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Altered Resting and Exercise Respiratory Physiology in Obesity

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Synopsis

Obesity, particularly severe obesity, affects both resting and exercise-related respiratory physiology. Severe obesity classically produces a restrictive ventilatory abnormality, characterized by reduced expiratory reserve volume. However, obstructive ventilatory abnormality may also be associated with abdominal obesity. Decreased peak work rates are usually seen among obese subjects in a setting of normal or decreased ventilatory reserve and normal cardiovascular response to exercise. Weight loss may reverse many adverse physiological consequences of severe obesity on the respiratory system.

Keywords

Obesity; Respiratory physiology; Exercise; Expiratory Reserve Volume; Oxygen consumption.

Introduction

Obesity (Body mass index or BMI ≥ 30 kg/m^2) is the most common metabolic disease in the world and its prevalence has risen worldwide, particularly in the United States. Data from the two National Health and Nutrition Examination surveys show that the prevalence of obesity has increased among adults aged 20–74 years in the United States from 15.0% (1976–1980) to 32.9% (2003–2004) [1]. Physicians are therefore routinely challenged by the co-morbidities associated with obesity. While the associations between obesity and increased risk of cancer, cardiovascular, endocrine, and rheumatologic diseases are well-described, the respiratory effects of obesity, outside sleep-related disorders, are less well known. It is now clear that respiratory function is impaired in obesity and the magnitude of impairment is more clearly demonstrable in severe obesity [2]. This review will focus on the effect of obesity on resting and exercise-related respiratory physiology.

Altered Resting Respiratory Physiology in Obesity

Obesity affects various resting respiratory physiologic parameters such as compliance, neuromuscular strength, work of breathing, lung volumes, spirometric measures, respiratory resistance, diffusing capacity, gas exchange, and airway responsiveness to methacholine (Table 1).

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Respiratory Compliance

Respiratory compliance is the ability of the respiratory system to stretch during a change in volume relative to an applied change in pressure. Total respiratory compliance may be reduced in severe obesity with obesity-hypoventilation syndrome to as little as one-third of the normal [3]. In other words, there may be up to a three-fold increase in elastic resistance to respiratory distension in severely obese individuals. This largely results from reduced distensibility of extrapulmonary structures from excess truncal fat [3]. However, increased pulmonary blood volume and increased closure of dependent airways also contribute to the low lung compliance seen in severely obese subjects [4]. These physiological changes are more pronounced during recumbency in obese subjects, as compared to normal weight subjects, due to the increased gravitational effects of the large abdomen [5].

Respiratory Muscle Strength

Obese subjects may demonstrate inefficiency of respiratory muscles, particularly the diaphragm. Reduced respiratory muscle strength and endurance, as suggested by static maximal inspiratory pressure values of 60-70% of normal subjects, have been described among three severely obese subjects with obesity-hypoventilation syndrome in a 1974 study by Rochester and Enson [4]. Recent studies have confirmed that obese subjects are at greater risk for inspiratory muscle fatigue both at rest and with exercise [6, 7]. Further, weight loss in severely obese subjects is associated with improved respiratory muscle strength and endurance [8]. A possible cause of impaired respiratory muscle function in obesity includes increased elastic load which the respiratory muscles are required to overcome during inspiration [8]. An overstretched diaphragm would place this respiratory muscle at a mechanical disadvantage, leading to decreased inspiratory muscle strength and efficiency [9]. Additionally, decreased skeletal muscle glycogen synthase activity in obese subjects may be associated with decreased isokinetic skeletal muscle endurance [10, 11], although it is not known if this phenomenon actually occurs in respiratory muscles. Further, fatty infiltration of respiratory and non-respiratory skeletal muscle in obese subjects has been well-documented [12-14], although its clinical significance related to muscle strength is unclear.

Work of Breathing at Rest

To overcome the reduced total respiratory compliance and respiratory muscle inefficiency, severely obese subjects may breathe rapidly and shallowly [6, 15]. This pattern of breathing is similar to that seen among patients with neuromuscular and musculoskeletal disorders [16]. This pattern of breathing is however associated with increased oxygen cost of breathing [15, 17]. The oxygen cost of breathing represents the oxygen consumed by the respiratory muscles per liter of ventilation and is an index of the energy required to breathe. Rochester showed that the oxygen cost of breathing is four-fold and ten-fold higher than normal among subjects with simple eucapnic obesity and obesity-hypoventilation syndrome respectively [15]. In a study by Kress *et al.* of eighteen severely obese patients, a 16% reduction in oxygen consumption was seen after elective intubation, mechanical ventilation and anesthesia from their resting baseline values, as compared to a <1% reduction in among eight controls [17]. This relative respiratory inefficiency among obese subjects suggests a decreased ventilatory reserve and a predisposition to respiratory failure in the setting of even mild pulmonary or systemic insults [17].

