

Article

A Non-Framework Multilevel Surgery May Reduce Mean Heart Rate in Patients with Very Severe Obstructive Apnea Having Confined Retroglossal Space and Framework

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Abstract: An elevated mean heart rate in untreated patients of obstructive sleep apnea (OSA) may lead to a higher risk of mortality and the development of various cardiovascular diseases. The elevation may positively relate to the severity of OSA and present in both wakefulness and sleep. A reduction in heart rate has been presented in reports of treating OSA patients with continuous positive airway pressure (CPAP). However, patients with very severe OSA may refuse use of CPAP devices and advocated surgeries, such as direct skeletal surgery or tracheostomy. It is unclear whether the non-framework multilevel surgery we reported previously can overcome the unfavorable anatomy and reduce mean heart rate, which serves as a risk factor of mortality. Here, we show that multilevel surgery reduced the mean heart rate from 68.6 to 62.7 with a mean reduction of 5.9 beats/min. The results suggest that the surgery may reduce the risk of consequences and mortality associated with an elevated mean heart rate, such as various cardiovascular diseases. We disclose these findings, along with the variations and possible risks to our future patients with very severe OSA who refuse or cannot use a CPAP device or reject direct skeletal surgery.

Keywords: palatoplasty; one-stage; retropharynx; hypertension; maxillomandibular advancement; comorbidity

1. Introduction

An elevated heart rate is a risk factor of mortality for cardiovascular diseases [1,2]. Historically, it has been a risk factor of mortality in both the general population and in the population with cardiovascular disease [1–8]. In terms of gender, an elevated resting heart rate is an independent predictor of noncardiovascular mortality in both genders, and of cardiovascular mortality in men, independent of age and hypertension [6]. In terms of age, it is a risk factor for mortality from all causes

in younger men and in middle-aged men and women [1]. Resting heart rate is a simple measurement with prognostic implications [7]. That is why drug-induced reductions in heart rate may be beneficial in several clinical conditions, such as myocardial infarction [2], congestive heart failure [2], and angina [7].

An elevated heart rate may be positively related to the severity of OSA [9–11]. It is associated with an increased risk of cardiovascular diseases, stroke, and all-cause mortality (e.g., the relative risks were 1.79, 2.15, and 1.92, respectively, compared to normal individuals [12]). Cicek et al. showed a higher mean heart rate in the severe OSA group than the other (mild or moderate) groups [9]. Kawano reported a positive Spearman correlation between apnea–hypopnea index (AHI) and mean heart rate in all three (24-h, wakefulness, and sleep) sections of time [10]. Konecny et al. reported that heart rate elevation is most easily noticeable during sleep for OSA patients with hypertrophic cardiomyopathy [13]. This association between elevated heart rate and the severity of OSA presents not only during the daytime but also at night-time during sleep [9,10]. An elevated heart rate seen during sleep suggests a high chance of the presence in mean daytime or 24-h heart rates.

Patients with very severe OSA usually have a confined retroglossal space and framework. They make up a distinct subgroup and show differences in several areas, from OSA of other severities. Their daytime awake partial pressure of oxygen may go as low as 77 mmHg [14]. Researchers classified very severe OSA in the literature into a general group of high AHI or respiratory disturbance index (RDI), from 40 [15,16], 50 [17–21], 60 [22–26], 70 [27], to 100 events/h [28]. These patients have minimal inspiratory movement of the lateral pharyngeal walls and a smaller cross-sectional area [20], more comorbidity due to hypertension [14], and associations with higher insulin resistance [29]. Patients with very severe OSA have a narrow retroglossal space and confined framework [30]. The narrow airway is difficult to enlarge via conventional uvulopalatopharyngoplasty (UPPP) or non-framework surgeries [23,31]. They are not necessarily obese, nor do they have a high body mass index (BMI) (e.g., see [23,25]). For those who refuse to use or cannot benefit from continuous positive airway pressure (CPAP), the advocated surgical procedures include direct skeletal surgery [30], bariatric surgery [32], and tracheostomy in patients meeting the set criteria [15,33]. In this distinct subgroup, our earlier reports showed that multilevel surgery could reduce postoperative AHI [34,35], desaturation frequency (mean desaturation index) [34], and desaturation level (mean oxyhemoglobin saturation of pulse oximetry (SpO₂) desaturation) [34] in order to improve mean SpO₂. However, it is not clear whether multilevel surgery can decrease postoperative resting heart rate in order to lower the risk of associated consequences and mortality.

