



Ventilatory Response at Rest and During Maximal Exercise Testing in Patients with Severe Obesity Before and After Sleeve Gastrectomy

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Abstract

Introduction Sleeve gastrectomy (SG) has become a widespread treatment option in patients affected by severe obesity. However, studies investigating the impact of the subsequent weight loss on the ventilatory response at rest and during physical exercise are lacking.

Methods This is an observational study on 46 patients with severe obesity (76% females), comparing parameters of ventilatory function 1 month before and 6 months after SG. Patients were first evaluated by resting spirometry and subsequently with an incremental, maximal cardiopulmonary exercise test (CPET) on treadmill.

Results The important weight loss of $26.35 \pm 6.17\%$ of body weight (BMI from 43.59 ± 5.30 to 32.27 ± 4.84 kg/m²) after SG was associated with a significant improvement in lung volumes and flows during forced expiration at rest, while resting ventilation and tidal volume were reduced (all $p \leq 0.001$). CPET revealed decreased ventilation during incremental exercise ($p < 0.001$), with a less shallow ventilatory pattern shown by a lower increase of breathing frequency ($\Delta BF_{\text{rest to AT}} p = 0.028$) and a larger response of tidal volume ($\Delta TV_{\text{AT to Peak}} p < 0.001$). Furthermore, a concomitant improvement of the calculated dead space ventilation, VE/VCO₂ slope and peripheral oxygen saturation was shown (all $p \leq 0.002$). Additionally, the increased breathing reserve at peak exercise was associated with a lower absolute oxygen consumption but improved exercise capacity and tolerance (all $p < 0.001$).

Conclusion The weight loss induced by SG led to less burdensome restrictive limitations of the respiratory system and to a reduction of ventilation at rest and during exercise, possibly explained by an increased ventilatory efficiency and a decrease in oxygen demands.

Keywords Bariatric surgery · Cardiopulmonary exercise test · Spirometry · Lung function · Ventilation

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Introduction

The worldwide increasing prevalence of obesity represents a major health burden and is associated with an increased risk for many cardiovascular and metabolic diseases and comorbidities [1]. Adipose tissue accumulation on chest wall, abdomen and in proximity of the upper airways may have an impact on lung function, even in the absence of a specific pulmonary disease. This may cause a limitation in thorax and diaphragm mobility, required for appropriate chest wall compliance and ventilatory efficiency [2, 3]. Indeed, impaired lung volume, expiratory flow, airway resistance and functional residual capacity were previously reported following even a modest weight increase [2, 4, 5]. It is worth mentioning that an associated marked reduction in expiratory reserve volume may lead to an increased alveolar surface tension and small areas of atelectasis resulting in reduced lung compliance and a potential ventilation-perfusion mismatch [2]. The causes of decreased dynamic lung volumes could be both mechanical and inflammatory [2, 4]. Indeed, obesity is correlated with increased levels of pro-inflammatory adipokines, which also affect lower airways, by promoting inflammatory processes, including local oedema [4, 6, 7]. The associated alterations in pulmonary flows and the increased respiratory muscle workload affect ventilation during exercise as well. Thus, patients with obesity tend to dynamically hyperinflate during exercise to counteract significant expiratory flow limitation, transferring the tidal volume (TV) to a more compliant portion of the respiratory system. However, hyperinflation reduces the efficiency of inspiratory muscles, leading to increased oxygen costs of breathing. Although this shallow and rapid ventilatory pattern may bypass counteracting elastic forces, the relative dead space ventilation increases [2, 4, 8, 9]. All these issues contribute to reducing the ventilatory efficiency during exercise in these patients [4, 10].

Bariatric surgery, especially sleeve gastrectomy (SG), is an increasingly recommended treatment option for patients with morbid obesity, leading to a reduction in the prevalence and incidence of several obesity-related comorbidities [11, 12]. Regarding the respiratory system, surgical treatment of obesity was associated with a significant improvement in pulmonary function and the associated respiratory complications [13–16]. However, there is limited evidence on the effect of massive weight loss on ventilatory response during maximal exercise, while most studies have mainly focused on resting lung volumes and capacity [17–20]. Moreover, no data on the specific impact of SG on ventilation are currently available, particularly during incremental exercise testing.

