AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2023, Vol. 00(00) 1–7
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DOI: 10.1002/ohn.218
http://otojournal.org
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Homocysteine Levels in Severe OSA Patients Before and After TORS-OSA Surgery

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Abstract

Objective. The increased risk of cardiovascular diseases owing to a high level of serum homocysteine has been widely reported. Literature has demonstrated that patients with obstructive sleep apnea/hypopnea syndrome (OSA) had a higher homocysteine level than control group. This study aimed to investigate the alteration of serum homocysteine levels in severe OSA patients receiving transoral robotic surgery (TORS).

Study Design. Retrospective chart review.

Setting. Tertiary academic medical center.

Methods. Data of polysomnography (PSG) and serum homocysteine levels before and at least 3 months after the surgery were collected and analyzed via paired *t* tests. A subgroup analysis based on the preoperative homocysteine level (≥15 mcmol/L, as hyperhomocysteinemia group) was conducted to compare the intergroup differences of homocysteine decrease. Pearson's correlation was used to survey the relationships between the changes of major PSG parameters and the levels of homocysteine decrease at baseline and after TORS-OSA surgery.

Results. Two hundred sixty-one patients with severe OSA were enrolled. There were significant improvements in major PSG parameters after TORS-OSA surgery. Homocysteine levels significantly decreased from 12.1 ± 3.9 to 11.4 ± 3.7 mcmol/L (difference = −0.7 ± 2.8 mcmol/L, $p = .001$) postoperatively, which was shown in the hyperhomocysteinemia group (difference = −2.9 ± 4.7 mcmol/L, $p = .007$) to a greater extent. Pearson's correlation revealed that ΔODI (oxygen desaturation index/h) was the predominant estimate with a positive association with Δhomocysteine ($r = 0.525$, $p = .012$).

Conclusion. TORS-OSA surgery could decrease homocysteine levels in OSA patients. The effects were more relevant in severe OSA patients with abnormal preoperative homocysteine levels.

Keywords

homocysteine, myocardial infarction, obstructive sleep apnea, OSA surgery, snoring, stroke, transoral robotic surgery

Received June 26, 2022; accepted November 17, 2022.

Homocysteine, an essential component in the human body, is a sulfur-containing intermediate product in the process of conversion from methionine to cysteine. Usually, a low level of homocysteine reflects the stable clinical condition of a man which is not under active inflammatory status. In 2002, Homocysteine Studies Collaboration conducted a meta-analysis and suggested that elevated levels of homocysteine is at most a modest independent predictor of ischemic heart disease and stroke in healthy populations. Furthermore, once the homocysteine level flares up to more than 15 mcmol/L, aka hyperhomocysteinemia, it will significantly increase the risks of cardio-/cerebrovascular diseases,[1,2] lower-extremity peripheral arterial disease,[3] heart failure,[4] and venous thromboembolism,[5] and so on. Therefore, identifying the root of homocysteinemia early and reversing this abnormality

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can be imperative for clinicians to further prevent the progression of cardiovascular consequences in patients.

Obstructive sleep apnea/hypopnea syndrome (OSA) is a common sleep-related breathing disorder characterized by recurrent upper airway obstruction during sleep, leading to repeated hypoxia, elevated $PaCO_2$, and sleep fragmentation.[6] OSA often leads to significant associated symptoms (habitual snoring and hypersomnolence), impaired quality of life and long-term health outcomes.[7] Additionally, accumulating studies have demonstrated that OSA is an independent risk factor for cardiovascular diseases.[8,9]

Several hematological biomarkers have been found possessing correlations with the severity of OSA. Moreover, there are emerging studies recently discussing the association between OSA and elevated homocysteine levels since these 2 factors could share similarities in the pathway on oxidative stress and chronic inflammatory status.[10,11] Given that the impact on health attributed to OSA is a worldwide concern, effective treatment of OSA becomes necessary for both physicians and patients. Thus, using homocysteine as an indicator for the treatment of OSA could potentially be beneficial in clinical practice.