A reduction in heart rate has been presented in reports of treating OSA patients with CPAP [11,36,37]. Long-term CPAP therapy may lead to an intra-group decrease in resting heart rate [36,37] or a significant inter-group reduction (CPAP vs. non-CPAP using patients) [38]. Efficiently treated CPAP users showed lower incidence of cardiovascular diseases than incompletely treated cases (e.g., 6.7% vs. 56.8% in [39]). Nevertheless, CPAP withdrawal usually results in a rapid recurrence of OSA and a rebound in heart rate [40]. Accurate mean heart rate is easily obtained by the recording and analysis of a polysomnography (PSG). Unlike manually interpreted or reported data such as AHI, RDI, or Epworth Sleepiness Scale (ESS), mean heart rate can serve a clinical role as an objective predictor of mortality or an objective measurement of surgical success. Here, in patients of very severe OSA, we replicated studies in the literature to examine the correlation between preoperative AHI and mean heart rate in sleep. We found that multilevel surgery, as an alternative treatment to CPAP, can reduce mean heart rate in sleep. We tested the correlation between changes in mean heart rate and essential sleep parameters, then compared the results to other treatments available in the literature.

2. Materials and Methods

2.1. Patient Enrollment

The patients enrolled were the same as those in our earlier work on the improvement of oxygen saturation [34]. From Mar. 2015 to May 2020, we enrolled consecutive patients who met the criteria of: 1. 20 years old or older, 2. AHI \geq 60 events/h, 3. refusal or unsuccessful CPAP (e.g., bad compliance or

high on-CPAP AHI referred from a sleep medicine specialist), 4. received a multilevel surgery at the nose, palate, and tongue base [35], 5. PSGs with AHI and mean heart rate before and after the surgery. We had no specific exclusion criteria.

2.2. Evaluation and Surgeries

We evaluated each patient by endoscopies before and after the surgery and conducted each PSG overnight in the level-1 sleep laboratory of our hospital with a certified technician. The nasal procedure, routine septomeatoplasty, was carried out with oral intubation. We performed Z-palatoplasty as illustrated in our earlier report [35]. The open tongue-base procedure was performed with transoral robotic surgery or transoral laser microsurgery. Please see our earlier report [34] for postoperative care and other settings.

2.3. Data Collection and Analysis

Each patient completed a PSG 6 months (193 ± 67 days) after the surgery, when the postoperative anatomy was considered stable (as the period of 3 to 6 months was adopted in the past reports, e.g., see [41,42]). We measured the mean AHI reduction, as a cross-study standard recommended by Caples, S. M. et al. [43], to compare our results with others in the literature. We examined the scatter plot to find out whether there were outliers and computed the Pearson correlation to display the association between preoperative AHI and mean heart rate. We compared the individual pre- and postoperative mean heart rate in the PSGs, then calculated the mean heart rate reduction. We conducted a paired *t*-test to analyze the differences in mean heart rate reduction and AHI reduction, against no difference after the surgery. To discover the main contributors to the postoperative mean heart rate change, we computed a Spearman correlation to display the association between proportion difference in mean heart rate (i.e., postoperative–preoperative/preoperative fraction of mean heart rate) and proportion difference in one of the following sleep parameters: AHI, hypopnea in AHI ratio [34], desaturation index, and mean SpO₂. Values of $p < 0.05$ were considered statistically significant.

