Respiratory Medicine
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Anne E. Dixon
Erick Forno *Editors*

Obesity and Lung Disease

A Guide to Pathophysiology, Evaluation, and Management

Second Edition

ATS American Thoracic Society

Humana Press

Respiratory Medicine

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ISSN 2197-7372 ISSN 2197-7380 (electronic)
Respiratory Medicine
ISBN 978-3-031-52695-4 ISBN 978-3-031-52696-1 (eBook)
https://doi.org/10.1007/978-3-031-52696-1

This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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Effects of Obesity on Lung Function

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A. E. Dixon, E. Forno (eds.), *Obesity and Lung Disease*, Respiratory Medicine,
https://doi.org/10.1007/978-3-031-52696-1_1

Introduction

The accumulation of adipose tissue, leading to the development of obesity, has a profound effect on human physiology, including significant effects on respiratory function due to the mechanical effects of excess adipose tissue on the balance of forces that normally act on the lung. In addition, adipose tissue produces hormones and other mediators, collectively termed adipokines, which are associated with low-grade systemic inflammation that can act indirectly on the respiratory system. However, at present, it is unclear whether this causes any measurable impairment in respiratory function. The changes in lung function associated with obesity can lead to respiratory symptoms in otherwise healthy people, which are accentuated in those with respiratory disease, as a result of interaction between disease pathophysiology and the direct and indirect effects of obesity. The outcomes of this interaction are complex and differ according to the disease and the outcome of interest. The major effects of obesity on lung function are summarized in Fig. 1.1 and suggest that, at least in adults and older adolescents, many of the changes in lung function result from changes in respiratory system mechanics and reduction in operating lung volume, whereas others may be due to other non-volume-related factors. In this chapter, the effects of obesity on lung function and the relationships

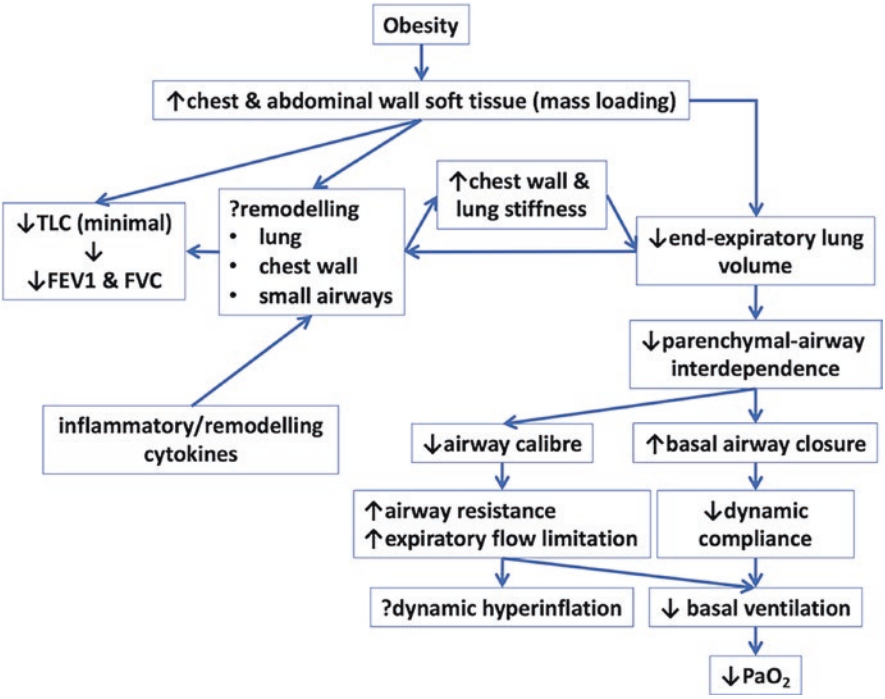

Fig. 1.1 The effects of obesity on lung function, illustrating likely mechanisms. See text for more detailed discussion

summarized in Fig. 1.1 will be reviewed along with the effects of these impairments on respiratory symptoms. Some of the changes in lung function seen with obesity in the paediatric population will be covered in Chap. 16 later in this book.