Lung Volumes

The most common and consistent indicator of obesity is a reduction in expiratory reserve volume (ERV, see Figures 1 and 2) [18]. This occurs because of displacement of the diaphragm into the thorax by the obese abdomen and increased chest wall mass [19]. Although this association is seen even with modest obesity [20], ERV decreases rapidly in an exponential relationship with increase in BMI (see Figure 2) [21].

On the other hand, obesity has fairly modest effects on the extremes of lung volumes at residual volume (RV) and total lung capacity (TLC) but a relatively larger effect in reducing functional residual capacity (FRC) [21]. This reduction is often so marked that FRC approaches RV [22] (see Figure 1). When the reduced FRC is equal to or lower than the closing volume, regional thoracic gas trapping may take place in obese subjects, as suggested by an elevated RV/TLC ratio [23, 24]. Further, in order to compensate for the reduced FRC, inspiratory capacity (IC) may be increased in severe obesity (see Figure 1).

As mentioned previously, TLC is usually preserved in most obese subjects, other than those with morbid obesity (weight-to-height ratio of ≥ 0.9 kg/cm) [2, 25], with excessive central adiposity (waist-to-hip ratio of ≥ 0.95) [26], or with obesity hypoventilation syndrome [15]. In the absence of the above conditions, a restrictive defect (TLC < lower limit of normal) should not be attributed to obesity, until other causes of restrictive impairment, such as interstitial lung disease, have been excluded.

Sequential studies after weight loss, usually in the context of bariatric surgery, usually show a marked improvement in ERV; intermediate improvement in RV and FRC with a more modest improvement in TLC [2, 8, 27, 28] (see Figure 3).

Spirometry

Obesity may be associated with a reduction in vital capacity (VC) and forced expiratory volume in one second (FEV_1), depending upon the age, type of body fat distribution (with central fat distribution having a relatively greater effect) [26], and severity of obesity. Previous studies have created the impression that only morbid obesity is associated with this restriction of VC [24] 29 but a recent large French population-based study by Leone *et al.* demonstrated that even *mild abdominal* obesity, even with a *normal* BMI, is associated with lower VC and FEV_1 in both men and women [30]. These findings have prompted a leading authority in this field to recommend the routine measurement of waist circumference prior to spirometry to allow the interpreting physician to take into account the restrictive effect of abdominal obesity on spirometric values [31].

Possible causes of reduced VC in obese subjects may be mechanical and inflammatory. Mechanical causes include decreased respiratory compliance (with consequently decreased lung volumes) and increased gas trapping from premature small airway closure (particularly at the lung bases). In addition, obesity is associated with both increased levels of pro-inflammatory adipokines (such as leptin, interleukin-6, and tumor necrosis factor-alpha [32]) and decreased levels of anti-inflammatory adipokines (such as adiponectin [32, 33]). The secretion of these adipokines by adipose tissue in chronic respiratory diseases may be regulated by chronic or intermittent hypoxia [34]. These adipokines in turn regulate systemic inflammation which is associated with impaired lung function [35-37]. Either directly or via systemic inflammation, adipokines may also affect inflammation of small airways, resulting in premature closure of the inflamed and edematous small airway. Additional mechanistic studies are needed to better understand the pathophysiological pathways by which adipokines may affect lung function.

FEV_1/VC ratio is usually normal or increased with obesity - the latter is thought to occur because of peripheral airway closure and resulting gas trapping disproportionately reducing the VC [23]. The implication is that while obesity may affect small airway function, it may not affect large airways. However, the latter impression may not be entirely true. A recent study by Leone *et al.* suggests that *abdominal* obesity may be associated with a reduced FEV_1/VC ratio, suggesting an effect on large airway caliber as well [30]. Thus, obesity may be associated with obstructive ventilatory abnormality, in addition to its well-known association with restrictive abnormality.

The effect of obesity on forced expiratory flow rates at low-lung volumes is less well-described. A study by Rubinstein *et al.* in 103 non-smoking morbidly obese men showed reduced maximum expiratory flow rate at 75% of exhaled vital capacity even after normalization for vital capacity, implying peripheral airflow obstruction [23]. This phenomenon is illustrated in Figure 4. Possible mechanisms may include obesity-related inflammation or edema of the small airways, thus decreasing their caliber.

Further, some but not all studies suggest that the effect of obesity on absolute lung function may be greater among men than among women, probably due to greater central fat distribution in men [38-41]. Yet, this absolute reduction in lung function may have a relatively greater impact on women, due to their smaller initial lung volume [19]. Whether a change in lung volume of this magnitude has a relatively greater impact on dyspnea among obese women, as compared to obese men, is unknown and warrants further research.