Treatment plans for OSA are established based on its etiology, disease severity, and possible OSA-related comorbidities. These include behavior modifications, oral appliances, continuous positive airway pressure (CPAP) therapy, and surgical intervention for anatomic correction of the upper airway.[12] CPAP therapy is the first-line treatment for adult OSA. However, variable CPAP compliance usually limits its effectiveness.[13] Sleep surgery aims to stabilize the upper airway during sleep and is an alternative and a salvage treatment for OSA patients who cannot tolerate or will not undergo CPAP or other conservative therapies. Nowadays, developments of transoral robotic surgery (TORS) provide a relatively new option for treating OSA. Papers with meta-analysis and systematic review on TORS for OSA patients have demonstrated the clinical benefits of robotic surgery.[14-17]

Considering that the role of the novel hematological biomarkers, such as homocysteine, may have certain values reflecting the severity of OSA and the related comorbidities, they may also become probable indicators for assessing the outcomes after treatment. Currently, there are studies observing the changes in plasma homocysteine levels following CPAP or mandibular advancement device (MAD) therapy.[18-21] However, none of the studies discussed the alteration of homocysteine level in OSA patients treated with upper airway surgery.

With the evidence[18-20] indicating that conservative OSA therapies could lower the OSA patients' homocysteine level, we hypothesized that the OSA patients receiving TORS may experience drop in homocysteine level to some extent as well, and expected the results would provide new insights in the future tasks of assessing the outcome value of TORS-OSA surgery. Therefore, we first evaluate the changes of homocysteine in severe OSA patients following TORS-assisted upper airway surgery.

Materials and Methods

This study was approved by the Institutional Review Board and Ethics Committee of the Chang Gung Memorial Hospital, Taiwan (CGMH IRB#: 202200602B0), and was performed according to the principles outlined in the Declaration of Helsinki. The study hospital, Kaohsiung CGMH, is an academic medical center and a tertiary referral hospital that serves an area with a population of 3 million in southern Taiwan.

Study Design

We designed a retrospective cohort study to primarily investigate the changes in the homocysteine level among the severe OSA (apneahypopnea index [AHI] ≥ 30/h) patients who refused or could not tolerate CPAP as a long-term therapy and then received TORS surgery. After analyzing the difference between the pre- and postoperative full-night polysomnographic (PSG) data and homocysteine values, a subgroup analysis to compare the decrease in homocysteine based on the preoperative homocysteine level was further conducted. Here, in our study, we followed the definition of the American Heart Association on the cardiovascular risks related to homocysteine level, designating those with the "homocysteine level < 15 mcmol/L" as "normal," and those with the "homocysteine level ≥ 15 mcmol/L" as "hyperhomocysteinemia" for analysis in subgroups.[22] Moreover, we performed an etiological survey to investigate the potential roles of PSG parameters contributing to the decline in homocysteine levels in severe OSA patients with hyperhomocysteinemia.

Patient Selection

Patients with the diagnosis of severe OSA and receiving TORS as the treatment from January 2016 to December 2021 were enrolled in this study. All of the patients had refused or failed conservative OSA treatments and consulted for surgical interventions as the salvage therapy. The selected OSA patients must complete the full-night PSG and blood tests before and at least 3 months after the TORS-OSA surgery. Patients with the following conditions were excluded: age < 20 or >65 years old, severe central apnea, previous history of upper airway surgery for OSA, currently well undergoing conservative OSA therapy, such as oral appliance or CPAP, body mass index (BMI) > 35 kg/m^2, contraindications for surgery under general anesthesia, shift worker or chronic use of sleep pills. Additional exclusion criteria in this study included: patients that were previously diagnosed and treated with myocardial infarction and stroke; patients with moderate to severe heart failure (New York Heart Association Class III and IV).