Adipose Tissue and Respiratory Mechanics

In adults over age 20, obesity is defined as a body mass index (BMI) >30 kg/m^2. However, BMI is a non-specific measure of body mass that includes both fat and lean mass, without any account of differences in fat distribution. Central obesity is associated with increased adipose tissue in the anterior chest and abdominal walls and visceral organs, whereas peripheral obesity reflects adiposity located peripherally on limbs, or in subcutaneous tissue. The effect of obesity on respiratory function is likely to be determined by the distribution of fat mass. Therefore, the increase in abdominal and chest wall fat in central obesity is more likely to push the chest wall inwards and push the diaphragm in a cranial direction, thus reducing thoracic volume at functional residual capacity (FRC) and expiratory reserve volume (ERV). A reduction in FRC is the most recognized abnormality in lung function due to obesity, but it varies greatly between individuals—there being only a moderate relationship with BMI [1]. The heterogeneity in lung volume response is likely due to variations in total fat mass, distribution of that fat, effects of ageing on the mechanical properties of the lung, airways and chest wall, and variations in chest and lung compliances. In addition, visceral fat is more metabolically active than subcutaneous fat, and its increase or dysfunction may therefore make a greater contribution to low-grade systemic inflammation in obesity. Adipose tissue is also found inside the thoracic cavity, predominantly as pericardial fat, which, when combined with obesity-associated increase in the volume of the heart and major blood vessels, can reduce the volume of the thoracic cavity [2].

Intra-abdominal and Intrathoracic Pressures

Obesity is associated with chronic increases in intra-abdominal pressure that may affect the pleural space by altering pressure across the diaphragm. Intra-abdominal pressure is increased in obese subjects compared to non-obese [3, 4] and is greater in men than women [4], likely due to the greater prevalence of central obesity in men. Indeed, intra-abdominal pressure correlates with markers of central obesity, such as the sagittal abdominal diameter [3, 4]. In addition, in contrast to intra-abdominal pressure, studies in supine anaesthetized subjects [3, 4] have shown that abdominal obesity, measured by waist circumferences and by sagittal abdominal diameter, is not correlated with pleural pressures. Since the relationship between abdominal pressure and pleural pressure is mediated by the diaphragm, the lack of correlation between the two may be due to compensatory increase in passive tension in the diaphragm in response to increased intra-abdominal pressure in the obese. Alternatively, factors other than increased abdominal pressures, such as changes in

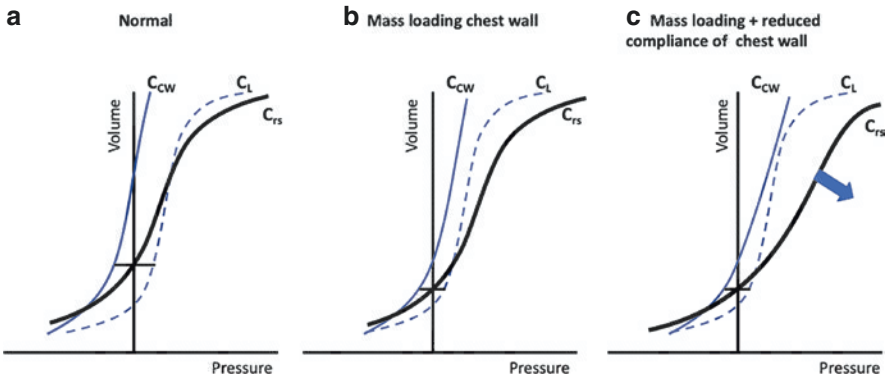

Fig. 1.2 Compliance curves for the chest wall (C_{CW}), lung (C_L) and respiratory system (C_{rs}) in normal-weight (**a**) and obese individuals (**b**, **c**). Functional residual capacity (FRC) as indicated by the solid line, where C_{rs} is zero, is reduced in the obese individual. C_{rs}, which is represented by the slope of the linear portion, of the solid line above FRC, is reduced

the mechanical properties of the chest wall, may also contribute to the altered lung volumes in obesity. Imaging studies of abdominal and thoracic fat have shown that both regions make a significant contribution to impairments of lung function in the obese [5].

Pleural pressures are also increased (i.e. less negative) in obese compared to non-obese adults at FRC. This is likely due to a rightward shift of the pressure-volume curve of the chest wall due to mass loading (i.e. compliance is unchanged; see below and Fig. 1.2) such that the outward recoil pressure from the chest wall is reduced at any given volume, which lowers FRC, thus raising pleural pressure by being on the lower part of the lung's pressure-volume curve. However, pleural pressure at FRC may even exceed atmospheric pressure in the dependent parts of the lungs [3, 4], which would occur with greater mass loading of the chest wall and with reduced lung elastic recoil (which would occur with age). The functional consequence is closure of small airways with potential effects on gas exchange and inspiratory threshold loading (increased inspiratory effort required to overcome the positive pressure for lung inflation to occur).

Respiratory System Compliance

One might expect that the stiffness (or its inverse being compliance) of the respiratory system, which comprises the lungs and chest wall, may be increased in obesity, due to structural alterations associated with obesity. There are, however, only a few studies that examine this, which are old and involve few subjects, with varying methodologies. Measurements of chest wall compliance require an absence of respiratory muscle activity since muscle activity stiffens the chest wall, which is difficult to achieve in non-paralysed subjects. Furthermore, supine oesophageal measurements in obesity pose problems of measurement noise and interpretation.