To our knowledge, this is the first study aiming to investigate the impact of SG and the associated weight loss on ventilation at rest and during exercise, evaluating respiratory function, breathing pattern, ventilatory efficiency and the effects

on exercise capacity, in a homogeneous population of severely obese patients.

Methods

This observational cohort study evaluated 46 patients with severe obesity. All study participants followed a regionally approved clinical pathway established for patients who were listed for and underwent SG (Veneto Region, resolution n.55/CR August 4, 2015). This study analysed observational data of this diagnostic-therapeutic pathway of clinical assistance between June 2017 and January 2019. All consecutive patients who were considered suitable candidates for SG after medical, surgical and functional evaluations were included in this study. Specifically, candidates were patients with II or III class obesity who, following the treatment algorithm proposed by the Italian Society of Obesity, were eligible for bariatric surgery [21]. After obtaining written informed consent, functional evaluation was performed about 1 month before and 6 months after SG. These assessments were part of the routine clinical approach, including surgical risk stratification and subsequent follow-up with a cardiopulmonary exercise test (CPET).

Patients older than 70 years of age, with an ASA physical status class IV as well as those refusing the surgical intervention, were excluded. Further exclusion criteria were psychotropic substance abuse, cardiovascular and orthopaedic diseases, which contraindicated or impaired the exercise test, and failure to perform a maximal CPET.

Spirometry

Standardized resting spirometry was executed in sitting position before performing the CPET. For each patient, repeated spirometric testing was performed, selecting the best attempt for data analysis. The acquired values for forced vital capacity (FVC), expiratory flow in the first second (FEV₁), peak expiratory flow (PEF), and maximal expiratory flow at 25–50–75% of the FVC (MEF₂₅₋₅₀₋₇₅) were compared with the predicted values for age, gender and BMI.

CPET

Exercise capacity and ventilatory response were assessed during incremental, ECG-monitored, maximal CPET. Tests were performed on treadmill, according to the modified Bruce protocol, with an integrated initial 5-min constant speed interval (2.7 km/h). The subsequent incremental part of the exercise test was performed until patients' exhaustion, reaching a Borg rating of perceived exertion $\geq 18/20$.

Respiratory gas exchange and ventilation (VE) were analysed breath-by-breath, averaging 20-s intervals during

rest and incremental exercise. The physiologic dead space ventilation at peak exercise ($V_{Dc}/V_{T_{max}}$) was calculated from the end tidal carbon dioxide partial pressure ($PETCO_2$) according to the N.L. Jones modification of the Bohr equation and corrected for apparatus dead space $V_{Dc}/VE = (PaCO_{2c} - PECO_2)/PaCO_2 - BF \times V_{Ds}/VE$, where V_{Ds} = apparatus dead space and $PaCO_{2c}$ is estimated from $PETCO_2$ ($PaCO_{2c} = 5.5 + 0.90 \times PETCO_2 - 0.0021 \times VT$) [22]. Ventilatory equivalents for oxygen (VE/V_{O_2}) and carbon dioxide (VE/V_{CO_2}) were determined at the first (anaerobic threshold, AT) and second ventilatory threshold (respiratory compensation point, RCP), respectively. VE/V_{CO_2} slope was calculated by linear regression from the start of the test, excluding initial hyperventilation, until the RCP. Peripheral oxygen saturation (SaO_2) was determined throughout the CPET.

Statistical Analysis

Data were elaborated with IBM-SPSS. Data are presented as mean, median and standard deviation. The Shapiro-Wilk test was used to check for normal distribution within the dependent variables. The comparisons from pre- to post-SG were performed using paired *t* tests for normal distributed variables; otherwise, the Wilcoxon-Mann-Whitney test was performed. A *p* value < 0.05 was considered statistically significant.