Interestingly, while increased fat mass may be negatively associated with spirometric lung function, increased lean mass (*i.e.* primarily muscle mass) may be positively associated with FEV_1 and to a lesser extent with VC, particularly among men [19, 42]. This protective effect of lean mass on lung function may be associated with stronger respiratory musculature [42] or larger overall thoracic size [19], although the mechanism remains uncertain.

Several longitudinal studies demonstrate that increasing weight gain is associated with more rapid loss of lung function (both FEV_1 and VC) [43-47]. Both mechanical and inflammatory mechanisms related to obesity as described above, may contribute to this relatively rapid deterioration in airway function and may predispose obese subjects to long-term adverse effects of cigarette smoking, respiratory infections, and occupational and environmental exposures. Further, obese subjects may improve their lung function by losing weight, suggesting that these detrimental effects of obesity do not involve irreversible structural remodeling of the airways [2, 8, 27, 28, 47, 48].

In addition to the above spirometric changes, severe obesity is associated with a decrease in maximum voluntary ventilation (MVV). This may be explained by respiratory muscle inefficiency, increased upper airway resistance, and inspiratory flow resistance [2]. MVV values in obese subjects usually improve following weight reduction [49].

Airway Resistance

An increase in airway resistance (as measured by body plethysmography) is reported in obese subjects [23, 50]. However, this may be attributable to breathing at low FRC which in turn results in a relatively decreased airway caliber throughout the tidal breathing cycle. This conclusion is supported by normal values of specific airway conductance [23]. Some studies have suggested that the increase in airflow resistance may not be due entirely to the reduced lung volume but have not described the specific cause of the additional resistance [51, 52].

Diffusing Capacity

Although diffusing capacity is usually preserved in obese subjects, both decreased and increased values are reported in the literature [2, 53]27. High values of diffusing capacity may result from increased pulmonary blood volume in obesity. On the other hand, diminished values may result from structural changes in the lung interstitium from lipid deposition and/or decreased alveolar surface area [53].

The effect of weight loss on diffusing capacity has been examined in a few small studies - values remained largely unchanged following surgical weight loss in two separate studies of 16 and 35 morbidly obese subjects by Thomas *et al.* 27 and Zavorsky *et al.* 54 respectively and following medical weight loss in 35 obese men in another study by Womack *et al.* 48

Gas Exchange

Obese subjects have high levels of ventilation-perfusion mismatch from atelectasis of under-ventilated dependent lung units, which continue to be well-perfused. This results in an increased alveolar-arterial oxygen tension gradient [$P(A\text{-}a)_{O2}$)] and reduced partial pressure of oxygen in arterial blood (PaO_2). This is worse in recumbent position. Sequential studies demonstrate that weight-reduction may be associated with improved PaO_2 [27, 28].

Despite their greater carbon dioxide production ($\dot{V}_{CO_2}$), the majority of obese subjects maintain a normal partial pressure of carbon dioxide in arterial blood ($PaCO_2$). In order to maintain normal PaCO2 levels in the face of high $\dot{V}_{CO_2}$, obese subjects generally demonstrate higher minute ventilation (V_e). If they are eucapnic, such individuals have only simple obesity. Patients with obesity hypoventilation syndrome, on the other hand, are unable to adequately augment their Ve and are therefore, hypercapnic. Whether an obese individual demonstrates simple eucapnic obesity or obesity hypoventilation syndrome depends less on the actual BMI value and more on his or her central ventilatory responses to hypoxia and hypercapnia [55]. Obesity, genetic predisposition, sleep-disordered breathing, and leptin resistance have all been proposed as possible mechanisms for this blunted ventilatory response to hypercapnia [56] (also see article in this issue by Mokhlesi).

Airway Responsiveness to Methacholine

The association between obesity and asthma has been covered elsewhere in great detail (see article in this issue by Beuther). It is however worth mentioning that the mechanical effects of obesity on the lungs may alter airway smooth muscle contractility and increase airway responsiveness [57]. Breathing voluntarily at low lung volumes may increase airway responsiveness to methacholine in lean non-asthmatic subjects [58]. In obese subjects breathing at low lung volumes, the airways remain at smaller caliber and the airway smooth muscle is at shorter length throughout the breathing cycle. It is possible that this would change the contractile properties of the airway smooth muscle, either by plastic adaptation to a shorter length [59] or alterations in actin-myosin cross-bridge cycling [60], resulting in an increase in airway smooth muscle contractility and an increase in airway responsiveness. Recent studies also raise the possibility that adipokines (high leptin and low adiponectin concentrations) may increase airway responsiveness [56, 61-64], although the mechanism remains unknown.

Altered Exercise Respiratory Physiology in Obesity (Table 2)

Oxygen consumption

Obesity is associated with increased rates of basal metabolism and oxygen consumption ($\dot{V}_{O_2}$) at rest [65]. However, since adipose tissue has a lower metabolic rate than other tissues, if $\dot{V}_{O_2}$ is standardized by expressing it per kilogram actual body weight, lower than normal values are obtained in obese individuals [65]. Similarly, an active, otherwise healthy, obese subject has reduced peak $\dot{V}_{O_2}$ if it is correlated to actual body weight, but normal or high if it is correlated to either height,[66] predicted body weight, or lean body mass [67].

