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Original Article

Long-term effects of surgical treatment on baroreflex function in patients with obstructive sleep apnea: an 18-month follow-up

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ABSTRACT

Objective: Depressed baroreflex sensitivity (BRS) is reported in obstructive sleep apnea (OSA). Improvement of BRS short-term after surgical treatment is also reported. We tested the hypothesis that surgical treatment not only improves clinical outcomes, but also improves BRS after 18 months.
Methods: Cardiovascular autonomic tests, polysomnography (PSG), and biochemical testing were prospectively evaluated in 54 OSA patients at three time points (preoperatively, 6 months and 18 months postoperatively) and compared with 20, age- and body mass index (BMI)-matched, healthy controls.
Results: The BRS increased after surgical treatment at 18-month follow-up, with results similar to the healthy control. Additionally, average O_2, mO_2 <90% (% per night), and lowest O_2 showed an increase after surgical treatment at the 18-month follow-up.
Conclusions: Besides improvement in clinical outcomes, depressed BRS in OSA patients is reversible and these patients have the potential for total recovery of baroreflex function after 18 months of treatment.

1. Introduction

Obstructive sleep apnea (OSA) is associated with nocturnal hypoxemia that has been proposed to depress baroreflex sensitivity (BRS) [1–4], increase oxidative stress, and cause endothelial dysfunction [5]. There have been several reports showing that patients with OSA have depressed BRS [1–4], and such dysfunction may contribute to the higher rate of cardiovascular morbidity and mortality reported in these patients [6,7]. Further, decreased numbers of circulating endothelial progenitor cells (EPCs) are reported to be predictive of future cardiovascular events, and EPCs could serve as a circulating pool of cells to replace dysfunctional endothelia [8].

Although continuous positive airway pressure (CPAP) is the primary treatment for OSA, there is a consensus that certain numbers of OSA patients can not or will not use CPAP, and the compliance rate of CPAP varies from 28% to 80% [9,10]. For patients that fail to receive CPAP, surgery is another treatment choice, and the efficacy and safety of multi-level surgery has been demonstrated in the literature [11–14].

The clinical outcome of OSA is often evaluated by parameters of polysomnography (PSG) and various clinical scores, such as the Epworth Sleepiness Scale. The effects of CPAP treatment on BRS have been demonstrated in several reports [15–18]. Our recent studies have shown the improvement of BRS in patients with OSA

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following surgical treatment [19] and demonstrated that OSA surgery not only improves six-month clinical outcomes, but also increases the number of circulating EPCs and antioxidant capacity, especially in patients with severe OSA [20]. To our knowledge, most of these studies either focus on acute effects or have a short follow-up period. Limited information is available on the effects of surgical treatment for OSA patients in terms of cardiovagal function and biomarkers of endothelial dysfunction for a longer follow-up period.

This study tested the hypothesis that OSA surgery not only improves the clinical outcomes, but also improves BRS and increases the number of circulating EPCs after 18 months. The successful clinical translation of these approaches has the potential of reducing cardiovascular risks and improving the quality of life.

2. Methods

2.1. Study design

This is a single-center, prospective study conducted at Kaohsiung Chang Gung Memorial Hospital, a medical center and main referral hospital serving an area with a population of 3 million in southern Taiwan.

2.2. Inclusion and exclusion criteria

Patients with OSA who failed CPAP therapy and planned to undergo upper-airway surgery were recruited. Patients were excluded if they: suffered from moderate-to-severe heart failure (New York Heart Association class III and IV); had any type of arrhythmia that prevented measurement of autonomic indices, or pacemaker implantation due to any cause; had underlying medical diseases known to affect the autonomic system, such as diabetes mellitus and chronic renal failure; had neoplastic disorders; had a history of stroke, critical carotid stenosis requiring carotid endarterectomy or stenting, myocardial infarction, or coronary artery disease status post percutaneous transluminal coronary angioplasty or bypass surgery; or had central or peripheral disorders known to affect the autonomic system, such as Parkinson's disease, diffuse Lewy-body disease, multiple system atrophy, and pure autonomic failure. For comparison, 20 age-, sex-, and body mass index (BMI)-matched subjects without any known cardiovascular risk factor or diseases and who did not take any medications were included as healthy controls.

