Respiratory function and the obesity paradox

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Purpose of review

Obese individuals have impaired respiratory function relative to their normal-weight counterparts. Despite these negative effects, obesity is paradoxically associated with better survival in individuals with chronic obstructive pulmonary disease (COPD). The purpose of this review is to describe this 'obesity paradox', to discuss the effects of obesity on respiratory function, and to speculate as to whether obesity-related alterations in respiratory mechanics can influence the natural history of COPD.

Recent findings

Given the known negative effects of obesity on respiratory physiology, it is reasonable to predict that obese COPD patients would be more likely to experience greater dyspnea and exercise intolerance relative to COPD patients of normal weight. However, recent evidence suggests that obese COPD patients have similar or better dyspnea scores during exercise and do not have diminished exercise capacity. These observations may be attributable to the fact that obese COPD patients have reduced operating lung volumes and higher inspiratory capacity to total lung capacity ratios than their lean COPD counterparts.

Summary

Obese patients with COPD do not appear to be at a disadvantage during exercise relative to lean COPD patients. Obesity may be associated with improved survival in COPD but specific mechanisms for this paradox remain to be elucidated.

Keywords

BMI, chronic obstructive pulmonary disease, pulmonary function

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Introduction

Obesity is a global problem that has been increasing in epidemic proportions in both adults and children [1] and has recently been declared a disease according to the Obesity Society [2]. Obesity is commonly classified as a BMI of 30 kg/m^2 or more. Based on this definition, the prevalence of obesity in adults is greater than 30% in the United States [3]. It is well established that obesity is associated with a number of comorbidities including hypertension, type II diabetes mellitus, dyslipidemia, and certain types of cancer [4••], and is associated with increased mortality rate and reduced longevity [5]. Obesity is also known to have an important impact on the respiratory system. For example, obesity can have deleterious effects on pulmonary function, respiratory mechanics, pulmonary gas exchange, the control of breathing, respiratory muscle performance, and exercise capacity, and has been linked to a range of respiratory conditions such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, asthma, pulmonary embolic disease, and aspiration pneumonia [6]. Obesity may also be related to the release of pro-inflammatory cytokines that contribute to systemic inflammation in COPD and asthma [7•]. The purpose of this review is three-fold. First, to briefly describe the concept of the 'obesity paradox' as it relates to the respiratory system. Second, to describe the effects of obesity on respiratory physiology at rest and during exercise in individuals with and without COPD. Finally, to speculate as to whether obesity-related alterations in respiratory mechanics can influence the natural history of this disease.

The obesity paradox

It is widely accepted that obesity in the general population is associated with increased mortality and greater disease risk. However, in those who have experienced major illness or chronic disease, it appears that obesity is paradoxically associated with improved survival. This 'obesity paradox' has been demonstrated in a number of cardiovascular conditions such as hypertension, heart failure, coronary heart disease, and peripheral arterial disease, and other populations such as individuals with chronic kidney disease, rheumatoid arthritis, AIDS, and geriatric populations [4••,8]. Several studies have also demonstrated that a low BMI is associated with adverse prognosis in patients with COPD [9–11]. Landbo *et al.*

