.7	0.684
Obesity, BMI>25 kg/m^2	106	58.9	74	41.1	0.001
Mean SBP (SD), mm Hg	130.5 (14.1)	-	128.5 (15.0)	-	0.056
Mean DBP (SD), mm Hg	78.3 (11.9)	-	75.9 (11.2)	-	0.004
Mean ESS (SD)	9.3 (5.7)	-	9.8 (5.8)	-	0.202

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ESS: Epworth Sleepiness Scale.

Cardiovascular complications at five year were summarized in Table 2.

Table 2. *Five year cardiovascular complication outcomes.*

	Cohort	Control	RR	P value	95% CI
Cardiovascular events	17	6	3.03	0.018	1.16-7.86
Stroke, CVA	5	3	1.69	0.475	0.40-7.16
CHD/IHD/AMI	12	3	4.24	0.017	1.18-15.29
TIA	0	0	-	-	-

CVA: cerebrovascular accident; CHD: coronary heart disease; IHD: ischaemic heart disease; AMI: acute myocardial infarction; TIA: transient ischaemic attack.

There was no cardiovascular related mortality among two groups. 17 events (incidence 9.44%) of significant cardiovascular complication occurred at cohort group, i.e. OSA screening positive group including 5 cases of ischaemic stroke, 7 cases of acute myocardial infarction (AMI) and 5 cases of ischaemic heart disease. 6 events (3.33%) of cardiovascular complications, including 3 cases of stroke and 3 cases of acute myocardial infarction occurred in control group. The five year relative risk (RR) of screening positive OSA for serious cardiovascular event is 3.03 (95% CI: 1.16-7.86; p=0.018). By stratification, the RR for stroke is 1.69 (95% CI: 0.40-7.16; p=0.475), while for CAD is 4.24 (95%CI: 1.18-15.29; p=0.017). The incidence of cardiovascular events among mild, moderate and severe OSA were 11.34%, 9.62% and 3.23% respectively. (Table 3) Moderate and sever OSA did not show higher incidence rate of cardiovascular complications.

Table 3. *Stratification of cardiovascular complications outcomes and severity of OSA.*

Obstructive sleep apnea	Frequency	%	CVD events	Incidence rate
Mild	97	53.9	11	11.34%
Moderate	52	28.9	5	9.62%
Severe	31	17.2	1	3.23%

Univariate analysis revealed that OSA screening positive patients, patients concomitant with HT or hyperlipidaemia, and smokers were significant risk factor of cardiovascular complications (p<0.05). (Table 4) Logistic regression model applied for the risk factors associated CVD complications, including screening positive OSA, age, sex, smoking status and concomitant chronic diseases, the final fitted model showed that OSA screening positive was an independently predictive factor for cardiovascular complication and coronary artery disease, RR was 3.68 (95%CI: 1.30-10.42, p=0.014) and 4.86 (95% CI: 1.23-19.15, p=0.024) respectively.

Table 4. *Predictive factors associated with cardiovascular events.*

	Number	CVD No.	%	RR	P-value	95% CI
OSA	180	17	9.4	3.03	0.018	1.16-7.86
Non-OSA	180	6	3.3	-	-	-
HT	189	17	9.0	2.72	0.034	1.05-7.06
Non-HT	171	6	3.5	-	-	-
DM	58	6	10.3	1.93	0.179	0.73-5.14
Non-DM	302	17	5.6	-	-	-
Hyperlipidaemia	89	11	12.4	3.02	0.008	1.28-7.11
Non-Hyperlipidaemia	271	12	4.4	-	-	-
CKD	26	3	11.5	2.05	0.265	0.57-7.40

	Number	CVD No.	%	RR	P-value	95% CI
Non-CKD	334	20	6.0	-	-	-
Obese	180	9	5.0	0.62	0.281	0.26-1.48
Non-Obese	180	14	7.8	-	-	-
Smoker	68	10	14.7	3.70	0.002	1.55-8.85
Non-Smoker	292	13	4.5	-	-	-

OSA: obstructive sleep apnea; HT: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease.

4. Discussion

This five year cohort study confirmed that patients with screening positive OSA have increased risk for cardiovascular complications. As OSA is prevalent, and there is estimation that as many as 85% of individuals with sleep apnea are undiagnosed and untreated. [18] Cardiovascular complications, i.e. stroke, coronary heart disease are the leading cause of death worldwide, more than half of those with stroke will have mental and physical impairment. [19] Epidemiological studies have concluded that untreated severe OSA is a large public health burden in terms of cardiac morbidity and mortality. [20, 21] Therefore, OSA screening and further intervention of cardiovascular risks should be implemented in the primary care.

There are vast number of patients have suspected to have obstructive sleep apnea in primary care. Due to limitation of clinical assessment and lack of diagnostic test, the usual practice for primary health care physicians is referring all those patients to respiratory physician or sleep center for confirmation test. Awareness of the long-term impact of undiagnosed OSA on the cardiovascular system need to stimulate increased OSA screening in primary care. Screening for OSA needs to take place in any adults who reports OSA symptoms, including snoring, witnessed apneas, nocturnal grasping/choking, unexplained daytime sleepiness, large neck size, sleep fragmentation and unrefreshing sleep. [22]

Continuous positive airway pressure (CPAP) functions as a pneumatic splint to maintain upper airway patency through all phases of sleep breathing. CPAP has been established as the treatment of OSA with the firmest evidence base. American Academy of Sleep Medicine (AASM) recommended CPAP as the standard treatment of moderate to severe OSA and self-reported sleepiness, while it is the optional treatment for mild OSA, improving quality of life or as an adjunctive therapy to lower blood pressure in hypertensive patients with OSA. [23] As the relationship of portable overnight pulse oximetry and its predictive association with serious cardiovascular events has established, it is recommend that early management of screening positive OSA and other cardiovascular risk factors should be strictly controlled in order to prevent serious complications or reduction in mortality. In addition, further studies are needed to determine whether better management of OSA leads to fewer cardiovascular events.

Limitation

All patients with risk factors for OSA screening were recruited from one primary care clinic, there may have limitation in generalizability of results. Time to cardiovascular events and dose effect of screening positive OSA severity and cardiovascular complications should be further studied to consolidate the predictive associative risk between screening OSA and CVD complications.

5. Conclusion

This five year cohort study shows that overnight pulse oximetry screening positive obstructive sleep apnea is an independent risk factor for serious cardiovascular events, or specifically for coronary artery disease. Well-structured management protocol for screening positive OSA patients and associated cardiovascular risk interventions should be formulated and implemented in the primary care setting.

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Conflict of Interest

The authors declare that they have no competing interests.

Authors Contributions

All authors read and approved the final manuscript.

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