Exercise-related increase in $\dot{V}_{O_2}$ is more marked in obese subjects as compared to normal-weight subjects, since additional energy is needed to move heavy body parts [66, 68]. Because of the high metabolic cost of performing even modest activity, an otherwise healthy obese subject may have good cardiovascular fitness, despite the reduced work capacity [66, 68].

Interestingly, the increased oxygen cost of performing mechanical work is predictable and well-worked out for cycle ergometer [66, 68]. The $\dot{V}_{O_2}$-work rate relationship is displaced upward by about 6 ml/min/kg. of extra body weight without any discernible change in the slope of the $\dot{V}_{O_2}$-work rate relationship (Figure 5) [66, 68]. This means that appropriate peak $\dot{V}_{O_2}$ reference

standard for an obese subject can be obtained by increasing the peak $\dot{V}_{O_2}$ standard obtained from predicted body weight by 6 ml/min for each kilogram above the predicted weight.

It should also be noted that cardiac and ventilatory reserves in an obese subject are limited in their ability to support the increased muscle oxygen requirement during exercise since the heart and the lungs do not increase in size commensurate with the subject's added weight [69]. This imposes physiological constraints on peak exercise performance in obese subjects who cannot attain the same peak work rates as normal-weight subjects [69].

Ventilatory Response to Exercise in Obesity

As discussed previously, obese subjects have increased $P(A\text{-}a)_{O2}$ and reduced PaO_2 at rest from atelectasis of peripheral lung units. This usually improves during exercise, because of the effect of deep breathing on expansion of atelectatic lung units. It is thus the only pulmonary condition in which arterial oxygenation improves during exercise [69]. Because ventilation-perfusion relationships usually normalize during exercise in the patient with uncomplicated obesity, exercise-related dead space ventilation measures (such as ventilatory equivalent for carbon dioxide or $V_e/\dot{V}_{CO_2}$ ratio at anaerobic threshold and dead space-tidal volume ratio) and exercise-related $P(A\text{-}a)_{O2}$ values are also normal.

Further, FRC is reduced in the resting state in obese subjects from ‘chest strapping’, as discussed previously. However, during heavy-to-peak exercise, while FRC reduces in lean subjects, it may actually increase in obese subjects [70]. Both groups, lean subjects and obese subjects, also develop (modest and similar levels of) expiratory flow limitation at peak exercise [70]. However, it is important to recognize that unlike lean subjects who easily tolerate this decline in expiratory flow, obese subjects have to increase their FRC (or hyperinflate) during peak exercise to avoid significant levels of expiratory flow limitation [70]. This dynamic hyperinflation may contribute to reduced tidal volume and increased respiratory rate and may contribute to a reduced ventilatory reserve during peak exercise [71].

Cardiovascular Response to Exercise in Obesity

Although work capacity is impaired in moderately obese subjects, peak oxygen pulse (a non-invasive determinant of stroke volume) and anaerobic threshold levels (related to percent predicted peak $\dot{V}_{O}{}^2$) are usually normal [66, 67, 69, 72]. This reflects the ‘training effect’ induced consequent to the demands of performing habitual activities while ‘loaded’ with a greater body mass [72]. Although resting heart rate is usually high in obese subjects, peak heart rate is usually normal, resulting in little heart rate reserve [72].

On the other hand, among asymptomatic severely obese subjects, abnormal indices of left ventricular diastolic filling pressures, as measured by pulse Doppler-echocardiography, more frequently develop during exercise, as compared to matched lean controls [73]. This may represent a subclinical form of cardiomyopathy in severely obese subjects [73].

Summary

Obesity, particularly severe obesity, affects both resting and exercise-related respiratory physiology. Obesity markedly reduces the expiratory reserve volume (ERV) and respiratory system compliance, classically producing a restrictive ventilatory abnormality. However, reduced FEV1/VC ratio (associated with abdominal obesity) and reduced maximum expiratory flow rates at low lung volumes in obesity may less often produce an obstructive ventilatory abnormality as well. Arterial hypoxemia resulting from ventilation-perfusion mismatch usually improves with exercise. Increased absolute rates of oxygen consumption ($\dot{V}_{O_2}$) both at rest and with exercise are seen in obese subjects. However, if $\dot{V}_{O_2}$ is standardized by expressing it per kilogram actual body weight, lower than normal values are obtained. Decreased peak work

rates are usually seen in a setting of normal or decreased ventilatory reserve and normal cardiovascular response to exercise in obese subjects. The best treatment of obesity is weight loss which reverses many of the adverse physiological consequences of obesity on the respiratory system.