Results

A total of 46 (11 M; 35 F) patients with morbid obesity (BMI 43.59 ± 5.30 kg/m², weight 122.12 ± 19.47 kg) were included in this clinical trial, with a mean age of 44.17 ± 11.22 years. At baseline, six patients (13%) were medically treated with oral hypoglycaemics (two with metformin and liraglutide, four only with metformin), while 14 patients (30%) were medically treated for arterial hypertension taking ACE inhibitors, Angiotensin II receptor blockers, Calcium channel blockers, Thiazides or an association of these. Six patients (13%) were asthmatic and were taking a combination of ICS/LABA and salbutamol on demand. Furthermore, 14 (30%) and 11 (24%) patients were active and former smokers, respectively. Also, 29 patients (63%) affirmed to conduct a sedentary lifestyle. However, after SG patients lost 32.14 ± 8.99 kg or $26.35 \pm 6.17\%$ of body weight, leading to a mean BMI of 32.27 ± 4.84 kg/m².

Pulmonary Function at Rest

Spirometric flows and volumes were on average above the lower limit of normal at baseline. After SG, there was a significant increase, both in volumes and forced dynamic flows (FVC, FEV_1 , MEF_{25} ; all $p \leq 0.001$), while the Tiffeneau index

was not significantly affected (Table 1). Resting ventilation was found decreased after massive weight loss, showing a reduced TV ($p < 0.001$), without a significant impact on breathing frequency (BF; Table 2).

Pulmonary Function During Exercise

After SG, ventilation significantly decreased at all levels of incremental workload, which was associated, at submaximal exercise, to a reduced TV and BF (all $p \leq 0.001$; Fig. 1, Table 2). However, the impact on patients' ventilatory pattern is also shown by a lower increase of the BF at submaximal exercise ($\Delta BF_{rest \text{ to AT}} p = 0.028$) and a larger response of the TV at vigorous/maximal exercise intensities ($\Delta TV_{AT \text{ to Peak}} p < 0.001$). Analysing ventilatory efficiency, a concomitant improvement of the calculated dead space ventilation ($V_{Dc}/V_{T_{max}}$), VE/V_{CO_2} slope and peripheral oxygen saturation was shown (all $p < 0.015$; Table 2).

These improved pulmonary flow/volume capacities and ventilatory efficiency were associated with a significantly increased breathing reserve at peak exercise ($p < 0.001$), also because the significant weight loss after SG decreased ventilation during exercise.

Cardiorespiratory Fitness

The ventilatory modifications were associated with an increased exercise capacity and tolerance post-SG. Patients showed an improvement in exercise time and peak oxygen consumption per kilogram body weight (VO_2/kg_{peak}), as well as a higher peak respiratory exchange ratio (RER) (all

Table 1 Spirometric parameters pre- and post-sleeve gastrectomy

	Evaluation pre-SG		Evaluation post-SG		<i>p</i> value
	Mean	SD	Mean	SD	
<i>n</i> = 46					
FVC (%)	103.85	± 12.84	111.95	± 12.31	$p < 0.001$
FEV_1 (%)	98.65	± 15.87	106.33	± 14.65	$p < 0.001$
PEF (%)	97.96	± 17.11	100.17	± 16.14	$p = 0.319$
MEF_{75} (%)	99.50	± 24.73	102.28	± 22.95	$p = 0.228$
MEF_{50} (%)	87.39	± 32.69	90.87	± 32.67	$p = 0.193$
MEF_{25} (%)	62.80	± 26.91	73.39	± 32.60	$p < 0.001$
FVC (l)*	3.71	± 0.80	3.99	± 0.92	$p < 0.001$
FEV_1 (l/s)*	2.99	± 0.73	3.21	± 0.83	$p < 0.001$
$FEV_1\%$ FVC*	80.21	± 6.53	80.48	± 8.32	$p = 0.760$
MEF_{25} (l/s)*	1.18	± 0.61	1.38	± 0.81	$p = 0.003$