We performed the statistical tests in MATLAB 9.4.0.813654 (MathWorks, Natick, Massachusetts, United States of America).

3. Ethical Statements

The study was approved by the Institutional Review Board of Chang Gung Medical Foundation, Taiwan.

4. Results

Twenty-seven very severe OSA patients were registered in this study. Twenty-four were male and three were female. A male prevalence (88.9%) confirmed the earlier reports on severe OSA patients (e.g., see [15,28,44]). The average BMI was 28.5 with a standard deviation (SD) of 3.5 kg/m². Their ages ranged from 29 to 63 years (mean = 47.4 with a SD of 10.6). No patient reported a medication history of taking beta-blockers or a past history of cardiovascular diseases. All patients underwent Z-palatoplasty (ZPP) and partial open tongue-base glossectomy. One patient had UPPP at another hospital. Twenty-five received septomeatoplasty. One and three patients underwent regular adenoidectomy and endoscopic sinus surgery, respectively. Table 1 lists their results for comparisons with those of others. There was one instance of postoperative bleeding 10 days after the surgery, causing an unexpected return to the operation room. See our earlier reports [34,35] for other effects of the surgery such as a reduction in desaturation and an improvement in oxygen saturation.

The surgery lowered the mean AHI from 73.8 to 33.2 events/h, $p < 0.001$. The SD was 10.3 and 20.4 events/h, respectively. Figure 1 illustrates the individual AHI reductions and a five-number summary of pre- and postoperative AHIs. Figure 2 shows the scatterplot and correlation of preoperative AHI vs. mean heart rate. The correlation for the data showed that preoperative mean heart rate was not related to the AHI in these very severe OSA patients, $r = -0.043$, $p = 0.83$, two-tailed test. The surgery

reduced the mean heart rate from 68.6 ± 7.3 to 62.7 ± 7.5 beats/min ($p < 0.001$). The mean heart rate reduction was 5.9 beats/min, with a 95% confidence interval of 3.4 to 8.4 beats/min. Figure 3 illustrates the individual mean heart rate reductions and a five-number summary of pre- and post-operative mean heart rates. A Spearman correlation for the data showed that the postoperative proportion difference in mean heart rate was not related to any of these parameters (AHI, hypopnea in AHI ratio, desaturation index, and mean SpO₂), $r = (-0.1652, -0.3404, -0.1566, \text{ and } -0.1447)$, $p = (0.4103, 0.0823, 0.4353, \text{ and } 0.4714)$, respectively (Figures 4–7).

Table 1. Results for patients receiving various surgeries. Order is numbered according to the surgery date. a: modified Z-palatoplasty (ZPP); A: uvulopalatopharyngoplasty (UPPP); b: tongue-base glossectomy; c: septomeatoplasty; d: bilateral endoscopic sinusurgery; e: adenoidectomy; Preop: preoperative; Postop: postoperative; AHI: apnea–hypopnea index.

Case #	Age (years)	Sex	Remarks	Preop AHI(/h)	Postop AHI(/h)	Preop Mean Heart Rate (Beats/min)	Postop Mean Heart Rate (Beats/min)
1	25	male	abce	79.4	29.1	74.9	68.2
2	34	male	abcd	66	0.8	79.4	74.8
7	58	male	abcd	62.6	77.6	79.5	70.1
14	43	male	ab	87.7	57	69.5	58.4
16	44	male	ab	69.7	9.6	61.4	64
21	48	male	abcd	62.9	60.8	77	64.9
22	63	male	Abc	65.7	43.8	64.7	54.2

