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ORIGINAL RESEARCH

# Effects of TORS-OSA Surgery on Lower Urinary Tract Symptoms, Overactive Bladder Symptoms, and Nocturia in Male Patients with Obstructive Sleep Apnea/Hypopnea Syndrome

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Objective: To determine the presence of lower urinary tract symptoms (LUTS), and overactive bladder (OAB) symptoms in men with obstructive sleep apnea/hypopnea syndrome (OSA) and the effects of transoral robotic surgery (TORS) for the treatment of OSA on these conditions.

Materials and Methods: One hundred twenty-three patients with a diagnosis of OSA were prospectively enrolled. The evaluations of LUTS and OAB symptoms were based on self-administered questionnaires containing international prostate symptom score (IPSS) and OAB symptom score (OABSS), respectively. Men with an OABSS urgency score of ≥2 and sum score of ≥3 were considered to have OAB. The therapeutic outcomes were assessed at baseline, and 12 weeks after TORS-OSA Surgery.

Results: There were significant differences in IPSS, and OABSS according to OSA severity. After TORS-OSA surgery, significant improvements on OSA severity, daytime quality of life (QoL) and nighttime sleep quality were observed. TORS-OSA surgery was also associated with a statistically significant improvement of LUTS, LUTS QoL score, and OAB symptoms (IPSS 22.1% decrease; IPSS QoL score 21.1% decrease; OABSS17.4% decrease) at post-operative 3 months' follow-up. The presence of OAB, and severe nocturia was significantly reduced from 22.8% to 11.4% (p=0.001), 5.7% to 0.8% (p=0.031) after TORS-OSA surgery. There were no patients who had acute airway compromise or massive bleeding peri- or post-operatively.

Conclusion: TORS upper airway surgery could improve LUTS and OAB symptoms on male patients with OSA in addition to improvement of major parameters of sleep study and sleep-related QoL.

Keywords: snoring, obstructive sleep apnea, lower urinary tract symptoms, overactive bladder symptoms, OSA surgery, transoral robotic surgery

#### Introduction

Obstructive sleep apnea/hypopnea syndrome (OSA) is a common disease. It affects approximately 4% to 5% of all middle-aged men.1 Untreated OSA is strongly associated with an increase of hypertension, coronary artery disease, myocardial infarction, stroke and even sudden death.<sup>2–7</sup>

Previous studies have shown a relationship between OSA and nocturia and polyuria, which are related to lower urinary tract symptoms (LUTS).<sup>8,9</sup> Nocturia has a negative effect on sleep and is associated with a decrease in the general state of

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health, and chronic medical illnesses including obesity, hypertension, diabetes, stroke, coronary artery disease, congestive heart failure. 10 The mechanism resulting in increased nocturia and nocturnal polyuria in patients with OSA has been attributed to elevated nocturnal atrial natriuretic peptide (ANP) excretion in subjects with elevated disease severity, esp. in OSA patients with apnea/hypopnea index (AHI, /hr.) greater than 15.9 It has also been suggested that the generation of negative pressure in the chest, caused by partial or full obstruction of the airway and sustained ventilatory efforts, will induce a signal of volume overload received by the heart and further increase urine output and nocturia in OSA patients. Improvements of nocturia in OSA patients have been described with nasal continuous positive airway pressure (CPAP) therapy. <sup>10</sup>

Overactive bladder (OAB) syndrome, defined as urgency, with or without incontinence, usually with urinary frequency and nocturia, 11 is a subset of storage LUTS, and has been estimated with the prevalence of 10% to 20% in men<sup>12</sup> and has a negative impact on quality of life (OoL). Treatment of male LUTS and OAB includes behavior therapy. pharmacotherapy and surgery targeting at the prostate or bladder. 13 OAB and male LUTS have also been linked to autonomic dysfunction. <sup>14</sup> Furthermore, our team reported that OSA induces nocturnal hypoxia and alters white matter integrity, and this impairment might play some role in autonomic dysfunction and sympathetic activation. 15 Lombardi et al suggested a dose response relationship between OSA severity and the degree of sympathetic overactivity and this association seems to be reversible as the treatment of OSA is implemented. 16 Previous studies have also demonstrated a positive association of OSA with OAB as well as a correlation between the severity of OSA and OAB in both men and women. 17 This implies that the two conditions may be linked by a common pathophysiological mechanism.