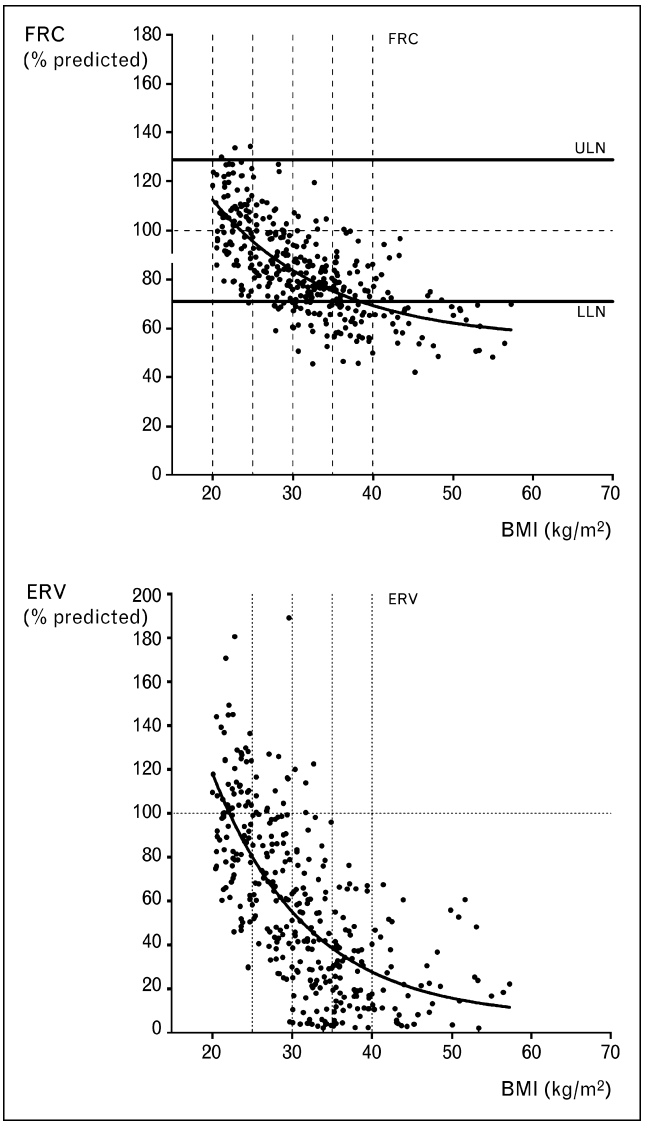
[10] found a significant effect of BMI on all-cause mortality in patients with severe COPD, with mortality being lowest in the obese patients and highest in those with the smallest BMI. However, this observation did not occur in patients with milder COPD, suggesting that obesity may exert differing effects depending on disease severity. This study, coupled with the work of others [9,11,12], demonstrated that obesity may be protective in patients with advanced COPD. Interestingly, this paradox may even occur in the absence of preexisting chronic respiratory illness. For example, Jee *et al.* [13] examined the association between BMI and the risk of death in over 1.2 million Koreans (without preexisting disease prior to study enrolment) and found that the risk of death from respiratory causes progressively decreased with increasing BMI, whereas risk of death from cancer and atherosclerotic cardiovascular causes increased with increasing BMI. The mechanisms underlying the above-mentioned findings on the obesity paradox remain unresolved. Why does obesity paradoxically improve survival in patients with COPD and why is a higher BMI associated with fewer respiratory-related deaths in those without preexisting respiratory illness? The remainder of this review will highlight the effects of obesity on respiratory function and we will then cautiously speculate what could be driving this paradox.

Resting physiological changes associated with obesity

The mechanical derangements of simple obesity and its effects on respiratory physiology are well established and have recently been reviewed by Salome *et al.* [14••]. Briefly, these mechanical derangements predispose obese individuals to having reduced respiratory system compliance with increased elastic loading of the inspiratory muscles [15–18], increased work and oxygen cost of breathing [19–21], reduced relaxation volume of the static respiratory system [15,22], and increased respiratory resistance [23]. Recent studies have shown in the supine position that obese individuals have measurable intrinsic positive end-expiratory pressure [24,25•]. Disruption of normal pulmonary gas exchange also occurs in obesity and is manifested by increased regional ventilation–perfusion mismatching (due to microatelectasis and airway closure). Reduced resting arterial partial pressure of oxygen (p_{O_2}) and increased alveolar-to-arterial p_{O_2} difference have been identified in subsets of individuals with morbid obesity [26].