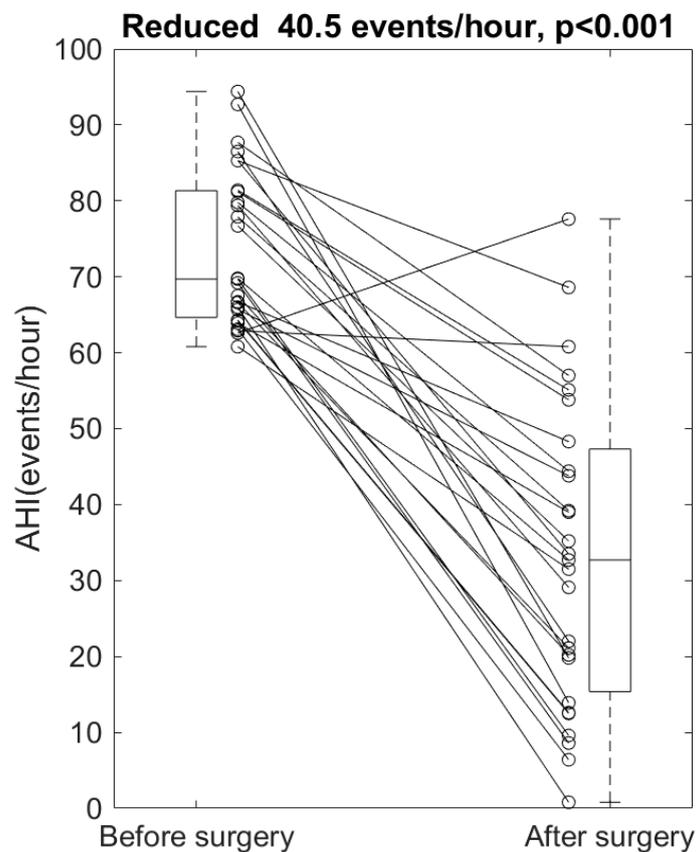


Figure 1. Individual apnea–hypopnea index (AHI) changes revealed a significant reduction after the surgery. Each boxplot displays a five-number summary: the minimum, the maximum, the median, and the first and third quartiles.

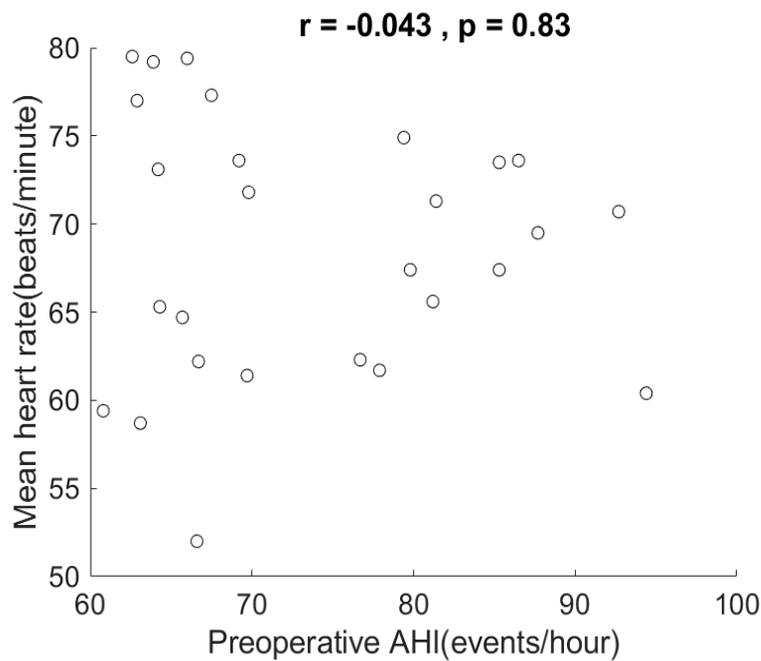


Figure 2. Scatter plot and correlation of preoperative AHI vs. mean heart rate. This shows that preoperative mean heart rate was not related to AHI in the very severe obstructive sleep apnea (OSA) patients in this study.