Forced spirometric volumes and flows were compared pre- and post-sleeve gastrectomy (SG). FVC forced vital capacity, FEV_1 expiratory flow in the first second, PEF peak expiratory flow, $MEF_{25-50-75}$ maximal expiratory flow at 25–50–75% of the forced vital capacity, $FEV_1\%$ FVC Tiffeneau index. “*” indicates parameters not normally distributed

Table 2 Ventilatory response to exercise pre- and post-sleeve gastrectomy

<i>n</i> = 46	Evaluation pre-SG		Evaluation post-SG		<i>p</i> value
	Mean	SD	Mean	SD	
VE _{rest} (l/min)	14.54	± 3.69	10.30	± 3.50	<i>p</i> < 0.001
VE _{AT} (l/min)	41.46	± 10.23	33.37	± 7.56	<i>p</i> < 0.001
VE _{max} (l/min)*	83.41	± 19.38	75.65	± 16.69	<i>p</i> < 0.001
TV _{rest} (ml)*	830.20	± 261.41	613.11	± 235.62	<i>p</i> < 0.001
TV _{AT} (ml)*	1674.13	± 543.73	1494.89	± 477.42	<i>p</i> < 0.001
TV _{max} (ml)*	2173.04	± 595.79	2168.39	± 613.46	<i>p</i> = 0.793
ΔTV _{rest to AT} (ml)*	843.93	± 437.04	881.78	± 451.14	<i>p</i> = 0.906
ΔTV _{AT to Peak} (ml)*	498.91	± 271.55	673.50	± 324.77	<i>p</i> < 0.001
BF _{rest} (l/min)*	18.48	± 5.44	17.63	± 4.96	<i>p</i> = 0.306
BF _{AT} (l/min)	26.00	± 6.70	23.37	± 5.17	<i>p</i> = 0.001
BF _{max} (l/min)*	41.74	± 9.00	37.59	± 6.98	<i>p</i> < 0.001
ΔBF _{rest to AT} (l/min)*	7.52	± 5.72	5.73	± 5.22	<i>p</i> = 0.028
ΔBF _{AT to Peak} (l/min)*	15.74	± 6.63	14.22	± 6.02	<i>p</i> = 0.136
BR _{max} (%)	18.41	± 16.22	30.24	± 16.22	<i>p</i> < 0.001
V _{Dc} /V _{Tmax} (%)*	12.09	± 6.23	9.63	± 6.69	<i>p</i> = 0.015
VE/VO _{2 AT} *	22.57	± 3.09	22.62	± 2.56	<i>p</i> = 0.739
VE/VCO _{2 RCP} *#	27.00	± 3.24	26.25	± 3.09	<i>p</i> = 0.058
VE/VCO _{2 slope} *	27.04	± 3.94	25.47	± 3.32	<i>p</i> = 0.002
PetCO _{2 rest} (mmHg)	33.76	± 3.43	30.51	± 3.11	<i>p</i> < 0.001
PetCO _{2 AT} (mmHg)	39.95	± 4.28	39.53	± 3.70	<i>p</i> = 0.384
SaO _{2 rest} (%)*	99.33	± 0.70	99.26	± 0.68	<i>p</i> = 0.597
SaO _{2 max} (%)*	97.89	± 1.29	98.52	± 0.75	<i>p</i> = 0.001

Effects of massive weight loss after sleeve gastrectomy (SG) on ventilation at rest and during incremental cardiopulmonary exercise testing. *VE* ventilation, *TV* tidal volume, *BF* breathing frequency, *AT* anaerobic threshold, $\Delta_{rest\ to\ AT}$ delta of the BF/TV from rest to the anaerobic threshold, $\Delta_{AT\ to\ Peak}$ delta of the BF/TV from the anaerobic threshold to peak exercise, *BR_{max}* breathing reserve at peak exercise, *V_{Dc}/V_{Tmax}* physiologic dead space/tidal volume at peak exercise, *VE/VO₂* ventilatory equivalent for oxygen, *VE/VCO₂* ventilatory equivalent for carbon dioxide, *RCP* respiratory compensation point, *PetCO₂* partial pressure of end-tidal carbon dioxide, *SaO₂* peripheral oxygen saturation. “*” indicates parameters not normally distributed. “#” indicates a sample size of 43 subjects because 3 patients have not reached the RCP

p < 0.001; Table 3). However, a reduced oxygen demand was found after SG as shown by a statistically significant decrease in absolute VO₂ at rest and during exercise (*p* < 0.001).