Pulmonary function test abnormalities in eucapnic obesity have been well documented. Expiratory reserve volume (ERV) and end-expiratory lung volume (EELV) (or functional residual capacity) have been shown to decrease exponentially with increasing BMI [22] and represent one of the most consistent and significant

Figure 1 Exponential regressions for functional residual capacity and expiratory reserve volume versus BMI in adults with normal airway function



The horizontal solid lines for functional residual capacity (FRC) are the average upper limit of normal (ULN) and lower limit of normal (LLN) for men and women. ERV, expiratory reserve volume. Reproduced with permission from [22].

effects of obesity on pulmonary function (Fig. 1). Corresponding increases in resting inspiratory capacity and the inspiratory capacity-to-total lung capacity (TLC) ratio (inspiratory capacity/TLC) have recently been reported in association with obesity [27••]. There is some evidence to suggest that increasing body weight is associated with modest reductions in TLC [22,28], which may be related to reduced thoracic expansion [29•]. There is little or no change in vital capacity and residual volume. There are increases in pulmonary resistance with little/no change in bronchial reactivity [30,31•]. The forced expired volume in 1 s to forced vital capacity ratio (FEV_1/FVC) is largely

preserved in obesity [32,33]. Effects on static inspiratory and expiratory muscle strength are variable and inconsistent [23,34]. Diffusing capacity of the lung for carbon monoxide is preserved [35] and transfer factor reflecting the relatively decreased alveolar volume is increased.

Physiological changes during exercise in obesity

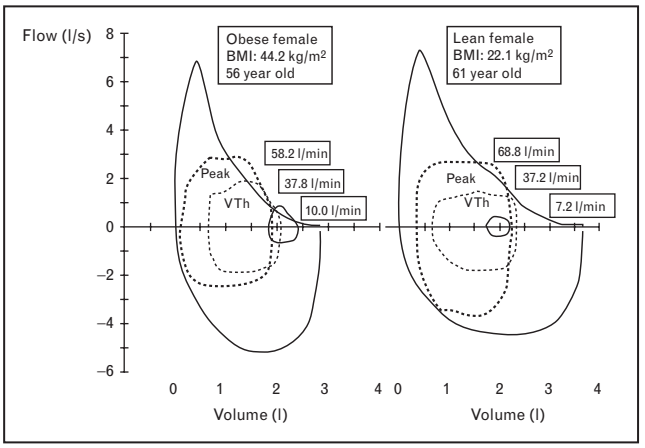
Oxygen uptake and carbon dioxide production (in absolute terms) are consistently higher at rest and during both weight-bearing and weight-supported exercise in obese compared with normal-weight individuals [19,21,36–42]. The increased metabolic requirements in obesity are related to increases in the energetic cost of moving heavier limbs during locomotion, reduced mechanical efficiency of the peripheral muscles, and increased work and O_2 cost of breathing [15,16,21,36,38,40–45].

Altered metabolic loading during exercise in obese individuals stimulates an increase in minute ventilation and therefore respiratory muscle contractile effort at any given submaximal work rate during exercise compared with lean controls [19,36,38,46]. Breathing pattern is relatively more rapid and shallow compared with lean individuals reflecting the increased mechanical restriction; this pattern minimizes increases in the elastic work and oxygen cost of breathing and optimizes breathing comfort [19,37,38,47]. Despite the shallow breathing pattern and increased oxygen cost of breathing, pulmonary gas exchange and arterial blood gas/acid–base status are relatively well preserved or actually improve during exercise in obesity [44,48].

Alterations in dynamic respiratory mechanics and effects on respiratory sensation

Reductions in resting ERV and EELV force obese patients to breathe close to residual volume where there is an increased propensity to develop expiratory flow limitation and an inability to decrease EELV with exercise compared with healthy controls [20,39,49,50] (Fig. 2). In some obese individuals, increased air-trapping (or dynamic lung hyperinflation) can occur as ventilation increases during activity. In this way, obese patients may actually pseudo-normalize their EELV allowing tidal volume to become positioned on a more compliant portion of the (predicted) pressure–volume curve of the respiratory system. Ofir *et al.* [19] reported that breathlessness for a given ventilation or oxygen consumption was essentially superimposed between groups of obese and normal-weight women. These findings were subsequently confirmed by Romagnoli *et al.* [46] and collectively suggest that the increased perception of exertional breathlessness in obesity reflects the normal awareness of increased ventilation and respiratory effort that accompanies the increased central (reflex) ventilatory drive. Respiratory mechanical/muscular factors, *per se*, appear not to contribute importantly to exertional breathlessness in obesity. Ofir *et al.* [19] argued that the increased resting inspiratory capacity in obesity and the dynamic increase in EELV during exercise optimized airway function and allowed the increased tidal volume expansion during exercise without further compromising respiratory muscle function.