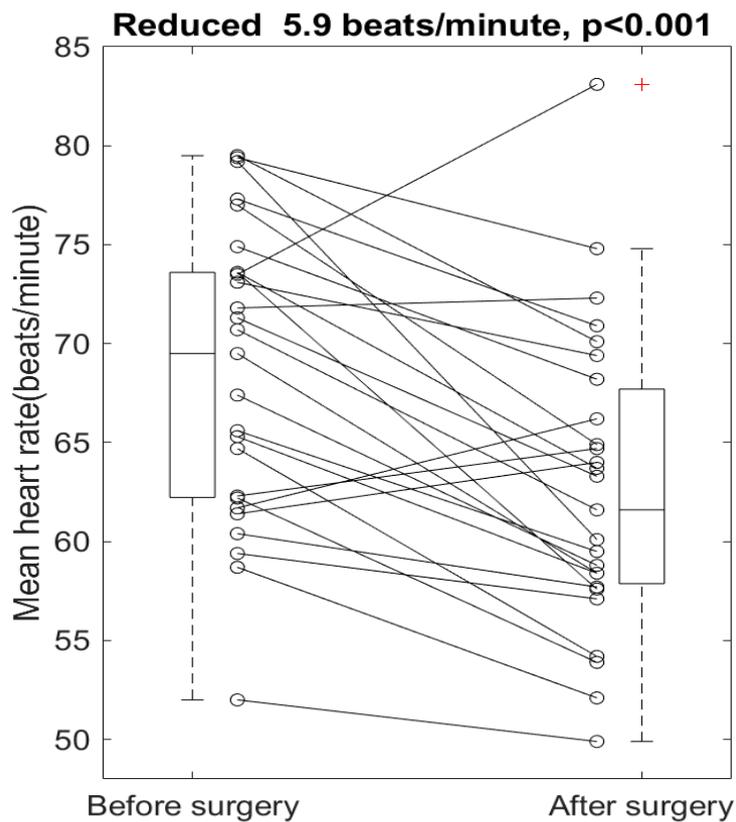


Figure 3. Individual mean heart rate changes revealed a significant reduction after the surgery. The surgery reduced the mean heart rate from 68.6 ± 7.3 to 62.7 ± 7.5 beats/minute ($p < 0.001$). Each boxplot displays a five-number summary: the minimum, the maximum, the median, and the first and third quartiles. There was an outlier in the postoperative mean heart rates.

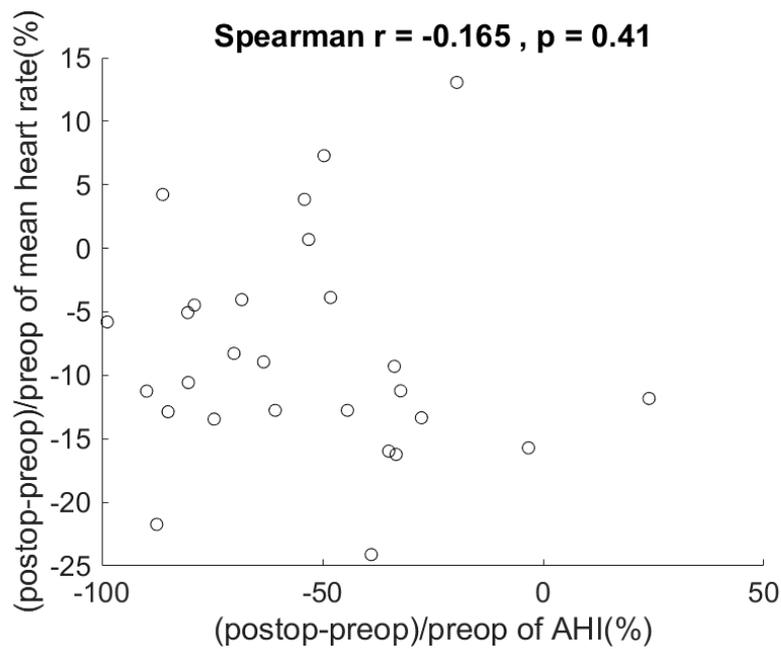


Figure 4. Scatter plot and correlation of change in AHI (defined here as (postoperative–preoperative)/preoperative AHI) vs. change in mean heart rate (defined here as (postoperative–preoperative)/preoperative mean heart rate). This shows that the change in mean heart rate was not related to the change in AHI.