Various treatment options are available for OSA, depending on an individual's medical history, and the specific cause of the obstruction and the severity of the disorder. Clinically, CPAP or oral appliance is the primary conservative treatment for patients with OSA. In fact, many individuals with OSA who could not tolerate or were not willing to accept these conservative treatment modalities for a long-term therapy will consider an alternative, including OSA surgery. Literature has demonstrated the clinical benefits and value of upper airway surgery for patients with OSA. 18-22

The tongue base/hypopharyngeal obstruction is one of the major causes of OSA, of which obstructive condition(s) are usually challenging for the majority of sleep surgeons and could be more suitably relieved by transoral robotic surgery (TORS).<sup>23</sup> TORS is a relatively new and innovative technique for OSA patients. TORS-assisted OSA surgery has demonstrated as a valid option with clinical evidence-based benefits by significantly decreasing the postoperative AHI (/hr.) with minor morbidities for selected OSA patients.<sup>24–26</sup>

Previous literature on OSA surgical treatment studies commonly reported the changes of polysomnographic parameters and snoring severity but did not report the treatment endpoint on health quality of lower urinary tract system. In the present study, we firstly evaluated the effect of TORS-assisted OSA surgery on LUTS and OAB symptoms in male OSA patients, as well as further analyzed the relations between severity of OSA and the improvement of LUTS and OAB after TORS-assisted OSA surgery.

#### Materials and Methods

This open label, prospective study was conducted between June, 2018 and September, 2020 at the Sleep Center and Department of Otolaryngology of the Kaohsiung Chang Gung Memorial Hospital (KCGMH). The study hospital, KCGMH, is a medical center and a main tertiary referral hospital that serves an area with the population of 3 million in southern Taiwan.

The study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (CGMH IRB #: 201800922B0 and 201800922B0C501), and was performed according to the ethical principles of Good Clinical Practice guidelines and the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patients before any study procedures were performed.

# Study Population

This study did not include female patients. Male patients with OSA, who aged 20 years or above and had failed conventional OSA treatments, were enrolled. OSA was diagnosed with a full-night sleep study, polysomnography (PSG), in the sleep laboratory of Sleep Center at the KCGMH. The comprehensive PSG examination, including electroencephalography, electrooculography, chin and anterior tibial electromyography, respiratory effort detectors,

nasal/oral flow sensors, and pulse oximetry, was performed using a standardized commercial device (Sandman SD32 +TM Digital Amplifier Embla, Colorado, USA). The AHI was calculated by using the total number of apnea and hypopnea episodes per hour of sleep. Patients were divided according to their OSA severity as normal (AHI<5), mild (AHI 5–14.9), moderate (AHI 15.0–29.9), and severe OSA (AHI≥30) groups.<sup>27</sup> Additionally, all PSGs were scored and read by a boarded physician who was unaware of the study and, therefore, blinded to the patients' participation in the study.

Patients with the following conditions were excluded: female patients, age < 20 or > 65 years old, moderate to severe heart failure (New York Heart Association class III and IV), severe central or peripheral neurological disorders, previous history of upper airway surgical treatment for OSA, currently undergoing conservative OSA treatments, such as oral appliance or CPAP, BMI > 35 kg/m², contra-indications for OSA surgery under general anesthesia, shift worker and/or chronic use of sleep pills. Additional exclusion criteria in this study included: patients that were previously diagnosed and treated with benign prostate hyperplasia and OAB; patients with neurogenic urinary bladder, urinary tract infection, and lower urinary track cancer; patients using diuretic medication, desmopressin, a1-blocker, 5a-reductase inhibitor, anticholinergic, and phosphodiesterase type 5 inhibitor and patients with a history of urogenital operation.

# Surgical Procedures of TORS-Assisted OSA Surgery

All procedures were performed by the corresponding author (H-C Lin) under general anesthesia. The techniques used were determined at the discretion of the treating sleep surgeon according to the findings on the severity of OSA disease with PSG and the condition of upper airway abnormality with the flexible fibroscopic examination and Propofol-induced sleep endoscopy. The surgical techniques are as our previous literature. 19–21,23,28

#### Assessment for LUTS and OAB

The evaluation of LUTS and OAB was based on a validated self-administered questionnaire containing International Prostate Symptom Score (IPSS) and OAB symptom score (OABSS), respectively.<sup>29–33</sup>

The IPSS contains seven questions (score 0–5; a maximum total score of 35 points) concerning lower urinary symptoms related to benign prostatic hyperplasia, and one question (IPSS-8) related to the patient's perceived quality of life (QoL) (score 0–6, indicating increasing severity of symptoms and low QoL). The patient experienced more severe symptoms will have higher score. Overactive Bladder Symptom Score (OABSS, score 0–15; mild OAB, 3–5; moderate OAB, 6–11; severe OAB, 12–15), which was based on a self-administered questionnaire relating to four areas: daytime frequency (Q1, 0–2), nighttime frequency/nocturia (Q2, 0–3), urgency (Q3, 0–5), and urgency incontinence (Q4, 0–5). In the present study, the patients with an OAB urgency score of  $\geq$ 2 and sum score of  $\geq$ 3 were considered to have OAB according to the severity classification proposed by Homma et al in 2006. All of results were evaluated at baseline and at least 3 months after the TORS-OSA surgery.