Figure 2 Tidal flow–volume loops at rest, ventilatory threshold, and peak exercise plotted within the respective maximal flow–volume loops in typical obese and normal-weight women



The lean participant increased tidal volume by encroaching on the inspiratory reserve volume with little change in end-expiratory lung volume. In contrast, the obese female started with significant tidal expiratory flow limitation at rest and experienced a large increase in dynamic end-expiratory lung volume (EELV) from rest to peak exercise. VTh, ventilatory threshold. Reproduced with permission from [19].

The combined effects of chronic obstructive pulmonary disease and obesity on respiratory physiology

Although both COPD and obesity are common health problems that have been studied extensively in isolation, the impact of their combination on respiratory pathophysiology and symptom intensity is unknown. It has been reported that a relatively high percentage of COPD patients are also obese, with some reports showing a prevalence of 18% [51] and others showing a prevalence of 54% [52]. The pathophysiological hallmarks of COPD are expiratory flow limitation and lung hyperinflation [53,54]. Preliminary studies indicate that the presence of airway obstruction does not alter the relationship between increasing BMI and lung volumes (ERV and functional residual capacity) seen in health [27••,31•]. In other words, these lung volume components also decrease exponentially as BMI increases in patients with

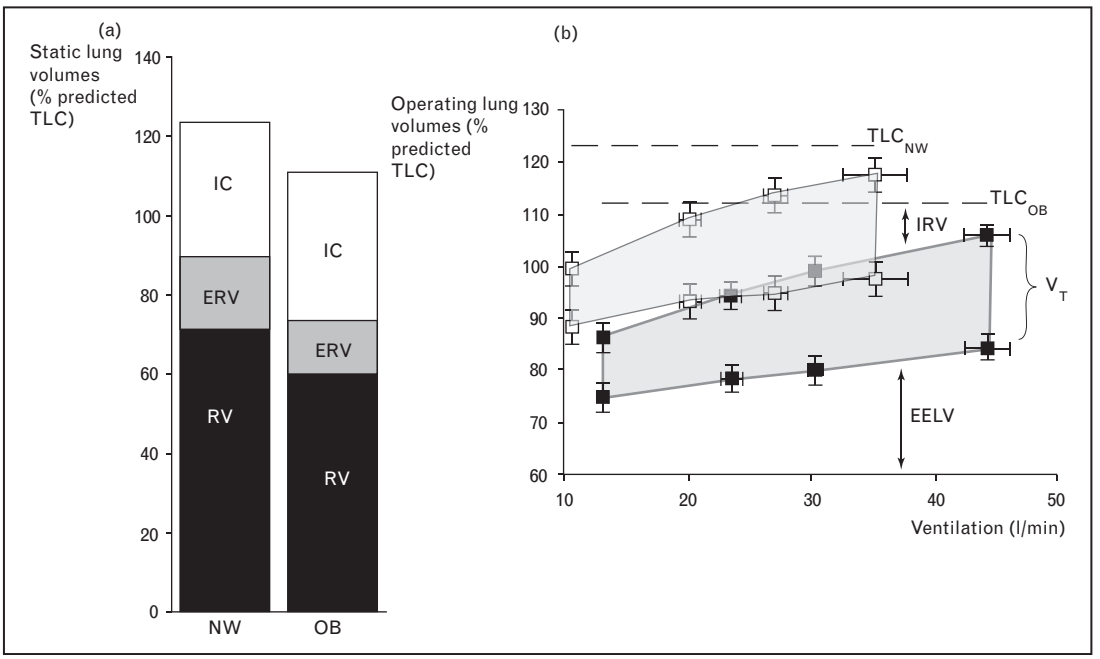
COPD. Obese COPD patients consistently demonstrate less lung hyperinflation and have a larger inspiratory capacity and inspiratory capacity/TLC ratio than their lean counterparts matched for FEV_1 [27••]. It is conceivable that, collectively, these physiological alterations convey potential advantages during physical activity.