Discussion

Pulmonary Function at Rest

The results of this clinical trial show that the massive weight loss after SG is associated with an improvement in mechanical restrictive ventilatory limitations. Previous studies attributed this obesity-related pulmonary impairment to excessive thoracic and visceral adipose tissue [8, 23, 24]. Although at baseline respiratory flows and volumes were substantially within normal limits, 6 months after SG, the unchanged Tiffeneau index in the presence

of increased dynamic pulmonary parameters (FVC and FEV₁) suggests a major impact of weight loss on restrictive components of ventilation. Analysing the pulmonary flows at different forced expiration levels and in accordance with the findings of Held et al., a more pronounced improvement was observed for small airways (MEF₂₅), compared with the pulmonary flows in larger airways (MEF₅₀ and MEF₇₅) [25]. Rubstein et al. stated that obesity carries flow limitations that could be explained, among other mechanisms, by a state of systemic inflammation and an increase in pulmonary blood volume, which lead to congestion of vessels and a reduction in the size of small airways [4, 26]. Moreover, MEF₂₅, which from a physiological point of view represents an objective measure of small airway resistance, is positively influenced by increased lung volumes [27]. Thus, an enhanced MEF₂₅ could be due to an improvement of both the generalised inflammatory state

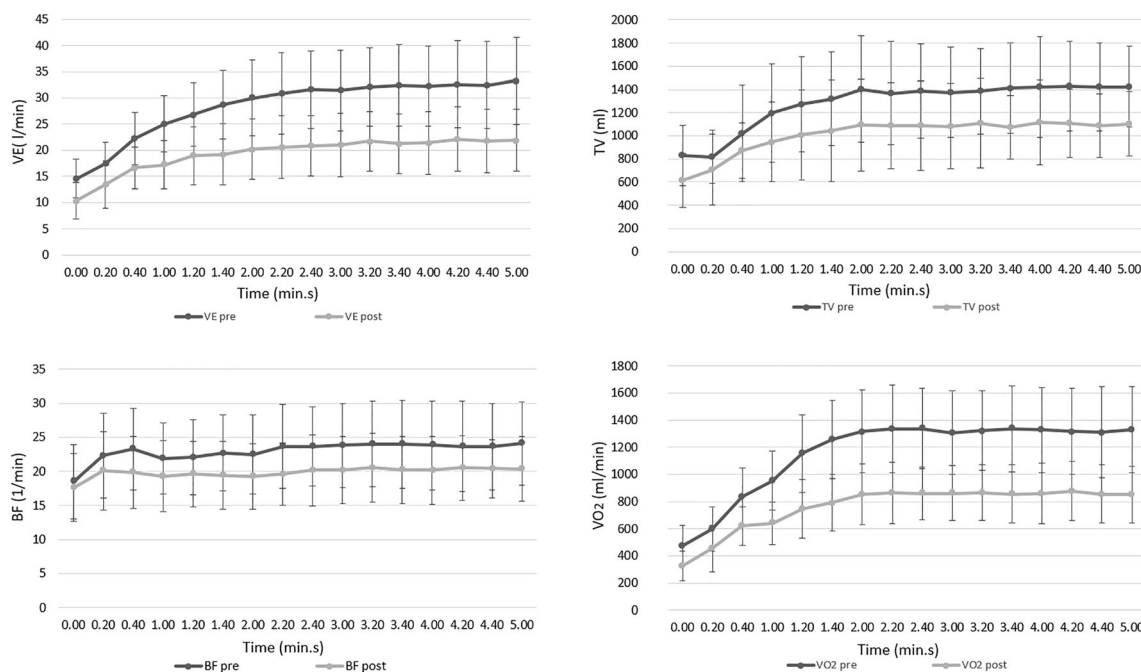


Fig. 1 Ventilatory response and oxygen consumption at submaximal exercise. Ventilatory response and oxygen consumption during the initial 5 min of CPET at constant load, before and after sleeve gastrectomy (SG). Patients with severe obesity presented after massive