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Table 1. Changes of Major Polysomnographic Indices in Severe OSA Patients Before and After TORS-OSA Surgery

Characteristics	Preoperative[b]	Postoperative[b]	Difference (post-pre)[b]	*p* value[a]
ESS	9.3 ± 4.6	7.1 ± 4.2	−2.2 ± 5.2	<.001
BMI (kg/m^2)	27.7 ± 3.9	26.6 ± 3.6	−1.1 ± 2.0	<.001
Sleep efficiency (%)	83.9 ± 12.9	85.9 ± 12.8	2.0 ± 13.7	.032
N1 (%)	54.9 ± 22.1	38.5 ± 20.1	−16.4 ± 26.6	<.001
N2 (%)	28.7 ± 19.7	41.0 ± 17.3	12.3 ± 23.4	<.001
N3 (%)	1.4 ± 4.3	2.0 ± 4.4	0.7 ± 5.7	.087
REM (%)	15.5 ± 11.3	18.4 ± 7.2	2.8 ± 12.4	.001
AHI (/h)	57.8 ± 18.4	35.6 ± 37.9	−22.2 ± 38.7	<.001
AHI in REM (/h)	57.2 ± 51.9	35.5 ± 25.9	−21.7 ± 52.0	<.001
Apnea, longest (s)	58.1 ± 22.7	45.1 ± 34.6	−13.0 ± 33.7	<.001
Hypopnea, longest (s)	72.3 ± 31.9	86.2 ± 47.5	13.9 ± 53.9	<.001
PO_2 < 90% (%)	17.7 ± 18.4	8.6 ± 14.3	−9.1 ± 15.6	<.001
mO_2 (%)	93.2 ± 3.5	94.3 ± 5.5	1.2 ± 5.8	.004
LSAT (%)	72.1 ± 11.9	80.7 ± 9.6	8.6 ± 10.5	<.001
ODI (/h)	45.6 ± 22.3	23.5 ± 21.7	−22.1 ± 21.3	<.001
Arousal index (/h)	52.3 ± 26.1	34.6 ± 25.1	−17.8 ± 31.7	<.001
Snoring index (/h)	407.3 ± 208.4	313.0 ± 213.1	−94.3 ± 291.4	<.001

N = 261; mean age = 42.2 ± 10.0 years.

Abbreviations: AHI, apnea/hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; LSAT, lowest saturation of oxygen; mO_2, mean saturation of oxygen; ODI, oxygen desaturation index; OSA, obstructive sleep apnea/hypopnea syndrome; PO_2 < 90%, percentage of time with saturation of oxygen below 90%; REM, rapid eye movement; TORS, transoral robotic surgery.

[a]Statistical analysis were performed using paired *t* tests, and $p < .05$ was viewed as of significance.

[b]The continuous data were presented as mean ± standard deviation.

Data Collection

The collected data included age and gender, Epworth Sleepiness Scale (ESS), BMI (kg/m^2), and major PSG-related indices, such as sleep efficiency (%), percentage of sleep stages on N1, N2, N3, and rapid eye movement (REM), AHI (/h), AHI in REM (/h), percentage of oxygen saturation less than 90% (PO_2 < 90%), mean saturation of oxygen (mO_2, %), lowest saturation of oxygen (LSAT, %), oxygen desaturation index (ODI, /h), arousal index (/h), and snoring index (/h). In this study, obstructive apnea was defined as a cessation of airflow with persistent respiratory effort for at least 10 seconds. Obstructive hypopnea was defined as a respiratory event with at least a 30% reduction in airflow or thoracoabdominal movement as compared to baseline, lasting at least 10 seconds, with ≥4% oxygen desaturation. Respiratory event with ≥50% reduction in airflow, with ≥3% oxygen desaturation or related arousal was also defined as a hypopnea episode. The AHI (/h) was the total number of apneas and hypopneas per hour of electroencephalographic sleep. The lab data with cardiovascular-related features, including homocysteine (mcmol/L), high-sensitivity C-reactive protein (hs-CRP) (mg/L), total cholesterol (mg/dL), and triglyceride (mg/dL), were also collected before and at least 3 months after TORS-OSA surgery.