2.3. Study protocol

The hospital's Institutional Review Committee on Human Research approved the study protocol (CGMH IRB 100-4351B and 103-7129B) and all of the study subjects provided informed consent. Each patient participated in a detailed interview regarding his/her personal health and a physical examination that included measurements of body height and weight. All of the subjects, including healthy controls, underwent a comprehensive sleep study (PSG). They then received a cardiovascular autonomic survey, including deep breathing and Valsalva maneuver (VM) tests as described by Low [21]. A 5-min resting electrocardiogram (ECG) recording was also performed for spectral analysis of heart rate (HR) variability. The autonomic tests were performed between 09:00 h and 12:00 h to exclude the possible influence of circadian variations. In addition, the autonomic tests were not carried out on the next morning after PSG. Blood samples were obtained for biochemical analyses and assessment of the profile of EPCs. For patients who received surgical treatment, all of the above studies were repeated twice, at 6 months and 18 months after the surgery.

2.4. PSG study

All-night, attended, comprehensive diagnostic sleep studies were performed at the hospital's Sleep Center, in a temperature-controlled and sound-attenuated room. Electroencephalography, submental electromyography, and electro-oculography were recorded by surface electrodes using standard techniques. Nasal and oral airflow were recorded by thermistors. Oxygen saturation was measured by pulse oximetry. Sleep stage scoring was performed at 30-s intervals by experienced technicians according to the standard criteria [22].

By definition, obstructive apnea was a cessation of airflow for at least 10 s with effort to breathe during apnea. Obstructive hypopnea was defined as an abnormal respiratory event with at least a 30% reduction in thoraco-abdominal movement or airflow when compared to the baseline, lasting at least 10 s, and with $\geq$4% oxygen desaturation [23]. The apnea–hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of electroencephalographic sleep, while OSA was defined as AHI > 5 per hour.

The severity of sleep-disordered breathing was classified according to the number of apneas and hypopneas during sleep. Subjects with AHI 5–15 were classified as mild OSA, AHI 15–30 as moderate OSA, and AHI >30 as severe OSA [24]. The controls had AHI <5. All PSGs were scored and read by an experienced physician who was blinded to the patients' participation in the study.

2.5. Cardiovascular autonomic assessment

HR was derived from continuously recorded standard three-lead ECG (Ivy Biomedical, model 3000; Branford, CT, USA) while arterial blood pressure (BP) was continuously measured using beat-to-beat photoplethysmographic recordings (Finameter Pro, Ohmeda; Englewood, OH, USA). The following parameters were obtained through tests computed by Testworks (WR Medical Electronics Company, Stillwater, MN): HR response to deep breathing (HR_DB), valsalva ratio (VR), and BRS. The detailed computing of HR_DB and VR were as described by Low [21]. BRS was derived from changes in HR and BP during the early phase II of VM by applying least-squares regression analysis as described by La Rovere [25].

Beat-to-beat RRI (the time between consecutive R peaks) changes were interpolated using a third-order polynomial and were re-sampled with an interval of 0.5 s. The signals were then transformed to the frequency domain with fast Fourier transform by using 512 samples. Spectral powers were divided into three frequency domains: high frequency (HF, 0.15–0.4 Hz), low frequency (LF, 0.04–0.15 Hz), and very low frequency (VLF, 0–0.04 Hz). The units for RRI power were ms^2. The normalized low- and high-frequency powers (LF normalized units, HF normalized units) were calculated as a percentage of overall power. The above computing process was conducted using Matlab version 7.5 (Mathworks).