### Outcome Measures

The follow-up schema included clinical examinations, full-night sleep study (PSG), and the questionnaire-based reevaluation of OSA-related symptoms (Epworth Sleepiness Scale<sup>34</sup> (ESS)) and Functional Outcomes of Sleep Questionnaire<sup>35</sup> (FOSQ), LUTS, and OAB before and at least 12 weeks following TORS-assisted OSA Surgery.

Safety measurements were composed of adverse events (AEs), such as: postoperative acute airway compromise, wound bleeding, etc., and any other possible TORS-related AEs that occurred after surgery.

# Statistical Analysis

The Kolmogorov-Smirnov test was used to confirm normal distribution. Quantitative variables were expressed with mean and standard deviation. While Wilcoxon signed-rank test was used to compare the changes of before and after TORS-OSA Surgery. McNemar test was used on paired nominal data. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0, Chicago, IL, USA).

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# **Results**

# Patient Disposition

A total of 123 male patients with mean age of  $42.8 \pm 9.5$  years and mean AHI of  $42.2 \pm 22.0$  /hr. were enrolled. There were 6 patients with mild OSA, 41 patients with moderate OSA and 76 patients with severe OSA were included in the study. Effects of TORS-OSA surgery on daytime sleepiness, major polysomnographic parameters are presented in Table 1. Changes of Functional Comorbidity Index, FOSQ, International Prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS) scores are shown in Tables 2 and 3.

Because there will be significantly increasing clinical and cardiovascular comorbidities along with the increase of OSA disease severity, we further divided our patients into mild/moderate and severe OSA groups for comparing the treatment outcomes (Tables 4–7).

After TORS-OSA surgery, significant changes and improvements on OABSS and IPSS were observed. TORS-OSA surgery was associated with a statistically significant improvement of LUTS, LUTS QoL score, and OAB symptoms (IPSS 22.1% decrease; IPSS QoL score 21.1% decrease; OABSS 17.4% decrease) at 3-month follow-up. The presence of OAB (OABSS-3 more than 2 and OABSS-total more than 3), and severe nocturia (OABSS-2 more than 3) was significantly reduced from 22.8% (28/123) to 11.4% (14/123) (*p*=0.001, by *McNemar test*), 5.7% (7/123) to 0.8% (1/123) (*p*=0.031, by *McNemar test*) after TORS-OSA surgery at 12-week follow-up. After TORS-OSA surgery, changes of presence of OAB in mild/moderate OSA patients and severe OSA patients were 25.5% (12/47) to 19.1% (9/47) (*p*=0.25, by *McNemar test*) and 21.1% (16/76) to 6.6% (5/76) (*p*=0.003, by *McNemar test*), respectively. Among the OAB subscore, nocturia subscore and urgency subscore were significantly reduced after TORS-OSA surgery, however, the frequency subscore and urgency incontinence subscore had no significant difference.

**Table I** Changes of Subjective Estimates of Daytime Symptoms and Major Polysomnographic Parameters in Men with OSA Before and After TORS-OSA Surgery (N = 123; Mean Age = 42.8±9.5 Yrs.)

	Pre-Operative	Post-Operative	Difference (Post Pre.)	P value <sup>a</sup>
ESS	8.61±4.44	6.87±3.81	-1.74±4.39	0.0001*
Sleep efficiency (%)	91.52±68.38	86.68±11.85	-4.83±68.91	0.2815
AHI (/hr.)	42.14±22.03	25.93±21.42	-16.20±22.97	<0.0001*
Mean O <sub>2</sub> saturation (%)	94.20±2.65	94.66±6.93	0.46±7.14	<0.0001*
LSAT (%)	75.08±11.82	84.04±7.78	7.96±10.82	<0.0001*
O <sub>2</sub> desaturation index (/hr.)	31.36±23.54	16.75±19.12	-14.62±20.13	<0.0001*

Notes: aBy Wilcoxon signed-rank test. Data expression with mean±SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; ESS, Epworth Sleepiness Scale; AHI, apnea/hypopnea index; LSAT, lowest oxygen saturation.