This probably explains the conflicting findings from those few studies. Taken together, data suggest that both chest wall and lung stiffness may be increased in some obese subjects, with considerable heterogeneity between individuals which has not been explored. What is important however, from a clinical standpoint, is not whether chest wall or lung mechanics are altered, but that there is considerable variation in mechanical alterations due to obesity, which will have variable effects on symptoms and underlying disease.

There are two seminal studies looking at respiratory system compliances in awake obese individuals; both are from the 1960s and performed in adults [6, 7]. With small numbers of $n = 12$ obese subjects in upright and supine positions [6] and $n = 15$ obese subjects in supine posture [7], oesophageal pressures were measured over a range of lung volumes, which were induced by either sucking or blowing air into a 'tank respiratory' (or 'iron lung') [7] or a body plethysmograph [6] to achieve passive inflation or deflation. This allowed subjects to remain in the 'relaxed' state where respiratory muscles were not activated. In both studies, chest wall compliance was decreased, particularly in those with obesity-hypoventilation syndrome [6]. In a more recent study of 14 obese, seated males, using a different methodology, chest wall compliance was not affected by obesity [8]. There are three studies of obese subjects under anaesthesia and paralysis, which removed respiratory muscle contribution to chest wall compliance [9–11]. Chest wall compliance was reduced in two studies by the same group [10, 11], but was normal in the other [9].

The results of studies looking at lung compliance are also conflicting. Lung compliance was normal in the two studies from the 1960s [6, 7], as well as in a subsequent study of nine subjects [12]. The studies of anaesthetized and paralysed individuals, however, revealed reduced lung compliances [9–11]. Again, these conflicting results need to be interpretated in light of the methodological challenges. Static lung compliance is measured as the slope of volume versus pressure, over an arbitrary volume starting at end-expiratory lung volume where the relationship should be linear. However, airway closure makes the curve 'S' shaped, becoming flatter (lower compliance) at lower lung volumes (which is what typically happens to FRC in obesity), and so compliance measurements are affected by the volumes over which they are calculated [12]. Increased pulmonary blood volume [13] and increased alveolar surface tension due to a reduction in FRC may also potentially contribute. Differences in methodology between studies including differences in posture, effects of anaesthesia and mechanical ventilation and patient selection mean that no strong conclusions can be made about whether obesity has any effect on lung compliance.

Aside from uncertainties of whether chest and lung compliances are reduced in obesity, the effects of mass loading seem much clearer. This is purely the effect of greater weight on the chest wall and abdomen, which compresses the respiratory system (reducing FRC) and increases the work of breathing, independently of any change in compliance. Mass loading experiments suggest that loading the chest wall produces a rightward shift of the chest wall's pressure-volume curve (see Fig. 1.2b) without a change in shape (compliance) [14]. FRC is decreased, and the respiratory system compliance curve, which is the summation of the chest wall and lung curves,

is also right-shifted and the slope (compliance) may or may not be affected. Mass loading of the abdomen, however, does reduce the compliance of the chest wall (Fig. 1.2c) [14], which would then alter total respiratory system compliance. Thus, during inspiration, the pressure required for any given tidal inspiration is greater, due to the summation of mass loading effects on the chest wall and abdomen. The differential effects of obesity on the chest wall versus abdomen may also partly explain the conflicting results in the literature.

Lung Volumes

Relaxation Volume: FRC

Obesity has a major effect on resting lung volume, causing a reduction in lung volume at relaxation, when the recoil pressures of the lung and chest wall are equal and opposite (Fig. 1.2). The relaxation volume of the lung usually equates to the functional residual capacity (FRC), which is very commonly reduced in obesity [1, 10]. FRC is exponentially related to BMI [1, 10], with reduction in FRC being detected even in overweight individuals [1]. This is illustrated in Fig. 1.3, which shows the relationship between BMI and FRC in a study of young adults, aged 28–30 years [15]. The reduction in FRC is also manifested by an increase in inspiratory capacity (IC). With increasing severity of obesity, the reduction in FRC may become so marked that the FRC approaches residual volume (RV), leaving the individual with a negligible expiratory reserve volume (ERV) [1]. In fact, in many studies, the reduction in ERV is one of the earliest and most marked changes in lung function that occurs with increasing weight [16].