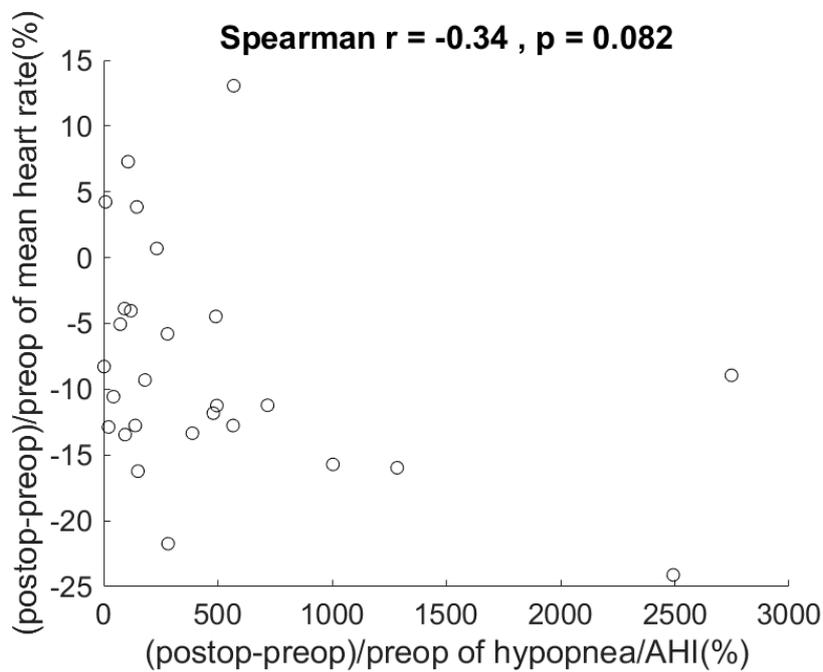


Figure 5. Scatter plot and correlation of proportion change in hypopnea/AHI (defined here as (postoperative–preoperative)/preoperative fraction of hypopnea in AHI) vs. change in mean heart rate (defined here as (postoperative–preoperative)/preoperative mean heart rate). This shows that the change in mean heart rate was not related to the proportion change in hypopnea/AHI.

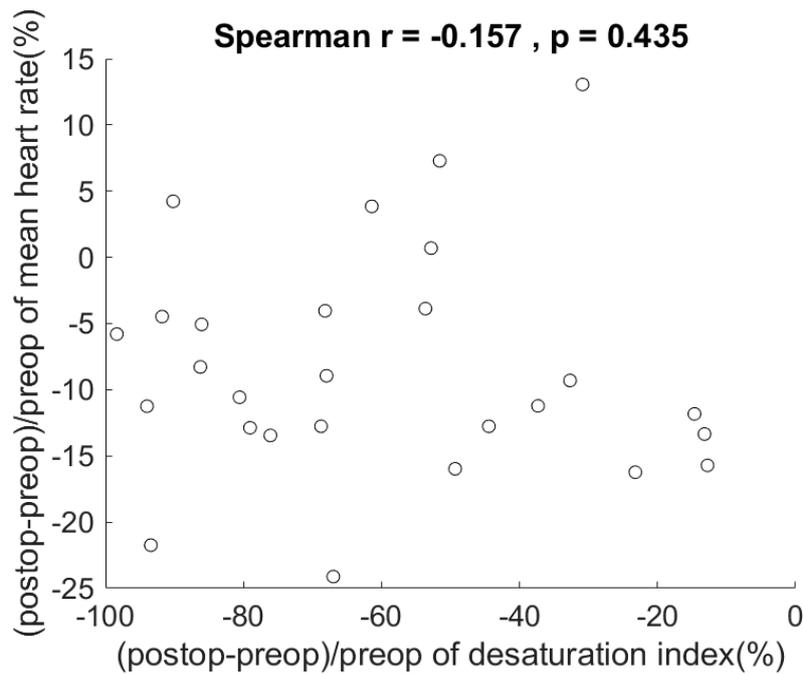


Figure 6. Scatter plot and correlation of change in desaturation index (defined here as (postoperative–preoperative)/preoperative desaturation index) vs. change in mean heart rate (defined here as (postoperative–preoperative)/preoperative mean heart rate). This shows that the change in mean heart rate was not related to the change in desaturation index.