Statistical Analysis

Paired *t* tests were first used to analyze the difference between the pre- and postoperative values in both the PSG and lab data in the overall subjects. Second, the patients were grouped based on their preoperative homocysteine level (<15 mcmol/L or ≥15 mcmol/L) in the analysis of their homocysteine decreases after TORS-OSA surgery. Additionally, we evaluated the relationships between the decline in the major PSG parameters and the homocysteine level in the hyperhomocysteinemia group using Pearson's correlation. A *p* value of less than .05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 22.0).

Results

A total of 261 patients with severe OSA including 14 women and 247 men with a mean age of 42.2 ± 10.0 years and a mean BMI of 27.7 ± 3.9 kg/m^2 were recruited. The basic characteristics and the PSG data before and after TORS were presented in **Table 1**. After TORS-OSA surgery, the majority of PSG parameters improved with significant decreases in ESS, N1 stage (%), AHI (/h), AHI in REM (/h), longest time of apnea (seconds), % of time with oxygen saturation less than 90% (%), ODI (/h), arousal index (/h), and snoring index (/h) as well as increases in sleep efficiency (%), N2 stage (%), % of REM stage (2.8 ± 12.4%, $p = .001$), mean oxygen saturation (%), and LSAT (%).

The changes of the homocysteine level and certain cardiovascular biomarkers before and after TORS-OSA surgery were shown in **Table 2**. The results demonstrated that there were significant decreases in the homocysteine

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Table 2. Changes of the Homocysteine, hs-CRP, Total Cholesterol, and Triglyceride Levels in Severe OSA Patients Before and After TORS-OSA Surgery

	Preoperative[b]	Postoperative[b]	Difference (post-pre)[b]	*p* value[a]
Homocysteine (mcmol/L)	12.1 ± 3.9	11.4 ± 3.7	−0.7 ± 2.8	.001
hs-CRP (mg/L)	2.3 ± 2.4	1.3 ± 1.3	−1.0 ± 2.0	<.001
Total cholesterol (mg/dL)	202.4 ± 37.5	190.1 ± 40.3	−12.3 ± 33.2	<.001
Triglyceride (mg/dL)	159.9 ± 90.8	134.2 ± 83.8	−25.6 ± 79.2	<.001

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery.
[a]Statistical analysis were performed using paired *t* tests, and $p < .05$ was viewed as of significance.
[b]The continuous data were presented as mean ± standard deviation.

(−0.7 ± 2.8 mcmol/L, $p = .001$), hs-CRP (−1.0 ± 2.0 mg/L, $p < .001$), total cholesterol (−12.3 ± 33.2 mg/dL, $p < .001$), and triglyceride (−25.6 ± 79.2 mg/dL, $p < .001$) levels.

Furthermore, we grouped the patients based on their preoperative homocysteine level (normohomocysteinemia vs hyperhomocysteinemia) for comparison of their homocysteine decreases after TORS-OSA surgery. The subgroup analysis (**Table 3**) showed that the homocysteine level declined substantially in both the preoperative normohomocysteinemia and hyperhomocysteinemia subgroups, and the extent was greater in the hyperhomocysteinemia group (difference −2.9 ± 4.7 mcmol/L, $p = .007$) than the normohomocysteinemia group (difference −0.4 ± 2.3 mcmol/L, $p = .044$). Thus, we further investigated the potential relationships between the improvement of major PSG parameters and decline in the homocysteine levels. The results disclosed that ΔODI was the predominant estimate with a positive association with Δhomocysteine by Pearson's correlation ($r = 0.525$, $p = .012$; **Table 4**).