2.6. Surgical procedures

The patients received Z-palatopharyngoplasty (ZPPP) or ZPPP plus radiofrequency tongue base reduction. All of the procedures were performed by H-C Lin under general anesthesia and with orotracheal intubation. The techniques used were determined at the discretion of the treating sleep surgeon based on the severity of OSA with PSG and conditions of upper-airway abnormality as examined by flexible fibroscopy. The detailed surgical techniques were as previously described [11,12,14].

2.7. Biochemical analysis

Blood samples were obtained by ante-cubital vein puncture in a fasting, non-sedative state and were analyzed by the hospital's central laboratory for glycohemoglobin (HbA1c), highly sensitive C-reactive protein (hs-CRP), and lipid profiles, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride.

2.8. Assessment of circulating EPC level

Peripheral blood EPC levels were measured by flow cytometry. To determine the EPC surface markers of CD45/CD34/CD133 and CD45/CD34/KDR, mononuclear cells were incubated for 30 min at 4 °C in a dark room with monoclonal antibodies against kinase insert domain-conjugating receptor (KDR) and CD133 (Miltenyi Biotec), phycoerythrin-conjugated KDR, CD133, fluorescein isothiocyanate-conjugated CD34 (Beckman Coulter), and Phycoerythrin-Cy5 conjugated anti-CD45 antibodies. Control ligand (IgG-phycoerythrin conjugate) was used to detect any non-specific association and define a threshold for glycoprotein binding. After staining, the mononuclear cells were fixed in 1% paraformaldehyde. An Epics XL flow cytometer (Beckman Coulter) was used for quantitative three-color flow cytometry analysis (1,000,000 cells per sample). Intra-individual variability and mean intra-assay coefficients of variance for circulating EPC numbers were all <4.0%.

2.9. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (inter-quartile range). Three separate statistical analyses were performed. First, continuous variables among the two groups (the control and OSA groups) were compared using independent Student's *t*-test for data with Gaussian distribution and the Mann–Whitney *U*-test for data with non-Gaussian distribution. Second, paired *t*-test (for normal distributed data) or non-parametric Wilcoxon test for paired samples (for data with skewness) were used to compare data before and after surgery (6 months or 18 months after surgery), including apnea/hypopnea parameters, cardiovascular autonomic parameters, biochemical laboratory parameters, and BMI. Third, the associations between measurements were evaluated by Pearson correlation tests for normally distributed data or by Spearman non-parametric test for data with skewed deviation. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using the IBM SPSS software package, version 17 (IBM, Inc., Armonk, NY, USA).

3. Results

3.1. Baseline characteristics of the study subjects

Forty-four OSA patients (39 men, five women) who were prepared to receive surgical treatment and 20 control subjects (14 men, six women) were enrolled. Table 1 shows the demographic and laboratory data of these subjects. There were significantly higher HbA1c levels in the patient group. BMI was higher in the patient group but the difference was not statistically significant. EPC level was lower in the patient group, but only CD133+/CD34+ (%) reached statistical significance, while the KDR+/CD34+ (%) did not. There was no significant difference between two groups in terms of age, gender, total cholesterol, LDL, HDL, *hs*-CRP, hemoglobin, or hematocrit level.

Table 1
Comparison of demographic and laboratory data between groups of control subjects and obstructive sleep apnea (OSA) patients.

	Controls ($N = 20$)	OSA ($N = 44$)	*p*
Age (years)	38.0 ± 8.4	41.0 ± 10.3	0.211
Sex (F/M)	6/14	5/39	0.069
BMI (kg/m^2)	25.9 ± 1.8	26.2 ± 2.9	0.062
HbA1c (%)	5.5 ± 0.3	5.7 ± 0.4	**0.036***
Total cholesterol (mg/dL)	190 ± 37	191 ± 33	0.954
Triglyceride (mg/dL)	100 [73, 133]	124 [80, 167]	0.218
HDL (mg/dL)	55.8 ± 8.6	53.0 ± 12.8	0.311
LDL (mg/dL)	112 ± 36	124 ± 32	0.237
hs-CRP (mg/dL)	1.54 [0.61, 3.35]	0.96 [0.66, 2.31]	0.529
Hemoglobin (mg/dL)	14.5 ± 1.3	14.9 ± 1.2	0.272
Hematocrit (%)	43.3 ± 3.3	44.2 ± 3.2	0.319
CD133$^+$/CD34$^+$ (%)	37.8 ± 14.0	26.2 ± 16.1	**0.006***
KDR+/CD34+ (%)	2.00 [1.12, 2.76]	1.02 [0.71, 2.18]	0.401

BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol. Values are expressed as mean ± standard deviation unless otherwise indicated.
*$p < 0.05$.

3.2. Comparison of cardiovascular autonomic and PSG parameters before and after surgery

Table 2 lists the cardiovascular autonomic and PSG parameters of the patients and controls. According to the baseline (before surgery) PSG, the patient number for mild, moderate, and severe OSA were 9, 11, and 24, respectively. All of the PSG parameters including AHI-total sleep time (TST), AHI-non-rapid eye movement sleep (NREM), mean oxygen saturation (mO_2) <90%, average O_2, lowest O_2, and desaturation index showed significant improvement at 6 and/or 18 months after surgery. As for the cardiovascular autonomic parameters, the patients with OSA had similar HR_DB, VR, and LF/HF ratio compared to the control subjects. The BRS before surgery in the patient group was significantly decreased. Then, the BRS significantly increased 6 months and 18 months after surgery, and became similar to the levels of the control group at 18 months after surgery (Fig. 1). There was no significant change in BP (either systolic or diastolic) after surgery, and the patient group had significantly higher diastolic BP than the control group throughout the study period. Although the systolic BP remained higher in patient group, the difference was not statistically significant.

3.3. Comparison of laboratory data before and after surgery

Comparing the laboratory data before and six months after surgery (Table 3), it showed significant increment of CD133$^+$/CD34$^+$ (%), whereas other data collected were similar between before and six months after surgery. In 18 months after surgery, the HbA1c and LDL were significantly decreased, but EPC levels, including both CD133+/CD34+ (%) and KDR+/CD34+ (%), were significantly increased when compared to the data before surgery.

3.4. Association analyses between cardiovascular autonomic parameters and factors affecting them

Correlation analysis was used to test the association between BRS and possible affecting factors, including BMI, PSG parameters, and biochemical laboratory data (Table 4). The left half of the table shows the correlation of BRS and these affecting factors at the initial (before surgery). BRS was significantly correlated with all PSG parameters except for lowest O_2 value. On the contrary, none of

Table 2
Comparison of apnea/hypopnea and cardiovascular autonomic parameters in each test.

	Control subjects	Before Tx	6 months	18 months
Apnea/hypopnea parameters				
AHI-TST (/h)	2.5 [1.2, 4.4]	35.4 [16.5, 59.7]	**18.6 [7.1, 43.1]***	**24.8 [12.7, 44.5]***
AHI-NREM (/h)	1.7 [0.8, 3.0]	35.7 [13.9, 59.6]	**16.3 [6.4, 42.1]***	**28.3 [9.6, 41.6]***
mO_2<90% (/h)	0 [0, 0.3]	4.4 [1.4, 11.2]	1.8 [0.6, 6.6]	**1.5 [0.1, 4.0]***
Average O_2 (%)	96.9 ± 0.7	95.3 ± 2.2	95.5 ± 2.0	**96.2 ± 1.4***
Lowest O_2 (%)	89.7 ± 3.4	78.6 ± 10.5	81.6 ± 11.5	**82.9 ± 9.5***
Desaturation index (/h)	0.9 [0.4, 1.5]	20.8 [5.8, 49.1]	**9.0 [3.4, 21.7]***	**10.1 [4.7, 26.1]***
Cardiovascular autonomic parameters				
HR_DB (beats/min)	16.9 ± 6.2	14.9 ± 6.1	15.7 ± 7.4	14.7 ± 6.3
Valsalva ratio	1.61 ± 0.24	1.69 ± 0.26	1.71 ± 0.27	1.69 ± 0.25
BRS (ms/mmHg)	3.6 [2.2, 4.3]	2.4 [1.7, 3.5]	**3.2 [2.1, 4.1]***	**3.7 [2.9, 4.8]***
LF (nu.)	54.0 ± 21.1	64.2 ± 16.1	64.0 ± 14.5	63.3 ± 15.7
HF (nu.)	45.9 ± 21.1	35.7 ± 16.1	35.8 ± 14.6	36.6 ± 15.7
LF/HF ratio	1.40 [0.66, 1.95]	1.84 [1.16, 2.93]	2.04 [1.00, 2.94]	2.06 [1.00, 3.18]
Systolic BP (mmHg)	129.2 ± 15.8	136.7 ± 13.6	134.6 ± 9.5	135.2 ± 9.0
Diastolic BP (mmHg)	78.7 ± 11.3	86.0 ± 12.5*	85.1 ± 9.9*	84.8 ± 10.1*