The relationship between BMI and FRC, shown in Fig. 1.3, is steeper in men than in women. This difference in slope is likely to result from differences in the prevalence of central obesity between men and women. Central obesity, associated

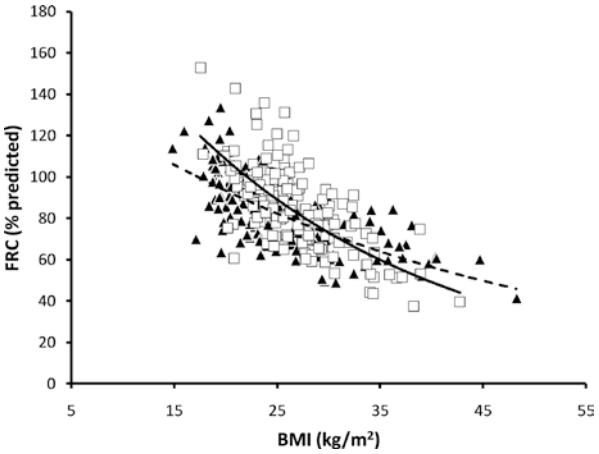

Fig. 1.3 Relationship between BMI and FRC in young men (open squares, solid line) and women (solid triangles, dashed line)

with greater fat deposition on the trunk and abdomen, is likely to have a greater effect on respiratory system compliance than peripheral fat distribution. Reductions in lung volumes are associated with both abdominal fat, measured by waist circumference [17], waist-to-hip ratio [18] or abdominal height [19], and thoracic or upper body fat, measured by sub-scapular skinfold thickness [20] or biceps skinfold thickness [16]. Sutherland et al. [5] used a wide range of body fat variables to determine the effect of fat distribution on lung volumes in healthy adults. Lung volumes were only loosely associated with BMI; however, both dual-energy X-ray absorptiometry (DEXA) and non-DEXA-derived measures of upper body fat showed highly significant negative correlations with FRC and ERV in both men and women. Both abdominal obesity and thoracic fat mass were similarly correlated with lung volumes. Improvements in lung volumes such as FVC, FRC and ERV, following moderate weight loss, were related to the cumulative loss of fat from the chest and subcutaneous abdominal and visceral fat, all of which may affect the mechanical function of the respiratory system [21].

Total Lung Capacity

In contrast, the effects of obesity on the upper and lower limits of lung volumes, total lung capacity (TLC) and RV are modest. Increasing body weight is associated with only small decrease in TLC [1, 22, 23], and RV is usually well preserved but may even be reduced in severe obesity [2, 22, 24–26]. As a result, the RV/TLC ratio remains normal or slightly increased in obese individuals [1, 25].

The magnitude of the reduction in TLC with increasing weight is proportionally smaller than the effect on FRC, at least until BMI exceeds 35 kg/m^2 [1]. Lung restriction of the magnitude associated with restrictive lung disease, defined as TLC below the lower limit of normal, is not commonly associated with obesity in the absence of other diseases. Prospective studies show that TLC increases with weight loss in both mild [27] and morbidly obese [28] subjects.

The reduction in TLC in the obese is likely at least partly due to impaired downward movement of the diaphragm, due to increased abdominal mass and/or compliance, which limits the room for lung expansion on inflation. In addition, deposition of fat in sub-pleural spaces [29] or elsewhere in the intrathoracic cavity might directly reduce lung volume by reducing the volume of the chest cavity. An exploratory study to investigate the mechanism for reduced TLC in obesity used MRI to measure intrathoracic volumes in obese and non-obese men and found increased mediastinal volume in the obese due to an increase in the volume of intrathoracic fat, the heart and major blood vessels [2]. At full inflation, the proportion of the intrathoracic volume occupied by inflated lungs was only 78% of the total in the obese compared with 88% in the controls, suggesting that the increased mediastinal volume may prevent full lung expansion in the obese and may therefore explain the slight loss of TLC with increasing BMI. However, the marked loss of TLC in obese subjects with lung restriction (TLC <80% predicted) was not explained by increased mediastinal volume, suggesting that other factors, such as reduced expansion of the

thoracic cage and reduced diaphragmatic excursion, may also be important in this subgroup [2]. Since respiratory muscle strength and maximum inspiratory and expiratory pressures have been shown to be intact in obesity [24, 30, 31], it is unlikely that these would be an important determinant of obesity-related reduction in TLC.