Discussion

In literature, certain laboratory biomarkers which could be related to increases in cardiovascular risks have been advocated. These include brain natriuretic peptide, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), cysteine, homocysteine, free fatty acids, 8-isoprostane, gamma-glutamyl transferase, glycated hemoglobin, adipokines, and adhesion molecules.[23] In our study, we adopted clinically common and practical biomarkers including hs-CRP, total cholesterol, and triglyceride as a comparison of homocysteine since these biomarkers were easily approached and were equally important in the clinical assessments of cardiovascular diseases. After the analysis, we found that all of the biomarkers significantly decreased after the treatment. The result shared resemblance to the past research. For instance, a recent systematic review by Mecenas et al.[24] evaluated the effects of oral appliances therapy on serum inflammatory cytokines of OSA patients. They concluded that there was improvement on certain serum cytokines, including CRP, after longer follow-up periods. In another cohort study[25] comprising 161 patients, the authors assessed the association between classical or modified OSA upper airway surgery and changes of cardiological metabolic biomarkers, as well as the overall cardiovascular risk, and discovered that there were significant decreases in glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and so on after surgery. Moreover, the increasing severity of OSA is highly associated with higher levels in the parameters related to metabolic syndrome.[26] Our study focused on severe OSA patients to investigate possible gainful benefits following OSA treatment in this most vulnerable OSA group. Based on the previous evidence, the results further implied that in these patients, there might be accompanying advantages as well on lowering the risks of cardiovascular diseases following treatment of OSA.

In 2017, Martí-Carvajal et al.[27] searched the Cochrane Central Register of Controlled Trials (a total of 15 randomized controlled trials involving 71,422 participants) for evaluating the impact of homocysteine-lowering interventions on cardiovascular events. They found that compared with placebo, homocysteine-lowering interventions were especially associated with reduced stroke outcome (homocysteine-lowering = 4.3% vs comparator = 5.1%, risk ratios 0.90, 95% confidence interval 0.82-0.99, 10 trials, N = 44,224) with high-quality evidence. Being one of the indicators related to cardiovascular diseases, homocysteine also plays a crucial role in OSA that deserves our attention.[10] Furthermore, there are emerging researches claiming that the concurrent presence of elevated homocysteine and OSA may be related to a higher risk of various cardiovascular diseases. An observational study conducted by Wu et al.[28] explored acute coronary syndrome (ACS) and its associations with inflammatory markers in OSA patients. They indicated that a higher homocysteine level, in especially moderate/severe OSA patients, was in relation to ACS undergoing percutaneous coronary intervention. Another study[29] focusing on the association between OSA and inflammatory markers in patients with or without coronary artery disease (CAD), on the other hand, figured out that a higher homocysteine level was presented in those with CAD and OSA. Moreover, a recent 7-year cohort study discussing the association between baseline homocysteine

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Table 3. Comparisons of Changes of the Homocysteine Level Before and After TORS-OSA Surgery Between the Normal Group (Preoperative Homocysteine Level < 15) and the Hyperhomocysteinemia Group (Preoperative Homocysteine Level ≥ 15)

	Preoperative[b]	Postoperative[b]	Difference (post-pre)[b]	*p* value[a]
Preoperative homocysteine				
<15 (mcmol/L, n = 224)	11.0 ± 2.1	10.6 ± 2.6	−0.4 ± 2.3	.044
≥15 (mcmol/L, n = 37)	19.4 ± 5.4	16.5 ± 5.6	−2.9 ± 4.7	.007

Abbreviations: OSA, obstructive sleep apnea/hypopnea syndrome; TORS, transoral robotic surgery.
[a]Statistical analysis were performed using paired *t* tests, and $p < .05$ was viewed as of significance.
[b]The continuous data were presented as mean ± standard deviation.