Tx, treatment; AHI, apnea/hypopnea index; BP, blood pressure; BRS, baroreflex sensitivity; HF, high frequency (0.15–0.4 Hz); HR_DB, heart rate response to deep breathing; LF, low frequency (0.04–0.15 Hz); mO_2, mean oxygen saturation; NREM, non-rapid eye movement; nu., normalized unit; TST, total sleep time.
*$p < 0.05$, by comparison with the data before treatment.

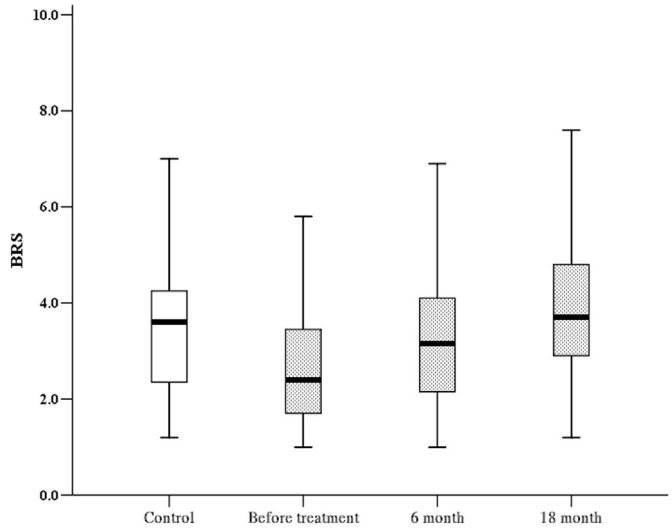

Fig. 1. The baroreflex sensitivity significantly and continuously increased and became similar to the control group by 18 months after surgery.

the biochemical data or EPC levels was significantly correlated with BRS. The right half of the table shows the correlation between the changes of BRS and the changes of the affecting factors, with the change value defined as 18 months after surgery measurement minus pre-surgery measurement. There were significant negative correlations between BRS change and the changes of BMI, desaturation index, and cholesterol level, respectively.

4. Discussion

To date, most studies, as well as our previous works, have demonstrated the treatment effect of BRS on OSA patients, either treated by CPAP or by surgery [15–19]. However, these studies either focus on the acute effects or have a short follow-up period (only 3–6 months). It is not known whether the treatment effects of BRS improvement are transient or persistent. The present study aimed to elucidate the surgical treatment outcomes and show serial changes of BRS and circulating EPCs in OSA patients without any vascular diseases over an extended period. This study also confirmed the hypothesis that OSA surgery not only improves clinical outcomes, but also improves BRS and increases the number of circulating EPCs at the 18-month follow-up.