Spirometry

Vital capacity (VC) is reduced due to a small reduction in TLC, but relative preservation of RV. There is a progressive linear decrease in VC with increasing BMI that parallels the decrease in TLC [1]. Similarly, increasing BMI is also associated with a decrease in both FEV1 and FVC [26, 32, 33]. However, this effect is small, and both FEV1 and FVC are usually within the normal range in healthy obese adults [32, 33] and children [34]. As a result, the FEV1/FVC ratio, which is a marker of airway obstruction, is usually well preserved or increased [20, 26, 33–35], even in morbid obesity [25]. Figure 1.4 shows data from a population of 1971 adults aged between 17 and 73 years [32] based on the per cent of predicted values. Although FVC is affected to a greater extent than FEV1 as BMI increases, FEV1/FVC ratio remains normal across the weight groups, even in the severely obese group. Studies looking at the effect of body fat distribution on spirometry have shown that abdominal obesity is a stronger predictor than either weight or BMI of reductions in FEV1 and FVC [19, 36], with one very large study of over 130,000 people suggesting that abdominal obesity may also be a risk for reduced FEV1/FVC ratio [36]. Moreover, weight gain following smoking cessation [37] or with increasing age [38] is associated with reductions in both FEV1 and FVC; the effect is greater on FVC than on FEV1 and greater in men than women, presumably because men gain more abdominal fat than women. It is important to note that these findings may differ in children, in whom FEV1 and FVC may actually be high among those with obesity, with greater increases

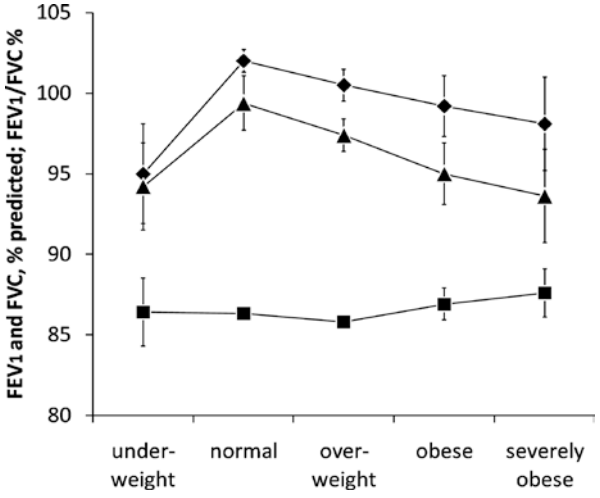

Fig. 1.4 Mean spirometric values, according to weight category, in adults (adapted from data in Schachter et al. Thorax 2001). FEV1 (diamonds) and FVC (triangles), as per cent predicted, and FEV1/FVC (squares) as a percentage

in FVC which nonetheless lead to a subnormal FEV1/FVC ratio, in a pattern that has been thought to result from airway dysanapsis [39]. It is unclear how or when spirometric patterns transition from this dysanaptic relationship (high FEV1 and higher FVC leading to low FEV1/FVC) to the restrictive deficit seen in adults.

Breathing Pattern

Increased stiffness of the respiratory system is likely to induce a rapid shallow pattern of tidal breathing, which is a typical response to an elastic load [40]. Indeed, previous studies have shown that tidal volumes are often reduced in severe obesity, and breathing follows a rapid, shallow pattern [24]. This alteration to breathing pattern is most apparent during exercise, when obese subjects preferentially increase their breathing frequency more, and tidal volumes less, than non-obese subjects [41, 42]. In mild-moderate obesity, tidal volumes at rest are often in the normal range [42–45], and the frequency and magnitude of regular sighs and deep inspirations appear similar to those in normal-weight subjects [43, 45]. Thus, obesity has a minor effect on breathing pattern and is only seen in severe obesity or when the system is under stress, such as during exercise or bronchoconstriction.

Peripheral Airway Function: Oscillometric Impedance and Nitrogen Washout

Since airway calibre is related to lung volume, reduction in FRC in the obese has significant effects on airway resistance and reactance during tidal breathing. Respiratory oscillometry produces parameters of respiratory system resistance (an index of airway calibre) and respiratory system reactance (an index of airway closure and severe narrowing—or lung de-recruitment) [46–49], both parameters being highly sensitive to heterogeneity in regional ventilation (regional time constants) [50]. Since reactance at common oscillometry frequencies (5–11 Hz) is dominated by dynamic lung compliance, frequency dependence of reactance is equivalent to frequency dependence of compliance, usually measured using an oesophageal balloon at differing respiratory rates. Frequency dependence of compliance has also been considered to indicate heterogeneity in regional time constants and, hence, small airway disease [51]. By extension, reactance indicates the same.

In addition to age, BMI and height are independent predictors of reactance in normative values, while weight and height are independent predictors of resistance [52]. Resistance is increased and reactance is decreased in obese compared with non-obese subjects [26, 44, 48, 53]. Although undoubtedly lung volume is a strong determinant of resistance and reactance, which may explain these relationships, there is evidence that lung volume changes do not fully explain those abnormalities. This suggests that there are mild or subtle abnormalities of airways, probably the peripheral airways, specific to obesity, or that there are other unmeasured effects of obesity on the lung, such as increased heterogeneity of regional ventilation.