Table 4. Pearson's Correlation Between Changes of the Homocysteine Level and Changes of the Major Polysomnographic Parameters in the Hyperhomocysteinemia Group (Preoperative Homocysteine Level ≥ 15 mcmol/L)

	ΔESS	ΔBMI	ΔAHI	ΔREM	Δ% of mO_2 < 90%	ΔMean O_2%	ΔLSAT	ΔODI	ΔArousal index
ΔHomocysteine									
r	−0.015	−0.067	0.259	0.055	0.268	0.231	0.026	0.525	0.120
p value	.947	.763	.232	.807	.253	.302	.905	.012[a]	.604

Abbreviations: AHI, apnea/hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; LSAT, lowest oxygen saturation; ODI, oxygen desaturation index; PSG, polysomnography; REM, rapid eye movement; Δ, changes of the data before and after treatment.
[a]Statistical significance was accepted when $p < .05$.

concentrations and the risk of the first ischemic stroke in hypertensive patients with OSA, concluded that the rising concentrations of homocysteine were independently associated with the risk of the first ischemic event.[11] Therefore, the decrease in risks of cardiovascular diseases following treatment of OSA may be crucial in consideration of the decline in homocysteine levels.[27]

The research directly investigating "drop in homocysteine level" following OSA therapy is limited with divergent results, and most are discussed in those receiving nonsurgical therapy. Since the compliance rate of nonsurgical therapy depends on the personal usage and clinical status (unlike the "compliance rate" of surgical intervention being 100%), it is also noteworthy that whether the patient adheres to the therapy should be taken into consideration for the true effect on homocysteine level changes. Research by Jordan et al.[19] found that continuous CPAP use effectively lowered the homocysteine level in OSA patients by about 30% and may decrease the risk for cardio-/cerebrovascular diseases, which was in accordance with ours; the dropout rate of CPAP use was 25% in this study. Another study[21] which investigated the effects on homocysteine in OSA patients treated with MAD and CPAP devices, instead, figured out that there were actually no changes in the homocysteine level following the treatments. Though not consistent with ours, the lower compliance rate (Severe OSA patients: 85.2 ± 17.6% using MAD; 67.0 ± 23.4% using CPAP) may result in less significant effect on the homocysteine level; besides, the authors also pointed out that the probability of the homocysteine levels before and after treatments both being within the referenced normal range may be the cause of the insignificant results, which was also recognized in a review study by Refsum et al.[30] Therefore, we subgrouped the patients based on the pre-operative homocysteine level for the analyses, and found a higher decrease in the hyperhomocysteinemia group compared to the normal group ($p = .018$, by independent *t* test), which indeed corresponds with the above statement by Refsum's study.[30] In addition, compared to previous studies majorly enrolling heterogeneous OSA patients with a wide range of AHI values, we only focused on those patients with severe OSA. In analysis of these risky patients, it helped us better elucidate the real influence on homocysteine changes after OSA therapy, which was significantly lower in comparison with the preoperative values and may be closer to real-world clinical practice.

As for the mechanisms of the alteration of homocysteine levels, ΔODI ($r = 0.525$, $p = .012$) was found significantly associated with Δhomocysteine in our study. This could be interpreted that the improvements in desaturation status after TORS-OSA surgery was related to a positive outcome in homocysteine changes; this close relationship between desaturation, especially the nocturnal oxygen desaturation, and homocysteine has already been proven in previous studies[25,31] as well. In other words, by maximally ameliorating the oxidative stress resulting from the desaturation status, it could theoretically continuously bring about the greatest amount of decrease in the homocysteine level.[21] Nonetheless, a noteworthy point here is that the patients in our study underwent TORS-OSA surgery as the main treatment since they had failed the conservative treatments in advance. The current research was found mainly discussing the impact on the homocysteine level after conservative OSA therapy such as CPAP or MAD, which was mostly seen in relatively less severe OSA as the first-line therapy. Though the homocysteine changes varied