The present study examines changes in cardiovascular autonomic tests, biomarkers of metabolic risk factors, level of EPCs, and clinical outcomes in OSA patients after surgery treatment up to 18 months after surgery. There are five major findings. First, the levels of LDL-C were significantly increased in OSA patients compared to those in healthy controls. The levels of CD133+/CD34+ (%) were significantly lower in OSA patients than in healthy controls. Second, the levels of CD133+/CD34+ (%) were significantly increased and the levels of LDL were significantly decreased, respectively, in OSA patients at the 18-month follow-up. Third, clinical efficiency after OSA surgery, as assessed by PSG, revealed that mO_2 <90% (% per

Table 3
Comparison of body mass index (BMI) and biochemical laboratory data in each test.

	Before Tx	6 months	18 months
BMI (kg/m^2)	26.2 ± 2.9	**25.7 ± 2.8***	25.8 ± 2.8
HbA1c (%)	5.7 ± 0.4	5.8 ± 0.3	**5.6 ± 0.3***
Total cholesterol (mg/dL)	191 ± 33	191 ± 30	194 ± 28
Triglyceride (mg/dL)	124 [80, 167]	124 [84, 168]	117 [84, 155]
HDL (mg/dL)	53.0 ± 12.8	53.0 ± 12.8	52.7 ± 11.7
LDL (mg/dL)	124 ± 32	117 ± 36	**116 ± 28***
hs-CRP (mg/dL)	0.96 [0.66, 2.31]	0.89 [0.60, 1.83]	1.08 [0.60, 1.89]
$CD133^+/CD34^+$ (%)	26.2 ± 16.1	**33.9 ± 15.9***	**48.0 ± 14.0***
KDR+/CD34+ (%)	1.02 [0.71, 2.18]	1.19 [0.70, 2.74]	**1.61 [0.99, 3.49]***

Tx, treatment; BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol.
*$p < 0.05$, by comparison with the data before treatment.

Table 4
Correlation analysis between baroreflex sensitivity, body mass index (BMI), apnea/hypopnea parameters, and biochemical data.

Spearman's correlation	BRS			ΔBRS	
	r	*p*		*r*	*p*
BMI (kg/m^2)	−0.043	0.741	ΔBMI	**−0.400**	**0.032***
AHI-TST (/h)	**−0.399**	**0.002****	ΔAHI-TST	−0.323	0.088
AHI-NREM (/h)	**−0.407**	**0.001****	ΔAHI-NREM	−0.310	0.102
mO_2<90% (/h)	**−0.476**	**<0.001****	ΔmO_2<90%	−0.227	0.236
Average (%)	**0.403**	**0.001****	ΔAverage	0.292	0.124
Lowest $O_{2\ (\%)}$	0.223	0.087	ΔLowest O_2	0.217	0.258
Desaturation index (/h)	**−0.370**	**0.004****	ΔDesaturation index	**−0.422**	**0.022***
HbA1c (%)	−0.008	0.954	ΔHbA1c	−0.004	0.981
Total Cholesterol (mg/dL)	−0.008	0.950	ΔChol	**−0.330**	**0.043***
HDL (mg/dL)	0.192	0.143	ΔHDL	−0.052	0.757
LDL (mg/dL)	−0.063	0.630	ΔLDL	−0.269	0.103
Triglyceride (mg/dL)	−0.191	0.145	ΔTG	−0.165	0.321
hs-CRP (mg/dL)	−0.021	0.871	ΔhsCRP	−0.057	0.735
CD133$^+$/CD34$^+$ (%)	0.136	0.407	ΔCD133$^+$/CD34$^+$ (%)	0.196	0.364
KDR+/CD34+ (%)	0.115	0.486	ΔKDR+/CD34+ (%)	0.077	0.652

Δ = Changes during the 18-months (data at 18-month follow-up minus baseline data).
Bold values denote *$p < 0.05$.
Bold values denote **$p < 0.05$.
AHI, apnea/hypopnea index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; mO_2, mean oxygen saturation; NREM, Non-rapid eye movement; TST, total sleep time. Values are expressed as mean ± standard deviation unless otherwise indicated.

night), average O_2, and lowest O_2 increased 18 months after surgical treatment. Fourth, the value of BRS increased 18 months after surgery, recovering to similar levels as the healthy control group. Finally, the baseline BRS value was negatively correlated with desaturation index, and the changes in the BRS (18-month follow-up minus baseline) were also negatively correlated with the changes in desaturation index.