weight loss a lower ventilatory response (VE), with reduced tidal volume (TV) and breathing frequency (BF). This was partially due to lower ventilatory demands because of decreased oxygen consumption (VO_2). Data are presented as mean and SD

and lung volumes, leading to a reduction of peripheral pulmonary resistances and of mechanical restrictive limitations.

Data also show a decrease in resting ventilation after SG that might reflect a reduction in global energy/oxygen demands and improved ventilatory efficiency. In fact, in accordance with previous studies, a reduction in resting absolute VO_2 was found [28–30]. Furthermore, as also observed by Matos et al., the resting ventilatory

pattern was characterized by a lower ventilation, mainly due to a reduction of the TV, which appears, however, sufficient to ensure adequate alveolar ventilation [19]. This suggests an optimization of ventilatory efficiency resulting from an improved pulmonary compliance and gas exchange [8]. Indeed, it is known that areas of atelectasis, frequently present in severe obesity, might be recovered and recruited for ventilation after massive weight loss [2, 4, 23].

Table 3 Physical exercise capacity

<i>n</i> = 46	Evaluation pre-SG		Evaluation post-SG		<i>p</i> value
	Mean	SD	Mean	SD	
Exercise time (min)*	14.94	± 2.54	17.39	± 2.43	<i>p</i> < 0.001
VO_2 rest (ml/min)	476.15	± 148.99	326.54	± 111.64	<i>p</i> < 0.001
VO_2 AT (ml/min)*	1716.65	± 488.52	1353.19	± 317.10	<i>p</i> < 0.001
VO_2 peak (ml/min)*	2442.93	± 622.88	2205.15	± 565.92	<i>p</i> < 0.001
VO_2 /kg rest (ml/min/kg)*	3.91	± 0.90	3.64	± 1.12	<i>p</i> = 0.227
VO_2 /kg AT (ml/min/kg)	14.17	± 2.86	15.09	± 2.94	<i>p</i> = 0.040
VO_2 /kg peak (ml/min/kg)*	20.27	± 3.84	24.70	± 5.67	<i>p</i> < 0.001
RER_{rest}	0.81	± 0.06	0.76	± 0.08	<i>p</i> < 0.001
RER_{max}^*	1.12	± 0.09	1.18	± 0.09	<i>p</i> < 0.001

Effect of massive weight loss after sleeve gastrectomy (SG) on patients’ physical exercise capacity and tolerance. VO_2 absolute oxygen consumption, AT anaerobic threshold, VO_2 /kg oxygen consumption per kilogram bodyweight, RER respiratory exchange ratio. “*” indicates parameters not normally distributed

Pulmonary Function During Exercise

Regarding the ventilatory response to submaximal exercise, a few other studies have observed similar results after bariatric surgery, namely a reduction of ventilation for the same amount of external workload. Indeed, the ventilation during submaximal exercise post-SG was found reduced in both its components, i.e. BF and TV (Fig. 1). However, there is still a lack of evidence regarding the ventilatory response during incremental effort until exhaustion and the previously examined populations were different and, in part, not homogeneous [28, 29, 31, 32]. The shown significantly lower increase of BF ($\Delta BF_{\text{rest to AT}}$) and the associated more pronounced response of TV ($\Delta TV_{\text{AT to Peak}}$) after SG suggest a less shallow ventilatory response pattern during incremental exercise (Table 2, Fig. 1). These adaptations become advantageous as the relative calculated dead space ventilation ($V_{\text{Dc}}/V_{\text{Tmax}}$) is probably decreasing not only as a result of the reduction in BF [33], but mainly because of the increased ability to exploit TV contributing to gas exchange. Indeed, alveolar ventilation can be improved more by increasing the breathing depth rather than by increasing the respiratory rate [34].