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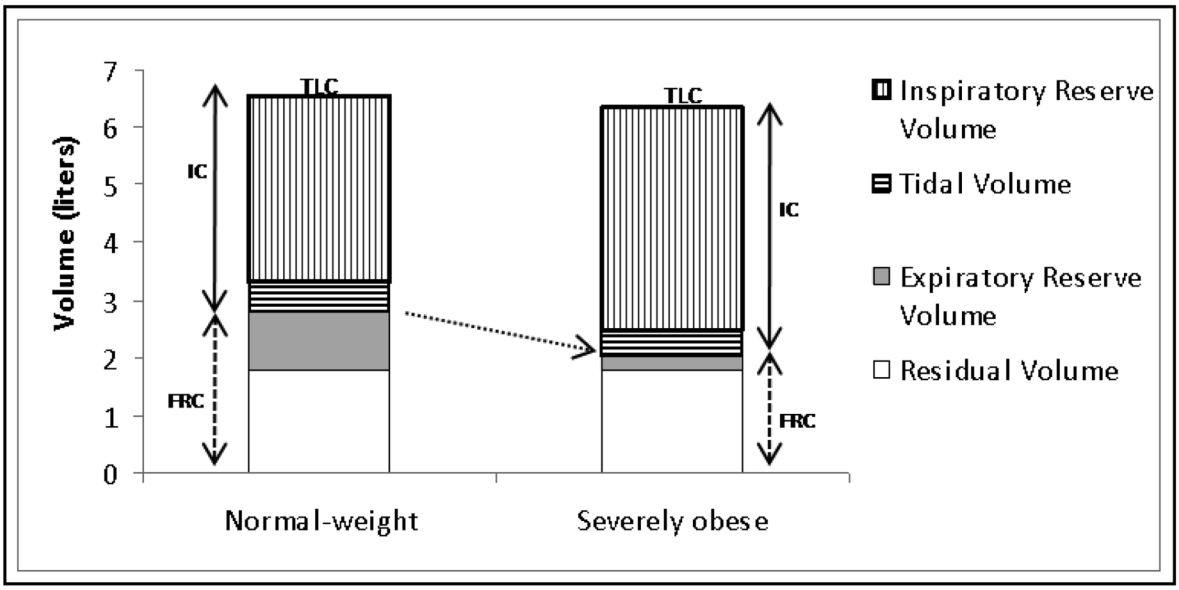

Figure 1.
Effect of obesity on lung volumes - Expiratory reserve volume (ERV) is decreased in obesity. Functional residual capacity (FRC), the sum of ERV and residual volume, is usually reduced as well, often approaching residual volume (see arrow). The decline in FRC in obese subjects is primarily the result of reduced ERV. Total lung capacity (TLC, the sum of FRC and inspiratory capacity or IC) is usually preserved. Therefore, in order to compensate for the reduced FRC, inspiratory capacity (IC), the sum of inspiratory reserve volume and tidal volume, may be increased in severe obesity.