According to our data, BRS continues to increase to levels similar to healthy control subjects 18 months after surgery. This finding suggests that the BRS impairment in OSA patients is reversible. After appropriate treatment, these patients have the potential for total recovery of baroreflex function and endothelium function, and this concept has not been mentioned previously. The mechanism involved in BRS impairment in patients with OSA is not completely known. In our previous study, it was found that the OSA patients have preserved cardiovagal function despite blunting of BRS [19]. The current study has the consistent finding showing that OSA patients have similar values of HR_DB and VR compared to the control subjects. This finding implies that the depressed BRS is more likely due to baroreceptor dysfunction than a lesion in the neural pathway.

The significant correlation between BRS and the AHI in PSG parameters, including AHI-TST, AHI-NREM, mO_2<90%, average O_2 saturation, and desaturation index, further suggests that recurrent apneas/hypopnea play an important role in BRS dysfunction of the OSA patients. The study by Somers et al., has demonstrated the interaction between baroreceptor and chemoreceptor reflex control [26]. A more recent report by Cooper et al., suggests that the hypoxic component of asphyxia reduces BRS, while the hypercapnic component is responsible for increasing BP and reflex 'set point' [27]. Therefore, we have recommended a notion that the interaction between baroreceptors and chemoreceptors may explain the reduced BRS in patients with OSA [19]. With the resolving of recurrent apneas/hypopnea, these patients' baroreceptor function gradually returns to normal after treatment. It might be argued that only the change in desaturation index (Δ desaturation index) has significant correlation with the amount of BRS change (ΔBRS). The changes in other AHIs of PSG do not correlate with BRS change. This is not surprising because the effects of interaction between the baroreceptor and chemoreceptor reflex are likely to be non-linear, and thus it is hard to show the effects by statistical analysis.

OSA has long been associated with hypertension [28–30], probably related to the enhanced sympathetic outflow and decreased BRS in these patients [3,31]. The effects of CPAP treatment on BP control have been extensively investigated [32,33]. Our previous work also reveals some BP-lowering effects after surgical treatment [19,20]. The current data shows significantly higher diastolic (but not systolic) BP in the OSA patient group compared to the control group. However, it should be noted that the patients with hypertension had taken medication for BP control throughout the study. Both systolic BP and diastolic BP were decreased after surgery, although the difference was not statistically significant. This 'non-significance' may be attributed to inadequate case numbers. Moreover, the index of sympathovagal balance, LF/HF ratio, was similar between groups of patient and control, and did not show a significant difference after surgery. This may be explained by the large variability of LF/HF ratio, and thus, a larger case number is necessary to reveal statistical significance.

As for the biochemical laboratory data, there was significantly higher HbA1c and lower CD133$^+$/CD34$^+$ (%) in the patient group before treatment than in the controls. OSA has been linked to insulin resistance, glucose intolerance, and diabetes in several reports [34]. Our data is consistent with findings in previous reports. Moreover, the HbA1c in OSA patients was significantly decreased 18 months after surgery, and became similar to the control group. It has been mentioned that the use of CPAP in non-diabetic and pre-diabetic patients with OSA reduces insulin resistance and reduces the risk of developing type 2 diabetes [35]. Our data shows that the surgical treatment may have the same effects. These results imply that the insulin resistance, or glucose intolerance, in patients with OSA is reversible rather than permanent, at least at the pre-diabetic stage. As for EPC levels, nocturnal hypoxemia has been proposed to increase the generation of free radicals and other reactive species, which may lead to endothelial dysfunction in OSA patients [5]. Several clinical studies have investigated the association between OSA and circulatory EPC. The findings have been inconclusive, with both negative [36,37] and positive results [5,38,39]. Our previous study demonstrated that CD133+/CD34+ (%) level was significantly decreased in OSA patients. At three months after surgery, the CD133+/CD34+ (%) level was significantly increased [20]. The current study showed that EPC levels, including both CD133+/CD34+ (%) and KDR+/CD34+ (%), continued to increase after