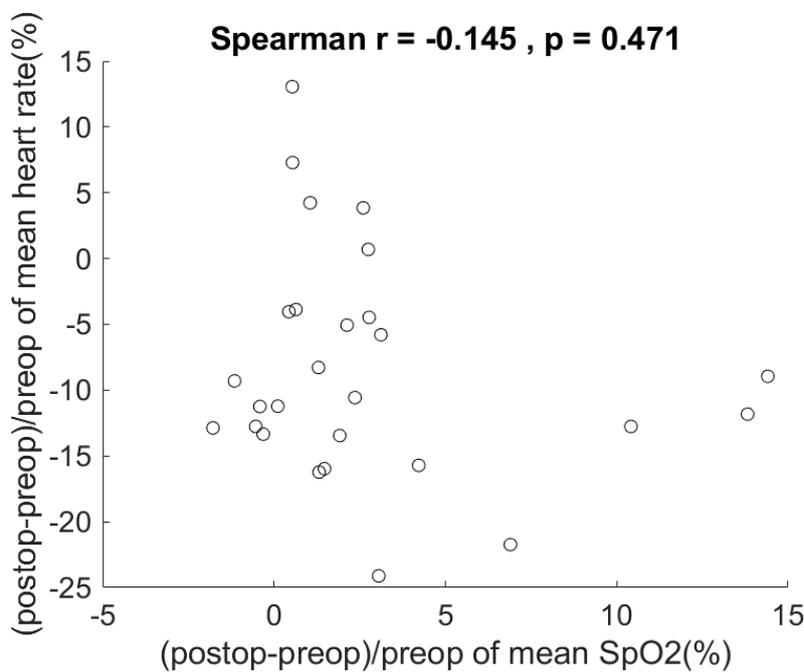


Figure 7. Scatter plot and correlation of change in mean SpO2 (defined here as (postoperative–preoperative)/preoperative mean SpO2) vs. change in mean heart rate (defined here as (postoperative–preoperative)/preoperative mean heart rate). This shows that the change in mean heart rate was not related to the change in mean SpO2.

5. Discussion

An elevated heart rate, serving as a risk factor of mortality and a predictive measurement for various medical conditions such as cardiovascular diseases [1–8], presents in severe OSA patients [9–11], and may help patients with several cardiovascular conditions if reduced [2,7]. In our results of the subgroup of very severe OSA, the non-framework multilevel surgery reduced the mean heart rate from 68.6 ± 7.3 to 62.7 ± 7.5 beats/min with a mean heart rate reduction of 5.9 beats/min, despite the unfavorable anatomy of the narrow retroglossal space and confined framework. Our sample size of 27 is small and consists of patients treated by a single surgeon, limiting the generalizability of the results. However, the results illustrate an effect size that is big enough to show significance. The heart rate reduction of 5.9 beats/min was inferior to Lin's 8.7 beats/min 6 months after maxillary–mandibular advancement [45] but better than Sumi's 4.5 beats/min after 3- to 4-day use of nasal CPAP [11], Mayer's 3.4 beats/minute after 6 months of nasal CPAP therapy [37], de Paula Soares's 2.4 beats/min 6 to 9 months after lateral pharyngoplasty [46], and those reporting no change in mean heart rate after their treatments (e.g., see [47–49], including Van der Cruyssen's patients after maxillary–mandibular advancement [49]). Because the lack of detailed information in the literature made statistical analysis impossible, this was just the order of the mean heart rate reductions (so as to enable the AHI comparisons below). Care must be taken when interpreting these comparisons due to possible different OSA severities in the databases and the effect size of the treatment (e.g., mean AHI reduction) across studies. The mean AHI reduction in the present study was 40.5 events/h, which was worse than Mickelson's 42.2 events/h [44] but better than Walker's 38.2 events/h [50] and Vilaseca's 14.4 events/hour [23] in patients with very severe OSA.