Impact of obesity on dyspnea and exercise tolerance in chronic obstructive pulmonary disease

In normal-weight patients with COPD (compared with health), the increased ventilatory demand of exercise (amplified by ventilation–perfusion abnormalities) results in dynamic pulmonary hyperinflation, which precipitates mechanical limitation and intolerable dyspnea at relatively low ventilations. In COPD, the severity of exertional dyspnea and exercise intolerance is closely linked to the magnitude of reduction in the resting inspiratory capacity and its further rate of decline during exercise as a result of dynamic hyperinflation [54].

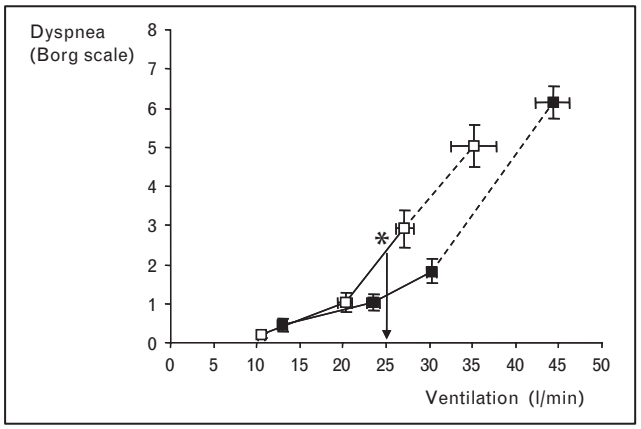
It is reasonable to anticipate that when the derangements of dynamic ventilatory mechanics of COPD are coupled with the increased metabolic demands and mass loading effects of obesity, dyspnea and exercise intolerance would increase [55,56]. Ora *et al.* [27••] postulated that in obese COPD patients, the relatively reduced EELV at rest and during exercise would partly counterbalance the negative sensory and mechanical consequences of severe lung hyperinflation present in FEV_1-matched nonobese patients with COPD. To test this hypothesis, these investigators compared dyspnea intensity ratings and ventilatory responses (breathing pattern and operating lung volumes) during symptom-limited incremental cycle exercise in well characterized groups of 18 obese ($BMI = 35 \pm 4\ kg/m^2$; mean ± SD) and 18 normal-weight ($BMI = 22 \pm 2\ kg/m^2$) patients with moderate to severe COPD [27••]. The obese COPD group had a significantly smaller resting EELV, ERV, and TLC (expressed as % predicted) and the inspiratory capacity/TLC ratio was significantly larger compared with normal-weight COPD (Fig. 3). The dynamic EELV was lower (expressed as % predicted TLC) at rest and throughout exercise in obese compared with normal-weight COPD (Fig. 3). Nevertheless, the rate of air-trapping or dynamic lung hyperinflation during exercise was similar in both groups. Obese COPD participants also had a significantly greater ventilation and oxygen uptake (expressed in l/min) at rest and throughout exercise compared with normal-weight COPD controls. Despite these effects, the combination of obesity and COPD was not associated with diminished exercise capacity or greater dyspnea at any work rate compared with normal-weight COPD individuals. In fact,

Figure 3 Static and rest to peak exercise lung volumes



(a) Static lung volumes measured by body plethysmography at rest. Expiratory reserve volume (ERV) and functional residual capacity (ERV + residual volume) were significantly lower in the obese group (OB) than in the normal weight (NW) group. (b) Lung volumes from rest to peak exercise in obese (black squares) and normal weight (white squares) patients with chronic obstructive pulmonary disease (COPD). End-expiratory lung volume (EELV) [standardized as a percentage of predicted total lung capacity (TLC)] was consistently lower at rest and throughout exercise in the obese than in the normal weight group. IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; V_T, tidal volume (shaded area). Values are mean ± SE. Reproduced with permission from [27••].