Specific airway resistance in obese subjects, which is adjusted for lung volume, is in the normal range [26, 31, 35, 54]. However, in a study of 276 healthy subjects aged between 28 and 30 years, specific conductance (the inverse of volume-adjusted resistance) correlated independently with BMI [15], after adjustment for known predictors (height and sex). Similar findings were reported from a small study comparing oscillatory resistance between obese and non-obese healthy subjects [55] that lung volumes only partly explained differences. Using multiple breath nitrogen washout as a measure of peripheral airway dysfunction, BMI was the sole predictor after adjustments for anthropometric factors and smoking [48].

Respiratory system reactance is abnormal in the obese [44, 48, 53], but the significance of this is not clear. The relationship between reactance and lung volume is such that it suddenly and dramatically decreases around closing volume [48, 56]. Therefore, reactance is severely impaired (very negative) when FRC encroaches upon closing volume [48, 57]. However, closing volume is normal in obesity [48, 58]. Therefore, abnormal reactance is probably explained by reductions in FRC, which bring it into the vicinity of closing volume, but without any increases in closing volume itself.

There is consistent evidence that if the FRC is very low, such that closing capacity exceeds the FRC, airway closure can occur during tidal breathing (see Fig. 1.5) [48, 58–60]. Closing capacity, and particularly the extent to which closure occurs within the range of tidal breathing, has been correlated with arterial PO_2 [58, 59]. Other consequences include atelectasis if insufficient deep breaths are taken, e.g. during illness and bed rest.

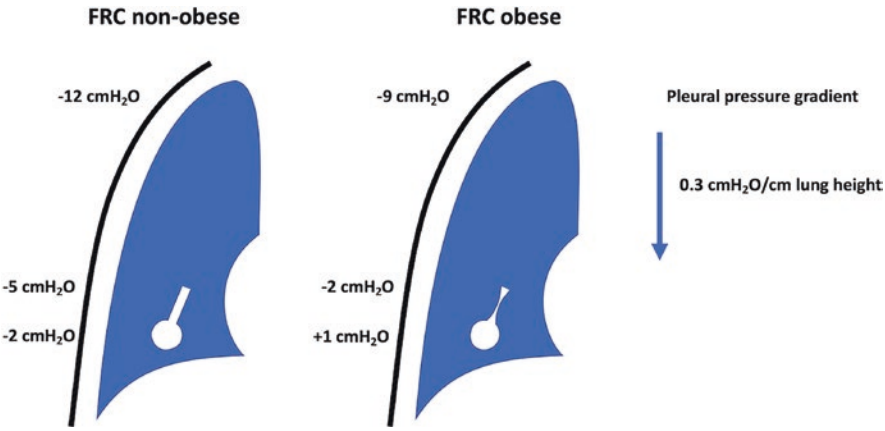

Fig. 1.5 Hypothetical gradients of pleural pressures in non-obese and obese subjects at FRC. Assuming a normal pleural pressure gradient in obesity, reduction in FRC increases pleural pressure and any particular gravitational lung zone, such that pressures at the lung base may even be positive, which promotes airway closure and expiratory flow limitation

Expiratory Flow Limitation During Tidal Breathing

Expiratory flow rates are closely related to lung volumes, so that maximal flow decreases rapidly as expired volume approaches RV. As shown in Fig. 1.6, the predicted maximal flow, shown in the dashed line, is maintained well above the flows generated during tidal expiration at normal FRC, but the obese subject, breathing tidally at very low FRC, has very little expiratory flow reserve available during tidal breathing. For the obese individual, breathing at low lung volume places the tidal flow volume loop in a region where it may encroach on the maximal flow, thus increasing the risk of tidal expiratory flow limitation.

Two studies [61, 62], using the negative expiratory pressure technique, have found evidence of expiratory flow limitation in 20% of severely obese subjects when upright. However, both expiratory flow limitation and breathlessness substantially increased when the subjects were placed supine. Quantification of expiratory flow limitation from the flow volume loop, as the percentage of the tidal volume that encroached on the maximal flow envelope, shows highly significant differences between obese and normal-weight women when seated at rest [42].

Respiratory oscillometry can also be used to detect expiratory flow limitation during tidal breathing [63], as the difference between inspiratory and expiratory reactance. However, this technique was developed in subjects with COPD, and it has not been validated in any other condition. With this limitation in mind, a study of 23 obese subjects without airway disease [64] found that the inspiratory-expiratory difference was higher in the obese compared with non-obese group but did not reach the threshold previously found to indicate expiratory flow limitation. Importantly, however, after methacholine-induced airway narrowing, expiratory flow limitation developed in 9/23 obese individuals compared with none of the non-obese group, despite similar falls in FEV.