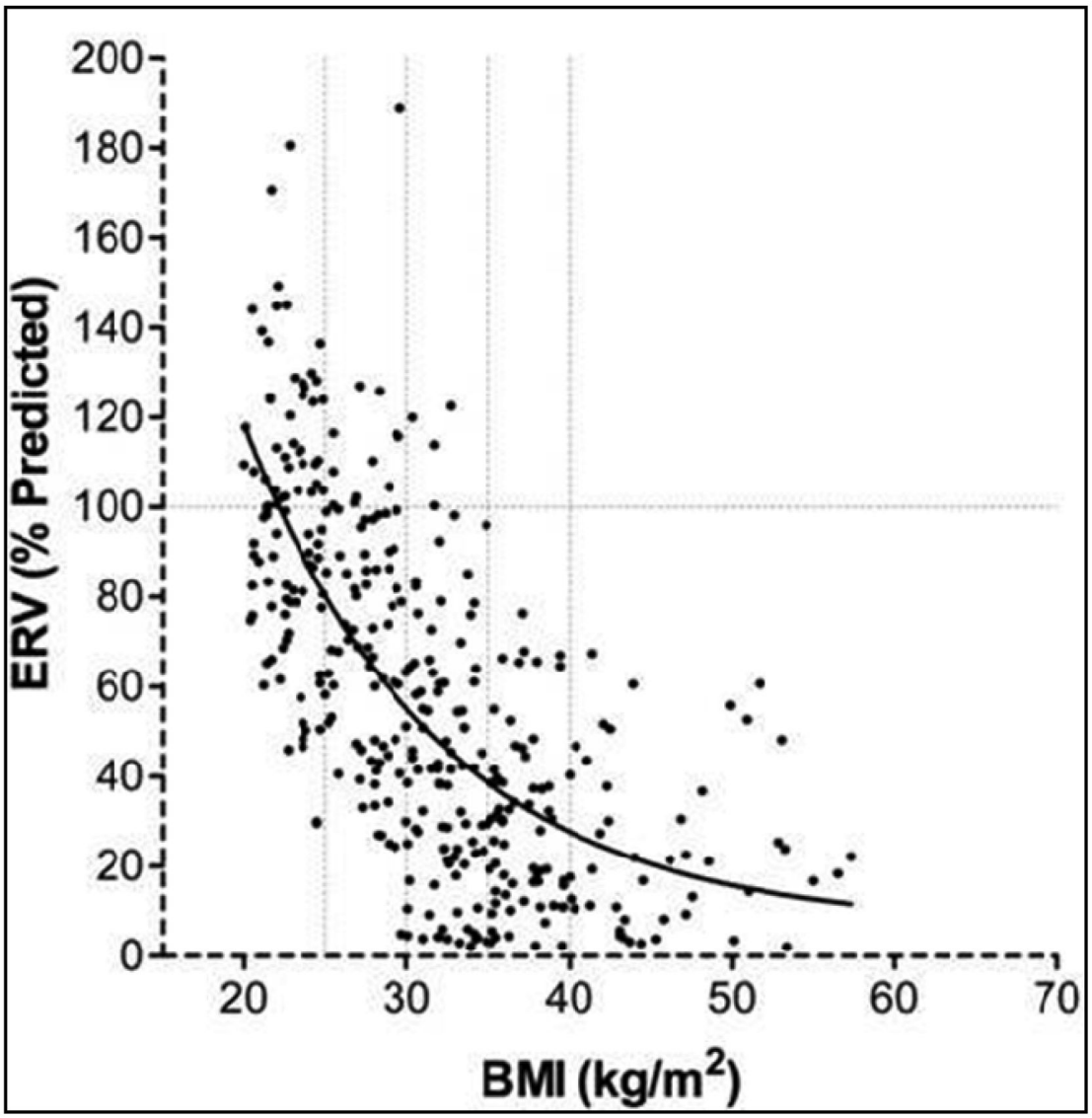

Figure 2.
Expiratory reserve volume (ERV) decreases rapidly in an exponential relationship with increase in body mass index (BMI). The best-fit exponential regression equation for ERV is as follows: ERV = 587.8 exp(−0.083 X BMI) + 6.5. The r^2 value for ERV was 0.49 ($p < 0.01$). Obtained with permission from Chest [21].