Figure 4 Relationship between dyspnea and minute ventilation in obese and normal-weight patients with chronic obstructive pulmonary disease



At a similar minute ventilation of 25 l/min (vertical line with arrow), dyspnea intensity was 1.2 ± 1.1 versus 2.4 ± 1.6 Borg units in the obese (black squares) versus normal-weight (white squares) individuals, respectively ($^{*}P < 0.01$). Reproduced with permission from [27••].

symptom-limited peak oxygen uptake (standardized as a percentage of the predicted normal value corrected for ideal body weight) was greater in the obese versus the nonobese COPD group. Moreover, in obese COPD individuals, dyspnea intensity ratings were reduced at any given ventilation or oxygen uptake compared with normal-weight COPD individuals (Fig. 4). A strong correlation ($r = 0.67$, $P < 0.00001$) was found between ratings of dyspnea intensity at a standardized ventilation and resting and dynamic EELV/TLC ratio in the whole group. The authors reasoned that the relatively reduced EELV at rest and throughout exercise (and the attendant advantages with respect to diaphragmatic function) were the most likely contributory factors to the reduced dyspnea intensity in obese COPD individuals. More recently, Laviolette *et al.* [57••] extended these observations in a larger population of COPD patients with a wide range of BMI values during constant load cycling. Again in that study obese patients with COPD were not at a disadvantage relative to their normal weight COPD counterparts and had a higher peak oxygen uptake. It is important to point out, however, that these findings occurred during weight-supported cycle exercise and may be different during weight-bearing exercise (i.e. treadmill) where the increased metabolic demands of obesity would be further exaggerated.

Static lung hyperinflation and survival in chronic obstructive pulmonary disease: the possible influence of obesity

Is it conceivable that the relatively reduced lung hyperinflation (and increased inspiratory capacity/TLC ratio) in overweight patients with COPD may carry some prognostic advantages? Indices of resting static lung hyperinflation such as inspiratory capacity and the inspiratory capacity/TLC ratio have emerged as independent predictors of increased respiratory and all-cause mortality in patients with COPD [58,59]. Thus, an inspiratory capacity/TLC ratio less than 25% was associated with very poor survival. However, the precise mechanisms underlying the association between lung hyperinflation and death from cardiovascular causes are unknown. It is noteworthy that improved respiratory system mechanics following lung volume reduction surgery was associated with improved survival in selected patients with advanced emphysema [60].

A reduced inspiratory capacity (expressed as % predicted or as a fraction of TLC) correlated well with poor peak symptom-limited oxygen uptake during incremental cycle exercise [61,62] – another independent predictor of poor survival in COPD [63]. The corollary is also true – that small improvements in inspiratory capacity following pharmacological or surgical lung volume reduction have been associated with improved exercise performance in COPD [64–67]. Thus, it is not unreasonable to postulate that obesity-associated lung volume reduction with consistently increased inspiratory capacity compared with lean patients with COPD may have some similar long-term benefits.

Conclusion

In western countries, 'the obese COPD patient' has emerged as an increasingly common clinical phenotype. It is clear that being underweight or having a low fat-free mass is associated with poor survival in COPD. By contrast, obesity is a recognized risk factor for insulin resistance, obstructive sleep apnea, and cardiovascular disease. Moreover, excessive abdominal fat may directly release pro-inflammatory cytokines that contribute to a systemic inflammatory syndrome in COPD [7•,68]. It is surprising, therefore, that an increased BMI appears to be associated with improved survival at least in patients with more advanced COPD. The pathophysiological basis for this apparent obesity paradox is unknown.

Is it possible that obesity-induced modification of the natural history of deteriorating respiratory system mechanics is sufficient to counterbalance the known deleterious systemic effects of obesity? A fundamental question is whether the reported benefits of an increased BMI in this population are derived from an increased fat-free skeletal muscle mass, from the effects of excessive adipose tissue on the mechanics of the respiratory system, or some combination of both. Prospective longitudinal studies that examine the interaction of changes in body composition and the temporal progression of pulmonary

function decline (after controlling for the relevant comorbidities) are needed to better understand this intriguing relationship between increased BMI and survival in COPD populations.

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 744–745).

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