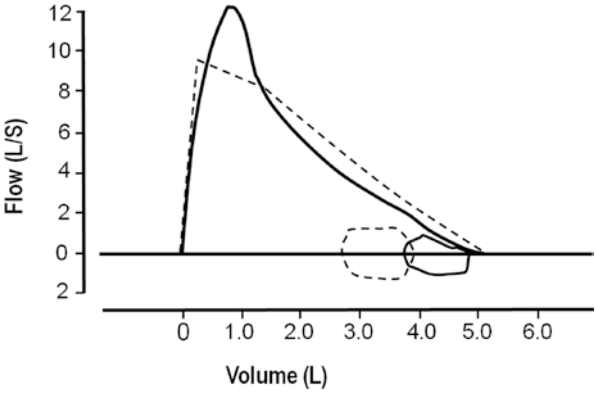

Fig. 1.6 Flow volume loop from a healthy, obese individual (BMI = 43). The dashed lines show the predicted normal flow volume and tidal loops. There is minimal airway obstruction, but because FRC is low, the tidal loop encroaches onto the maximal loop, putting this individual at risk of expiratory flow limitation during tidal breathing

Intrinsic PEEP and Dynamic Hyperinflation

The presence of expiratory flow limitation during tidal breathing promotes the development of intrinsic positive end-expiratory pressure (iPEEP) and dynamic hyperinflation in obstructive airway disease, where it is an important determinant of respiratory symptoms. Pankow et al. [62] were able to detect iPEEP in all six severely obese subjects in whom they were able to make the measurement, even in the absence of expiratory flow limitation. The mechanism for iPEEP in the absence of EFL is unknown but could be due to persistent post-inspiratory activity of the diaphragm, which has previously been observed in severely obese subjects [24]. iPEEP is a potential cause of respiratory symptoms in the obese since it is an additional elastic load that must be overcome at the beginning of each inspiration.

Obese individuals are more prone to dynamic hyperinflation during exercise and bronchoconstriction, because of reduced FRC and expiratory flow limitation, airway closure and iPEEP during tidal breathing. High-dose methacholine challenge in obese and normal-weight, non-asthmatic subjects resulted in significantly greater hyperinflation, with obese subjects starting from a lower baseline FRC [44]. This was also associated with greater perception of breathlessness. End-expiratory lung volume increases only slightly during exercise in obesity, and breaths are more flow limited at rest and during unweighted (cycling) exercise [42, 65], but this is not associated with any greater breathlessness at equivalent work rates, compared with normal-weight subjects [42, 66, 67].

Breathless During Exercise

Breathlessness during exercise is a common complaint among obese individuals. In population studies, subjects with the highest BMI quintile have the greatest risk of dyspnoea with exertion, despite being at least risk of airway obstruction. Standardized weight-bearing exercise tests, such as the 6-minute walk test, show that exercise capacity is reduced in obese adults [68, 69] and children [70] compared to normal-weight controls. However, increased exertional symptoms in the obese are most likely due to the increased metabolic cost of the energy needed to move heavy limbs and drive the respiratory muscles [71], rather than due to deconditioning or abnormalities of airway or lung mechanics. Studies using weight-supported exercise, such as with a cycle ergometer, show that peak exercise capacity, in terms of both peak work rate and oxygen consumption, is normal in healthy obese subjects suggesting that they are not deconditioned [42, 66, 67].

The ventilatory response to inhaled CO_2 [41] and the relationships between oxygen consumption and minute ventilation, and between breathlessness and both oxygen consumption and minute ventilation, are all normal in the obese [42]. Because obese subjects have an increase in inspiratory reserve due to reduced FRC, there is sufficient reserve to increase tidal volumes to meet ventilatory demands [42, 65]. Taken together, these observations suggest that the ability of the obese to increase ventilation in response to increasing metabolic demand is not impaired and that

changes in lung volumes or airway mechanics due to obesity make little contribution to respiratory discomfort during exercise.

Ventilation Distribution

Regional ventilation measured in obese individuals using 2-dimensional ventilation imaging [72–74], and more recently with 3-dimensional imaging technology [53], consistently shows that ventilation is reduced at the lung bases, but increased in the upper zones. This is likely due to the relationships between FRC and closing capacity described above, such that greater reductions in FRC increase the likelihood of basal airway closure, hence causing a relative diversion to the upper zones [73]. Regional changes in respiratory system compliance or mass loading might also affect basal lung expansion; however, there are no published data on these potential mechanisms.