**Table 2** Changes of Functional Comorbidity Index and Functional Outcomes of Sleep in Men with OSA Before and After TORS-OSA Surgery (N = 123)

	Pre-Operative	Post-Operative	Difference (Post Pre.)	P value <sup>a</sup>	
Functional Comorbidity Index					
FCI	0.38±0.76	0.37±0.70	-0.02±0.41	0.6547	
Functional Outcomes of Sleep Questionnaire					
FOSQ-I	2.80±1.01	2.66±0.97	-0.15±0.65	0.0083*	
FOSQ-2	2.52±0.91	2.31±0.37	-0.21±0.70	0.0015*	
FOSQ-3	2.79±0.95	2.56±0.81	-0.23±0.65	0.0003*	
FOSQ-4	2.51±0.89	2.41±0.77	-0.11±0.58	0.0463*	

Notes: <sup>a</sup>By Wilcoxon signed-rank test. Data expression with mean±SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; FCI, Functional Comorbidity Index; FOSQ, Functional Outcomes of Sleep Questionnaire.

Table 3 Changes of Prostate and Bladder Symptoms in Men with OSA Before and After TORS-OSA Surgery (N = 123)

	Pre-Operative	Post-Operative	Difference (Post - Pre)	P value <sup>a</sup>	
International Prostate Symptom Score (IPSS)					
IPSS total	6.46±5.60	5.03±4.88	-I.43±2.84	<0.0001*	
IPSS-8	2.13±1.66	1.68±1.37	−0.45±1.01	<0.0001*	
Overactive Bladder Symptom Score (OABSS)					
OABSS-I	0.80±0.68	0.77±0.70	-0.02±0.24	0.2568	
OABSS-2	1.01±0.84	0.84±0.69	-0.17±0.61	0.0024*	
OABSS-3	0.87±1.12	0.59±0.84	-0.28±0.84	0.0002*	
OABSS-4	0.20±0.59	0.18±0.46	-0.02±0.47	0.7762	
OABSS-total	2.88±2.14	2.38±1.71	−0.50±1.48	0.0001*	

Notes: <sup>a</sup>By Wilcoxon signed-rank test. Data expression with mean±SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; IPSS, International Prostate Symptom Score; IPSS-8, QoL score; OABSS, Overactive Bladder Symptom Score.

**Table 4** Changes of Subjective Estimates of Symptoms and Brief Polysomnographic Data in Men with Mild/Moderate OSA Before and After TORS-OSA Surgery (N = 47; Mean Age =  $43.3\pm10.2$  Yrs.)

	Pre-Operative	Post-Operative	Difference (Post Pre.)	P value <sup>a</sup>
ESS	8.55±4.27	7.70±4.47	0.84±4.71	0.224
Sleep efficiency (%)	102.41±109.10	86.43±9.06	15.97±109.63	0.596
AHI (/hr.)	20.80±5.34	17.94±13.51	−2.86±13.34	0.071
MeanO <sub>2</sub> saturation (%)	95.29±1.31	95.69±1.31	−0.40±1.34	0.061
LSAT (%)	80.68±9.75	84.96±5.73	-4.28±10.05	0.006*
Desaturation index (/hr.)	10.91±7.21	8.38±8.28	2.52±7.39	0.023*

Notes: <sup>a</sup>By Wilcoxon signed-rank test. Data expression with mean±SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; ESS, Epworth Sleepiness Scale; AHI, apnea/hypopnea index; LSAT, lowest oxygen saturation.

**Table 5** Changes of Subjective Estimates of Symptoms and Brief Polysomnographic Data in Men with Severe OSA Before and After TORS-OSA Surgery (N = 76; Mean Age = 42.5±9.1 Yrs.)

	Pre-Operative	Post-Operative	Difference (Post Pre.)	P value <sup>a</sup>
ESS	8.65±4.57	6.36±3.28	2.29±4.12	<0.0001*
Sleep efficiency (%)	84.75±12.76	86.84±13.35	-2.09±14.30	0.068
AHI (/hr.)	55.33±17.63	30.87±23.87	24.46±23.84	<0.0001*
MeanO <sub>2</sub> saturation (%)	93.52±3.03	94.02±8.70	-0.49±9.04	<0.0001*
LSAT (%)	71.62±11.71	81.86±8.64	-10.23±10.71	<0.0001*
Desaturation index (/hr.)	43.48±21.37	21.70±21.86	21.78±21.83	<0.0001*

Notes: aBy Wilcoxon signed-rank test. Data expression with mean±SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; ESS, Epworth Sleepiness Scale; AHI, apnea/hypopnea index; LSAT, lowest oxygen saturation.