Mean heart rate in sleep is affected by not only the medical conditions mentioned above, but also other controllable or uncontrollable variables. Mean heart rate in sleep may increase after short-term heavy physical activity, such as in cyclists after a two-week period of intensified training [51]. However, mean heart rate may drop during good-quality sleep of stages 3 and 4 (e.g., see [52]). For each person, studies found an intrinsic night-to-night variation under controlled submaximal physical activity to be about 5–8 beats/min [53–56]. The difficulty in controlling the intrinsic variation and individual physical activity before each PSG is a limitation of the present study. Apart from treatment effect, this probably contributed to the variation in the mean heart rate reduction in Figure 3.

OSA is characterized by the recurrent collapse of the upper airway in sleep, leading to chronic intermittent hypoxia. Chronic intermittent hypoxia has been well reported to elevate circulating epinephrine levels [57–61], which have a strong positive relationship with platelet aggregation [57–60]. Elevated serum epinephrine levels result in an elevated heart rate in OSA [57–61]. Studies showed that treatment of OSA by nasal CPAP decreases the epinephrine level and platelet aggregability and restores the physiological periodic pattern of platelet aggregability [57,62]. Future studies are needed to investigate whether heart rate reduction goes through the same mechanism of decreasing epinephrine level and platelet aggregability following multilevel surgery in very severe OSA patients.

An elevated heart rate is associated with a higher risk of developing hypertension and atherosclerosis (e.g., see [2] for a review). The mean heart rates in patients with refractory hypertension (uncontrolled hypertension despite the administration of at least five antihypertensive drugs [63]) rise more [64] than those with resistant hypertension (hypertension with no identifiable cause in which blood pressure levels remain uncontrolled despite using at least three antihypertensive drugs (including a diuretic, if tolerated) at full doses [63]). Compared to resistant hypertension, patients with refractory hypertension have an even greater prevalence and severity of OSA [64]. More severe OSA may have hypertension that is more difficult to treat. This may be due to the fact that a higher sympathetic tone in patients with very severe OSA can cause more hyperinsulinemia and insulin resistance which can eventually promote the development of atherosclerosis [2]. Moreover, the hemodynamic disturbances related to a higher heart rate directly affect the arterial wall, promoting further development of atherosclerotic plaques [2]. Future long-term studies are needed to confirm whether the heart rate reduction remains in the long run following multilevel surgery, and whether it reduces the incidence of developing atherosclerosis, or helps to treat hypertension.

6. Conclusions

Despite the unfavorable anatomy in very severe OSA patients, non-framework surgery reduced the mean heart rate from 68.6 to 62.7 beats/min with a mean heart rate reduction of 5.9 beats/min. The results suggest that this surgery may reduce the risk of consequences and mortality associated with an elevated mean heart rate. We will disclose these findings to our future patients with very severe OSA who refuse or cannot use a CPAP device or reject direct skeletal surgery. We will also inform them of the thus far undetermined contributors to the reduction, variation, and potential risks.

Author Contributions: E.I.H. conceptualized the study, analyzed the PSGs, ran the analysis, and wrote the primary draft of the manuscript. C.-K.L., C.-M.L., Y.-C.H., and J.-A.S. registered the patients, read the PSGs, and revised the manuscript. S.-Y.H. and Y.-C.L. registered the patients, interpreted the data, and provided essential comments on the manuscript. All authors have read and agreed to the published version of the manuscript.

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