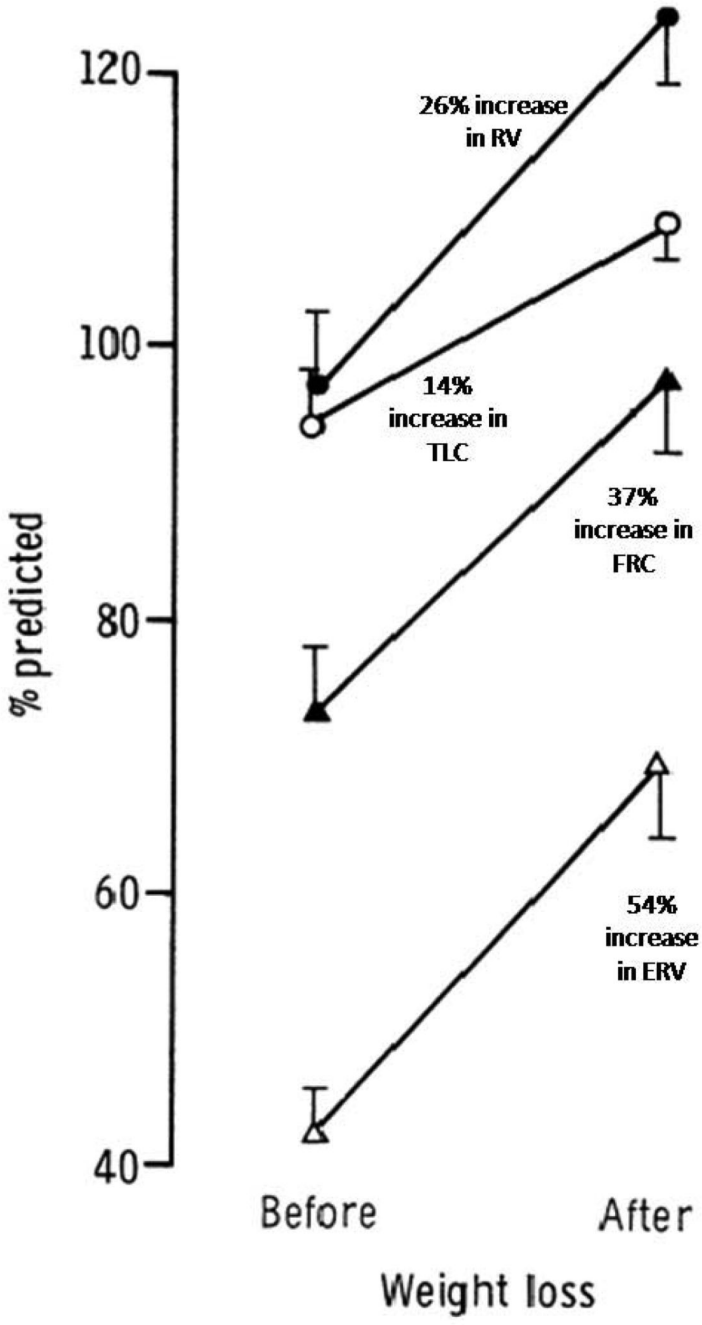

Figure 3.
Vertical banded gastroplasty in a study by Thomas *et al.* 27 was associated with a mean weight loss of 34.2 kg in 29 morbidly obese subjects. Resulting change in static lung volumes (expressed as change in percent predicted values from baseline) are summarized. Bar lines indicate one standard error of the mean (SEM). Greatest improvement in expiratory reserve volume (ERV); intermediate improvement in residual volume (RV) and functional residual capacity (FRC); and least improvement in total lung capacity (TLC) was seen following surgical weight loss.
Obtained with permission from Thorax [27].

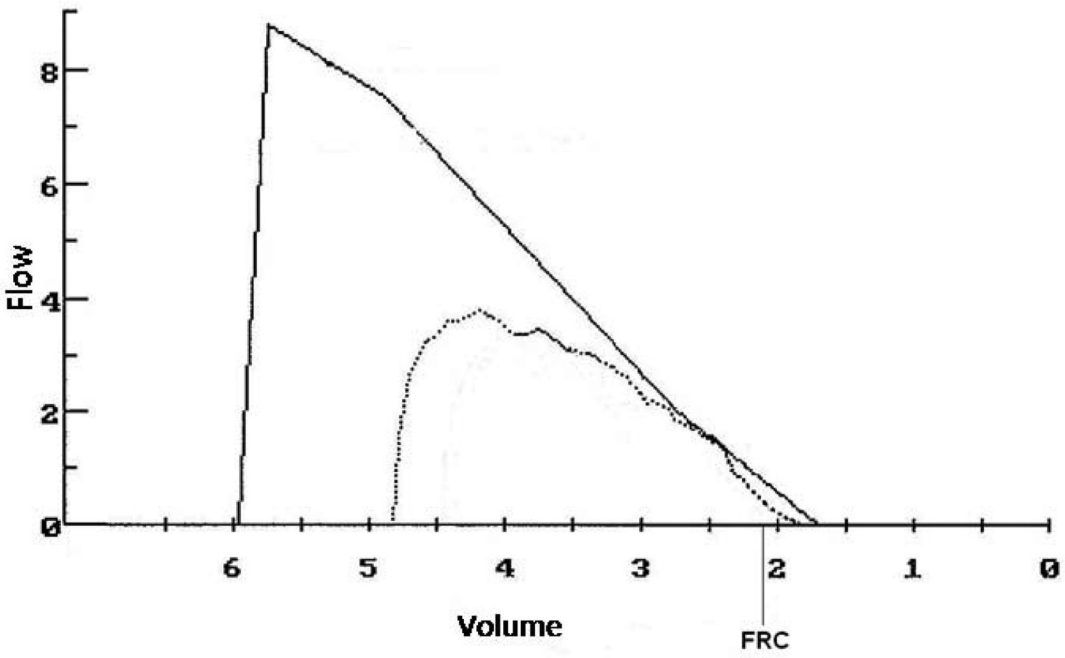

Figure 4.

Expiratory flow volume curve (dashed line) from a woman with BMI=50 kg/m^2. Solid line shows the predicted curve. Both TLC (79% predicted) and FRC (68% predicted) are reduced, but maximal flows are well preserved and the FEV_1/FVC is normal. Nevertheless, expiratory flows at low lung volumes are reduced relative to the predicted values derived from the vital capacity.

Obtained with permission from Cheryl Salome, Ph.D., Woolcock Institute of Research, University of Sydney.