In this study, there were no patients who had acute airway compromise or acute massive bleeding after surgery. Additionally, there were 24 patients (19.5%) who addressed lumping throat after surgery, however, none of these patients reported severe dysphagia and had obvious impact on swallowing in this cohort.

#### **Discussion**

Patient reported outcome (PRO) instruments are considered the gold standard for capturing the subjective patient experience. 36-38 Classically, the evaluation of treatment outcomes for OSA patients usually focused on the changes of PSG

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Table 6 Changes of IPSS, OABSS and Sleep-Related Quality in Men with Mild/Moderate OSA Before and After TORS-OSA Surgery (N = 47)

	Pre-Operative	Post-Operative	Difference (Post Pre.)	P value <sup>a</sup>
International Prostate	e Symptom Score (IPSS)			
IPSS total	6.06±4.83	5.04±4.60	1.02±2.43	0.002*
IPSS-8	2.19±1.44	1.83±1.17	0.36±1.09	0.038*
Overactive Bladder S	ymptom Score (OABSS)			
OABSS-I	0.66±0.60	0.66±0.60	0.00±0.21	1.000
OABSS-2	1.00±0.83	0.87±0.65	0.13±0.54	0.107
OABSS-3	0.96±1.10	0.77±0.96	0.19±0.58	0.021*
OABSS-4	0.17±0.56	0.11±0.31	0.06±0.53	0.480
OABSS-total	2.79±2.00	2.40±1.70	0.38±1.21	0.048*
Functional Outcomes	of Sleep Questionnaire (I	FOSQ)		
FOSQ-I	2.87±1.08	2.81±1.04	0.06±0.53	0.405
FOSQ-2	2.46±0.91	2.37±0.77	0.09±0.59	0.331
FOSQ-3	2.77±0.98	2.62±0.87	0.15±0.63	0.124
FOSQ-4	2.45±0.80	2.40±0.80	0.04±0.46	0.527

Notes: <sup>a</sup>By Wilcoxon signed-rank test. Data expression with mean±SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; IPSS, International Prostate Symptom Score; IPSS-8, QoL score; OABSS, Overactive Bladder Symptom Score; FOSQ, Functional Outcomes of Sleep Questionnaire.

Table 7 Changes of IPSS, OABSS and Sleep-Related Quality in Men with Severe OSA Before and After TORS-OSA Surgery (N = 76)

	Pre-Operative	Post-Operative	Difference (Post Pre.)	P value <sup>a</sup>
International Prosta	ate Symptom Score		<u> </u>	
IPSS total	6.71±6.04	5.03±5.08	1.68±3.05	<0.0001*
IPSS-8	2.09±1.79	1.59±1.49	0.50±0.96	<0.0001*
Overactive Bladder	Symptom Score			
OABSS-I	0.88±0.71	0.84±0.75	0.04±0.26	0.180
OABSS-2	1.01±0.86	0.82±0.73	0.20±0.65	0.009*
OABSS-3	0.82±1.14	0.49±0.74	0.33±0.97	0.003*
OABSS-4	0.22±0.60	0.22±0.53	0.00±0.43	0.739
OABSS-total	2.93±2.23	2.37±1.73	0.57±1.64	0.001*
Functional Outcom	es of Sleep Questionnaire			
FOSQ-I	2.76±0.96	2.57±0.91	0.20±0.71	0.011*
FOSQ-2	2.57±0.91	2.28±0.70	0.29±0.75	0.002*
FOSQ-3	2.80±0.94	2.53±0.77	0.28±0.67	0.001*
FOSQ-4	2.55±0.92	2.41±0.75	0.15±0.65	0.058

Notes:  ${}^a$ By Wilcoxon signed-rank test. Data expression with mean  $\pm$ SD. \*Statistical significance was accepted when p<0.05.