surgery. At 18 months after surgery, the CD133+/CD34+ (%) level was higher than the control group. The extremely high CD133+/CD34+ (%) level in OSA patient after surgery has not been reported before, and needs further studies to elucidate its physiological significance.

Our data reveals that there is no correlation between BMI and BRS, but the change in BMI significantly correlates with the change in BRS. There is strong evidence that obesity is associated with diminished BRS [40–42]. However, the correlation between BMI and BRS was not consistent in different reports. Significant correlation between BMI and BRS were found in the studies by Laederach–Hofmann et al. and by Skrapari et al., but not in the study by Krontoradova et al., [42]. It is likely that the mechanism connecting obesity and diminished BRS is complicated and involves multiple pathways, such as increased sympathetic activity, impaired glucose tolerance as well as other metabolic disturbance. The dominant mediating pathway may be different in different patient groups. For example, the study by Krontoradova was performed in children, adolescents, and young adults, while the other two were carried out in middle-aged persons. This may explain the inconsistent correlation between BMI and BRS.

The effects of ZPPP and/or tongue base surgery to improve the PSG parameters of apnea/hypopnea have been discussed in several previous reports [11,12,14,43]. The principles behind the treatment are based on the reduction in the volume of redundant tissues, stiffening of the flaccid soft palate, and suspension of the collapsed tongue base to maintain airway patency. The data here did show significant improvements for most of the apnea/hypopnea parameters on PSG at six months after the surgery. Nevertheless, the improvements in AHI-TST, AHI-NREM, and desaturation index seem to be diminished at 18 months after surgery compared to six months after surgery. There is a paucity of information on long-term follow-up for OSA patients in terms of the effects of surgical treatment, and this issue is beyond the scope of the current study. In spite of the residual OSA, the BRS becomes 'normalized' at 18 months. The result is actually compatible with the data in our previous study, which shows no significant BRS difference between the patients with mild OSA and normal subjects [19]. The underlying mechanism causing blunting of BRS in OSA patients is not totally elucidated. There may be a threshold or cumulative effect to result in impairment of baroreflex dysfunction. Further study addressing pathophysiology is necessary to clarify this issue.

This study had several limitations. The study had relatively small case numbers and half of the patients had severe OSA (24/44). Therefore, further analysis for the autonomic changes on varying severity of patients is unavailable. In addition, some of the patients took medication to control hypertension, and the medication effects on cardiovascular autonomic function were not eliminated. The beta-blockers, calcium channel blockers, and diuretics may have influence on the test results. Due to ethical considerations, these drugs were not stopped before the tests. However, we confirmed that those patients who received anti-hypertensive treatment had not changed their drugs during the study period (ie the influence from the medication is the same on each test and may be omitted in the comparison). Finally, the follow-up period of our study was only 18 months, which is too short to evaluate cardiovascular risk and long-term prognosis. Although the current study shows that patients with OSA have recovery of baroreflex function after surgical treatment, and the relationship between reduced BRS and poor prognosis has been established in several kinds of cardiovascular diseases [25,44,45], long-term cardiovascular risk and the prognosis of these patients remained unclear. A cohort study with longer follow-up period is necessary to study whether patients with OSA really have reduced risk of cardiovascular events after surgical treatment.

Both depressed BRS and decreased circulating EPC levels in OSA patients are reversible. These patients have the potential for total recovery of baroreflex function and circulating EPC levels according to the data at 18 months after surgery.

Ethical approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research (CGMH IRB 100-4351B and 103-7129B).

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Conflict of interest

All authors declared that they have no competing interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.017.

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