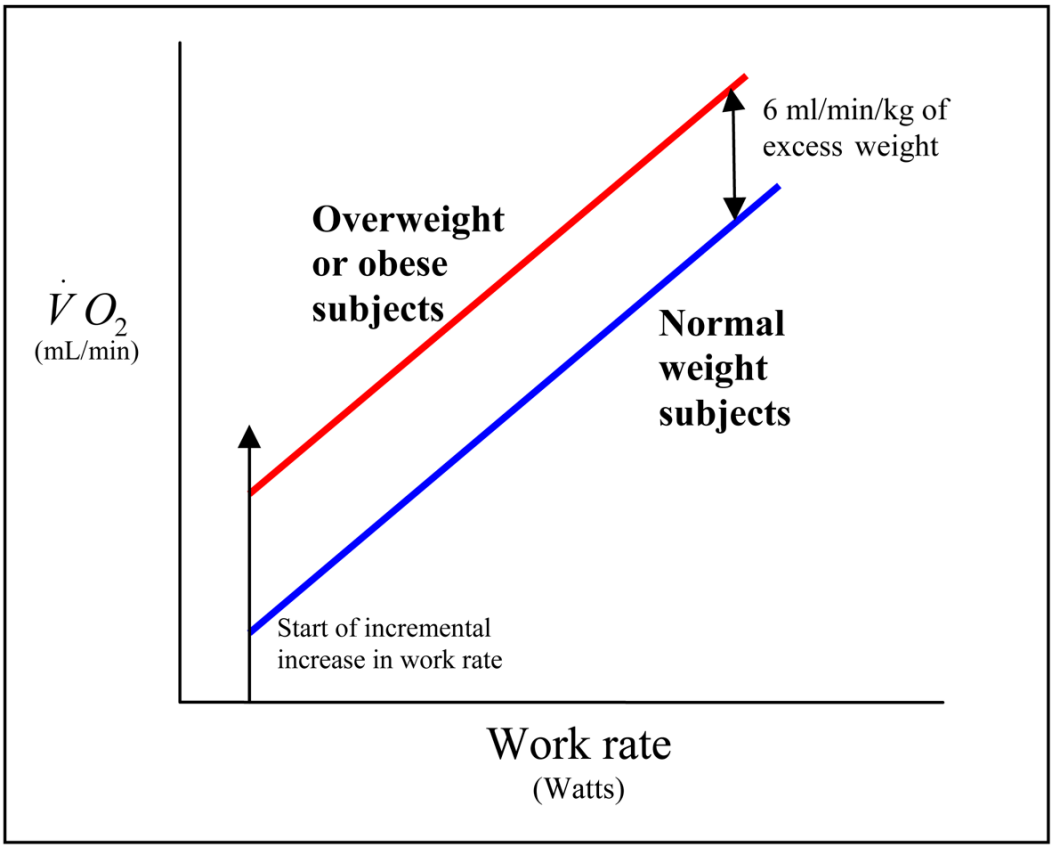

Figure 5.
Obesity displaces the $\dot{V}_{O2}$ -work rate relationship upward by about 6 ml/min/kg of excess body weight, but the slope itself is unchanged (Adapted from Figure 4.5, Principles of Exercise Testing and Interpretation, Wasserman et al., Fourth edition, Lipincott Williams & Wilkins, Philadelphia, PA, 2005 – copyright permission obtained from Lipincott Williams & Wilkins).

Table 1

Altered Resting Respiratory Physiology in Obesity

Physiologic Parameter	Effect of Obesity
Respiratory Compliance	Decreased
Respiratory Muscle Strength	Decreased
Work of Breathing at Rest	Increased
Vital Capacity (VC)	Normal or Decreased*
Forced Expiratory Volume in One Second (FEV_1)	Normal or Decreased
Ratio (FEV_1/VC)	Normal, Increased or Decreased
Maximal Expiratory Flow Rates at Low Lung Volumes	Decreased
Longitudinal loss in FEV_1 and VC	Increased
Expiratory Reserve Volume (ERV)	Decreased
Functional Residual Capacity (FRC)	Usually Decreased
Residual Volume (RV)	Normal
Inspiratory Capacity (IC)	Normal or Increased
Total Lung Capacity (TLC)	Normal or Slightly Decreased
Airway Resistance	Increased
Specific Airway Conductance	Normal
Diffusing Capacity	Variable
Alveolar arterial oxygen tension gradient [$P(A\text{-}a)_{O_2}$)]	Increased
Airway Responsiveness to Methacholine	Often Increased

* The negative association between VC and obesity is better described with abdominal obesity [30].

Table 2

Altered Exercise-Related Respiratory Physiology in Obesity

Physiologic Parameter	Effect of Obesity
$\dot{V}_{O_2}$ peak	Decreased (for actual weight); Normal or Increased (for ideal weight)
$\dot{V}_{O_2}$-Work Rate relationship	Displaced Upwards
Anaerobic Threshold (percent predicted peak$\dot{V}_{O_2}$)	Normal
Peak Heart Rate	Normal
Peak Oxygen Pulse	Normal
Ventilatory Reserve	Normal or Decreased
Ventilatory Equivalent for Carbon Dioxide at Anaerobic Threshold	Normal
Dead Space-Tidal Volume Ratio	Normal
Arterial Partial Pressure of Oxygen	Normal/may Increase
Alveolar-Arterial Oxygen Tension Gradient	May Decrease