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery; IPSS, International Prostate Symptom Score; IPSS-8, QoL score; OABSS, Overactive Bladder Symptom Score; FOSQ, Functional Outcomes of Sleep Questionnaire.

parameters, such as: AHI, O<sub>2</sub> desaturation severity and bedpartner's subjectively scoring the patients' snoring intensity, etc. As the surrogate outcome for evaluating the value of OSA treatment, AHI and O2 desaturation status are not sufficient examinations of treatment outcomes and does not completely capture the spectrum of OSA and clinically meaningful endpoints.<sup>39</sup> Furthermore, any OSA treatment is based, not only on improving breathing patterns during sleep, but also on alleviating the health-related (primarily cardiovascular and endocrine), behavioral (daytime sleepiness, QoL), functional

(performance, driving), and social (disruptive snoring) consequences of the disorder, all of which must be weighed against OSA surgical complications and side effects.<sup>39</sup> In this study, our results demonstrated that TORS-OSA surgery, one of the principal treatment options for OSA, did not have major serious peri-and post-operative complications and can improve the LUTS and OAB in male OSA patients in addition to improvement on classical parameters (data on PSG and daytime hypersomnolence) of OSA treatment success. We also noted that the severe OSA group had 25.0% improvement in IPSS and 19.5% improvement in OABSS post TORS, which improvements were 16.8% in IPSS and 13.6% in OABSS in mild/moderate OSA group. The OSA patients with more severe baseline OSA disease severity might have more improvement in IPSS and OABSS after TORS-OSA surgery.

Numerous pathways may underlie OAB in OSA which could be reversed by TORS-OSA therapy. First, ischemia and hypoxia may have a role in bladder neuropathy and overactive bladder. It has been shown that repeating cycles of ischemia/reperfusion and hypoxia/reoxygenation leading to oxidative and nitrosative products, and bladder overactivity in the ischemic bladder in a rabbit model.<sup>40</sup> In 2015, Witthaus et al<sup>41</sup> demonstrated that increased urinary frequency and total urine output, and detrusor instability developed in rats exposed to obstructive sleep apnea/hypopnea conditions. These changes were associated with bladder oxidative stress characterized by significant increases in tissue levels of malondialdehyde and advanced oxidation protein products. In the same year, we conducted a prospective study with evaluating the number of circulating endothelial progenitor cells (EPCs, reflecting the degree of endothelial impairment; CD133(+)/CD34(+) [%], KDR(+)/CD34(+) [%]), biomarkers for oxidative stress (thiols and TBARS) in 62 OSA patients. Our results demonstrated that clinical efficiency after OSA surgery assessed by PSG showed improvement and mean systolic blood pressure (night and morning) reduction in the severe OSA group as well as increasing the number of circulating EPCs and antioxidant capacity, especially in patients with severe OSA. 42 Additionally, based on the available evidence of improved mean O2 saturation after TORS-OSA therapy, we would speculate that the reduction of the OSA-associated hypoxia may finally lead to restore O<sub>2</sub> saturation of the pelvic vasculature, which could lead to improve ischemic change of bladder or prostate, and improve LUTS and OAB. Furthermore, our data showed urgency subscore (OABSS Q4) and nocturia subscore (OABSS Q2) was significantly improved after surgery. We believe that bladder instability and nocturnal urine production might normalize after TORS-OSA therapy.

Regarding the impact of body mass index (BMI, kg/m<sup>2</sup>) on overactive bladder severity and OSA, Cardozo et al<sup>43</sup> used pooled data from seven randomized placebo-controlled trials to evaluate relationships between baseline BMI and OAB. Their results showed that the baseline incidence of urgency, a key symptom of OAB, tended to increase with increasing BMI. Our current data revealed BMI was slightly reduced from 26.9 to 25.8 after TORS-OSA therapy, which might partially explain the mechanisms of improved OAB and LUTS after OSA treatment.

The limitations of this study are: 1) single surgeon's and institute's experience, 2) the patients served as their own control before vs after TORS-OSA surgery with a lack of a control group, 3) this study was still a short follow-up and the outcomes may be different based on time after surgery. The results of the long-term outcomes should be extended, 4) we recognize there were a relatively small number of subjects studied and a larger case series should be conducted in future studies, and 5) our experience and data are limited to Asian patients. It could be important to publish our data and further compare the difference among different ethnic populations. Also, the major disadvantage of robotic surgery is the relatively high out of pocket expense making the procedure unattainable for the average person without private insurance assistance.

In conclusion, our study TORS-assisted OSA surgery could not only improve major parameters of sleep study and sleep-related QoL, but also improve LUTS and OAB symptoms on male patients with OSA, especially in patients with severe OSA.

#### **Ethics Committee**

Ethics committee approval was obtained from the institutional review board and ethics committee at the Chang Gung Memorial Hospital, Taiwan (CGMH IRB #: 201800922B0 and 201800922B0C501).