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from study to study, substantial decreases were observed in most of them, which were recognized to be related to the improvements in sleep and desaturation-related indices.[18,32] This longitudinal cohort study aimed to evaluate the alterations of homocysteine levels in the severe OSA patients who received TORS-assisted upper airway surgery, and discovered the associations with the improvements in PSG parameters. We found that not only the majority of patients' PSG data improved generally, but the homocysteine level significantly decreased from 12.1 ± 3.9 to 11.4 ± 3.7 mcmol/L (difference = -0.7 ± 2.8 mcmol/L, $p = .001$) postoperatively. Additionally, the hyperhomocysteinemia group had much decreases in the homocysteine level (difference = -2.9 ± 4.7 mcmol/L, $p = .007$) compared to the normohomocysteinemia group (difference = -0.4 ± 2.3 mcmol/L, $p = .044$), which was positively related to the changes of ODI ($r = 0.525$, $p = .012$). Given that TORS-assisted OSA surgery is also one of the effective treatments for severe OSA patients,[14] our study may provide deeper insights for clinicians in evaluating patients regarding the postoperative OSA-related inflammatory status in the future.

There are several limitations in our research. First, the homocysteine level may still be affected by multifactors, such as other concurrent diseases or medications which were not measured in our study. We only adopted the OSA patients with stable clinical conditions that were suitable for surgical interventions, and without previous or current severe cardio-/cerebrovascular disorders. Since there were no obvious physiological changes based on these patients' life patterns under close follow-up, this confounding effect was greatly minimized and may be less influential in this study from our perspective. Second, we set "3 months" as a meaningful cutoff timing for the re-examinations. It remains unknown whether a different or longer follow-up period contributes to a distinct outcome. The results of the long-term changes on homocysteine levels should be investigated. Also, the major disadvantage of robotic OSA surgery is relatively high out-of-pocket expenditure, making the procedure unattainable for people without private insurance assistance. Finally, the relatively small sample size may potentially affect the results to some extent. Future studies with more samples are still warranted to clarify this issue.

In conclusion, our study demonstrates that TORS-assisted upper airway surgery could not only improve major parameters of sleep study, but also improve the homocysteine levels in patients with severe OSA, especially in the patients with abnormal hyperhomocysteinemia preoperatively. These findings could have clinical benefits for severe OSA patients in reducing the risk of OSA-associated cardiovascular comorbidities.

Acknowledgments

The authors thank the research grant from the Ministry of Science and Technology Research Project (MOST 108-2314-B-182A-111-MY2), Taiwan. The authors also thank Drs Meng-Chih Lin, Mao-Chang Su, Chien-Hung Chin, Yung-Che Chen, and Kuo-Tung Huang for assistance in manuscript preparation. Drs Lin, Su, Chin, Chen, and Huang are from the Sleep Center and the Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan. They do not have any financial compensation for their contribution to this study.

Author Contributions

Li-Wen Chiu, data collection and interpretation, wrote the manuscript; **Chung-Wei Lin**, data collection and interpretation, statistical analysis, wrote the manuscript; **Pei-Wen Lin**, data collection, analysis and interpretation, critical revision of the manuscript; **Han-Tan Chai**, data analysis and interpretation, critical revision of the manuscript; **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; **Hsin-Ching Lin**, designed study, data collection and interpretation, wrote the manuscript and final approval. 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.

Disclosures

Competing interests: Dr. Hsin-Ching Lin received 2 research grants from Intuitive Surgical Inc, Sunnyvale, CA. However, Intuitive Surgical Inc had no role in the design or conduct of this study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Dr. Li-Wen Chiu, Dr. Chung-Wei Lin, Dr. Pei-Wen Lin, Dr. Han-Tan Chai, Prof Chun-Tuan Chang, Prof Michael Friedman, Dr. Anna M. Salapatas declare no potential conflict of interest.

Sponsorships: This study was sponsored by the grant from the Ministry of Science and Technology Research Project (MOST 108-2314-B-182A-111-MY2), Taiwan. This study was also partially sponsored by Intuitive Surgical Inc, Sunnyvale, CA. However, Intuitive Surgical Inc had no role in the design or conduct of this study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Funding source: The authors have no proprietary or commercial interest in any materials discussed in this article.

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