Patients' ventilatory efficiency was subsequently also analysed by examining the ventilatory equivalents for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2). As also described by Wilms et al., there are no significant differences with regard to VE/VO_2 at the anaerobic threshold after massive weight loss [35]. Nevertheless, the concomitant improvement of VE/VCO_2 and $V_{\text{Dc}}/V_{\text{Tmax}}$ might suggest that weight loss increased ventilatory efficiency, likely because of adaptations of ventilatory mechanics and gas exchange [36, 37]. Finally, the increase in peripheral oxygen saturation at peak exercise after SG, although clinically not significant, could further confirm an improvement in ventilatory efficiency [38].

The improved ventilatory pattern with the associated reduction of dead space ventilation and the likely better ventilatory efficiency will reduce ventilatory demand during exercise, which is also due to reduced oxygen costs/consumption. The patients' potentially higher ventilatory capacity (i.e. maximum voluntary ventilation based on FEV_1) along with the lower ventilatory volume during exercise lead to the shown increased breathing reserve at maximal effort after SG [33, 39]. Our findings suggest that ventilation is not a factor limiting exercise in these patients. However, after a massive weight loss, the reduced ventilation and improved ventilatory efficiency lead to a lower work of breathing. Indeed, patients who can rely on major breathing reserves are less constrained by ventilation [8].

Cardiorespiratory Fitness

Results of the present and previous studies show that the substantial weight loss after SG led to improved exercise

capacity and tolerance [17, 35, 40, 41]. However, despite the associated increase in peak VO_2/kg , absolute VO_2 decreased at all exercise intensities (Table 3; Fig. 1). This is probably explained by a decrease in energy/oxygen demands due to a lower weight-related workload, lower costs of breathing and by a quantitative loss in lean mass that generally accompanies the loss of adipose tissue [42]. Furthermore, the decrease in absolute VO_2 could also be influenced by a qualitative alteration of skeletal muscle function, i.e. a deterioration of peripheral oxidative muscle metabolism [28, 30, 43, 44].

Limitations and Perspectives

The findings of this observational study refer to the first 6 months after SG; long-term studies are therefore needed to investigate whether the effects on ventilation and aerobic capacity are long-lasting. Additionally, the impact of SG on ventilatory efficiency should be further investigated by specifically designed clinical trials, evaluating pulmonary perfusion, diffusion and ventilation. Finally, the effects of bariatric surgery on obesity-related ventilatory disorders, such as obesity-hypoventilation syndrome or obstructive sleep apnoea syndrome, should be addressed by future research.

Conclusion

This is the first study to investigate the impact of SG on ventilation at rest and during incremental exercise, evaluating respiratory function, breathing pattern/efficiency and the effects on exercise capacity, in a highly selected and homogeneously treated study population of severely obese patients. It is possible to affirm that the massive weight loss during the first 6 months after SG leads to an improvement in respiratory restrictive limitations and in ventilation mechanics that contribute to a more efficient ventilation both at rest and during exercise. The subsequent lower ventilation can also be explained by a reduction in oxygen demand. Moreover, the decreased ventilatory response to exercise might be due to an increased ventilatory efficiency with a less shallow breathing pattern and a reduced oxygen consumption during incremental exercise intensities. The adaptations described lead to an increased breathing reserve at peak exercise, which might indicate from a clinical point of view that patients' exercise capacity is less prone to be impaired by ventilation. Finally, even though exercise capacity and tolerance improved after SG, the significant decrease of absolute oxygen consumption may reflect the associated loss of functional muscle mass.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were part of routine clinical evaluations in accordance with the institutional ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of Informed Consent Informed consent was obtained from all participants included in the study.

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