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# **Acknowledgments**

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#### **Author Contributions**

Yao-Chi Chuang: data collection and interpretation, wrote the manuscript; Pei-Wen Lin: data collection, analysis and interpretation, critical revision of the manuscript; Hsin-Ching Lin: designed study, data collection and interpretation, wrote the manuscript and final approval; Chun-Tuan Chang: statistical analysis and critically reviewed the manuscript; Michael Friedman: data interpretation and critical revision of the manuscript for important intellectual content; Anna M Salapatas: data analysis and critical revision of the manuscript; Chih-Yun Li: data interpretation, statistical analysis and critical revision of the manuscript. Additionally, all authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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#### Disclosure

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#### References

- 1. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230–1235. doi:10.1056/NEJM199304293281704
- 2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea. A population health perspective. Am J RespirCrit Care Med. 2002;165:1217-1239. doi:10.1164/rccm.2109080
- 3. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046-1053. doi:10.1016/S0140-6736(05)71141-7
- 4. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA. 2003;290:1906–1914. doi:10.1001/jama.290.14.1906
- 5. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307:2161-2168. doi:10.1001/ jama.2012.4366
- 6. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307:2169–2176. doi:10.1001/jama.2012.3418
- 7. Sahlin C, Sandberg O, Gustafson Y, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. Arch Intern Med. 2008;168:297-301. doi:10.1001/archinternmed.2007.70
- 8. Kemmer H. The relationship between sleep apnea and overactive bladder. Curr Urol Rep. 2009;10:448-450. doi:10.1007/s11934-009-0071-2
- 9. Umlauf MG, Chasens ER, Greevy RA, et al. Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep. 2004;27:139–144.
- 10. Margel D, Shochat T, Getzler O, et al. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. *Urology*. 2006;67:974-977. doi:10.1016/j.urology.2005.11.054

11. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: report from the standardization sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002;21:167–178. doi:10.1002/nau.10052

- 12. Wu TH, Shen YC, Lee WC, et al. Effect of mirabegron on erectile function in sexually active men with bothersome overactive bladder symptoms. *J Chin Med Assoc.* 2020;83:55–59. doi:10.1097/JCMA.000000000000000000
- 13. Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol*. 2013;64:118–140. doi:10.1016/j.eururo.2013.03.004
- 14. Chen LC, Kuo HC. Pathophysiology of refractory overactive bladder. Low Urin Tract Symptoms. 2019;11:177–181. doi:10.1111/luts.12262
- 15. Chen HL, Huang CC, Lin HC, et al. White matter alteration and autonomic impairment in obstructive sleep apnea. *J Clin Sleep Med*. 2020;16:293–302. doi:10.5664/jcsm.8186
- Lombardi C, Pengo MF, Parati G. Obstructive sleep apnea syndrome and autonomic dysfunction. Auton Neurosci. 2019;221:102563. doi:10.1016/j. autneu.2019.102563
- 17. Ipekci T, Cetintas G, Celik O, et al. Continuous positive airway pressure therapy is associated with improvement in overactive bladder symptoms in women with obstructive sleep apnea syndrome. *Cent European J Urol.* 2016;69:78–82. doi:10.5173/ceju.2016.674
- 18. Lin HC, Friedman M, Chang HW, et al. The efficacy of multilevel surgery in adults with obstructive sleep apnea/hypopnea syndrome. Laryngoscope. 2008;118:902–908. doi:10.1097/MLG.0b013e31816422ea
- 19. Lin HC, Friedman M, Chang HW, et al. Z-palatopharyngoplasty plus radiofrequency tongue base reduction for moderate/severe obstructive sleep apnea/hypopnea syndrome. *Acta Otolaryngologica*. 2010;130:1070–1076. doi:10.3109/00016481003606240
- 20. Lin HC, Friedman M, Chang HW, et al. Minimally invasive single-stage multilevel surgery for OSA in Asian patients. *JAMA Otolaryngol Head Neck Surg.* 2017;143:1–8. doi:10.1001/jamaoto.2016.3103
- 21. Lin HC, Friedman M, Chang HW, et al. Z-palatopharyngoplasty combined with endoscopic coblator open tongue base resection for severe OSA. Otolaryngol Head Neck Surg. 2014;150:1078–1085. doi:10.1177/0194599814524722
- 22. Lin HC, Hwang MS, Liao CC, et al. Taste disturbance following tongue base resection for OSA. *Laryngoscope*. 2016;126:1009–1013. doi:10.1002/lary.25580
- 23. Lin HC, Friedman M. Transoral robotic OSA surgery. Auris Nasus Larynx. 2021;48:339-346. doi:10.1016/j.anl.2020.08.025
- 24. Justin GA, Chang ET, Camacho M, et al. Transoral robotic surgery for obstructive sleep apnea: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2016;154:835–846. doi:10.1177/0194599816630962
- 25. Miller SC, Nguyen SA, Ong AA, et al. Transoral robotic base of tongue reduction for obstructive sleep apnea: a systematic review and meta-analysis. *Laryngoscope*. 2017;127:258–265. doi:10.1002/lary.26060
- 26. Meccariello G, Cammaroto G, Montevecchi F, et al. Transoral robotic surgery for the management of obstructive sleep apnea: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol*. 2017;274:647–653. doi:10.1007/s00405-016-4113-3
- 27. Iber C, Ancoli-Israel S, Chesson AL, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1<sup>st</sup> ed. Westchester, IL, USA: American Academy of Sleep Medicine; 2007.
- 28. Lin HC, Weaver EM, Lin HS, Friedman M. Multilevel obstructive sleep apnea surgery. Adv Otorhinolaryngol. 2017;80:109–115. doi:10.1159/000470879
- 29. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The measurement committee of the American Urological Association. *J Urol.* 1992;148:1549–1557. doi:10.1016/S0022-5347(17)36966-5
- 30. Inoue S, Hayashi T, Teishima J, et al. Comparative analysis of robot-assisted, laparoscopic, and open radical prostatectomy regarding lower urinary tract symptoms: a longitudinal study. *Urol Sci.* 2020;31:21–27. doi:10.4103/UROS.UROS\_44\_19
- 31. Homma Y, Yoshida M, Seki N, et al. Symptom assessment tool for overactive bladder syndrome: overactive bladder symptom score. *Urology*. 2006;68:318–323. doi:10.1016/j.urology.2006.02.042
- 32. Chou EC, Hung MJ, Yen TW, et al. The translation and validation of Chinese overactive bladder symptom score for assessing overactive bladder syndrome and response to solifenacin treatment. *J Formos Med Assoc*. 2014;113:506–512. doi:10.1016/j.jfma.2012.07.044
- 33. Choi EP, Lam CL, Chin WY. Validation of the International Prostate Symptom Score in Chinese males and females with lower urinary tract symptoms. *Health Qual Life Outcomes*. 2014;12:1. doi:10.1186/1477-7525-12-1
- 34. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. the Epworth sleepiness scale. *Chest.* 1993;103:30–33. doi:10.1378/chest.103.1.30
- 35. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20:835–843.
- 36. Basch E. New frontiers in patient-reported outcomes: adverse event reporting, comparative effectiveness, and quality assessment. *Annu Rev Med*. 2014;65:307–317. doi:10.1146/annurev-med-010713-141500
- Basch E. Missing patients' symptoms in cancer care delivery—the importance of patient-reported outcomes. JAMA Oncol. 2016;2:433–434. doi:10.1001/jamaoncol.2015.4719
- 38. Basch E. Patient-reported outcomes harnessing patients' voices to improve clinical care. N Engl J Med. 2017;376:105–108. doi:10.1056/NEJMp1611252
- 39. Kezirian EJ, Weaver EM, Criswell MA, et al. Reporting results of obstructive sleep apnea syndrome surgery trials. *Otolaryngol Head Neck Surg.* 2011;144:496–499. doi:10.1177/0194599810396791
- 40. Azadzoi KM, Yalla SV, Siroky MB. Oxidative stress and neurodegeneration in the ischemic overactive bladder. *J Urol.* 2007;178:710–715. doi:10.1016/j.juro.2007.03.096
- 41. Witthaus MW, Nipa F, Yang JH, et al. Bladder oxidative stress in sleep apnea contributes to detrusor instability and nocturia. *J Urol.* 2015;193:1692–1699. doi:10.1016/j.juro.2014.11.055
- 42. Lu CH, Lin HC, Huang CC, et al. Increased circulating endothelial progenitor cells and anti-oxidant capacity in obstructive sleep apnea after surgical treatment. Clin Chim Acta. 2015;448:1–7. doi:10.1016/j.cca.2015.05.023
- 43. Cardozo L, Herschorn S, Snijder R, et al. Does BMI, gender or age affect efficacy/tolerability of solifenacin in the management of overactive bladder? *Int Urogynecol J.* 2017;28:477–488. doi:10.1007/s00192-016-3130-5

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