Gas Exchange

Mild hypoxaemia and increased alveolar-arterial oxygen difference are frequently reported, even in eucapnic obese individuals [9, 10, 28, 58, 75], and have been associated with abdominal obesity in the morbidly obese [76]. Reduction in oxygenation is unlikely to be due to abnormalities of gas transfer since most studies suggest that DLCO is normal [7, 23, 41, 77], even in morbid obesity [25]. Indeed, some studies suggest that DLCO is increased in extremely obese subjects [23, 35], probably as a result of the increase in blood volume [23].

Regional ventilation-perfusion mismatch in the dependent zones of the lung is a potential determinant of hypoxaemia in obese individuals. Although an increase in blood volume in the obese could improve the homogeneity of perfusion and increase perfusion in the apices of the lung, the distribution of perfusion is predominantly to the lower zones, and individuals with reduced ventilation in the lung bases are likely to be at risk of ventilation-perfusion mismatch [73]. The extent to which gas exchange abnormalities in the obese are reversible is unclear, since some weight loss studies show improvements in arterial oxygen tensions [28, 60, 78] while others report no change [27, 79]. Hakala et al. [79] found no increase in oxygenation with weight loss, even though there were significant improvements in FRC and most subjects no longer had closing capacities above FRC.

Effects of Obesity on Respiratory Function in Disease

The detrimental effects of obesity on lung function may have an impact on the outcomes of respiratory disease, although the effects are complex. In asthma, obesity is associated with greater prevalence and incidence of the disease [32, 34, 80] and may also be associated with worse clinical outcomes [81, 82], particularly in mild [83]

or well-controlled [84] disease. In COPD, increasing BMI is associated with a reduced risk of death in patients with more severe disease, but not in those with mild COPD [85]. Although these relationships appear paradoxical, the mechanical effects of obesity on lung function are likely to be important contributing factors to many of the effects of obesity in respiratory disease.

How could the mechanical effects of obesity on lung function modify asthma pathophysiology? Asthma is characterized by airway obstruction, airway inflammation and airway hyperresponsiveness. One hypothesis suggests that breathing at reduced tidal volumes could affect the contractility of airway smooth muscle, thereby increasing the responsiveness of the muscle [86]. However, if this does contribute to the clinical expression of asthma, it does not affect airway hyperresponsiveness in the obese since the severity of AHR is not increased in the obese [54, 83, 87, 88]. Moreover, there is inconsistent evidence of an association between BMI and airway responsiveness in studies of random populations [32, 34, 89]. An alternative hypothesis is that the reduction in operating lung volume in the obese has the potential to amplify the symptoms associated with bronchoconstriction. Bronchoconstriction in the obese is associated with increased airway closure compared to non-obese controls [90], and thus the mechanical consequences of bronchoconstriction could be greater on the obese. Bronchoconstriction at low lung volume increases the risk of expiratory flow limitation and causes greater dynamic hyperinflation in obese asthmatic [87] and non-asthmatic [44] subjects, which may increase the severity of dyspnoea [91]. Greater elastic loading during bronchoconstriction because of hyperinflation, reflected by greater changes in respiratory system reactance in obese than non-obese subjects [44, 45] but not detected by changes in FEV1, may explain why some obese asthmatics have more severe symptoms than their lean counterparts, despite similar change in spirometry [92].

In COPD, it has been proposed that reduced operating lung volumes in obese patients may provide a mitigating influence on the intensity of exertional dyspnoea, by counterbalancing the negative mechanical consequences of severe lung hyperinflation [93, 94]. Because the obese COPD patients start from a much reduced FRC, dynamic hyperinflation during exercise does not result in such severe loss of inspiratory reserve as in non-obese COPD patients. The interactions between obesity and respiratory disease are discussed in detail in later chapters.

In restrictive lung disease, increased BMI is associated with better survival in patients with idiopathic pulmonary fibrosis [95–97].

Interpretation of Lung Function

Obesity has surprisingly little effect on spirometry, lung volumes and diffusing capacity for carbon monoxide. Therefore, significant restriction with abnormally low TLCs or diffusing capacity should indicate that diagnoses other than obesity may be present. The effects on peripheral airway function (oscillometric impedance and ventilation heterogeneity measured by inert gas washout) are greater. However,

there are relatively few published normative values for these parameters, which makes considering the effects of obesity as possible causes of abnormal tests more important. Confidence of the limits of normality for standard lung function tests is less at the extremes of age and height, and obesity may add further to the uncertainty in these individuals, which should be considered when interpreting their lung function results.

Acknowledgements Dr. Cheryl Salome and Professor Norbert Berend co-wrote the first original version of this chapter. Dr. Salome in particular is acknowledged for doing the bulk of the work in the original chapter, as well as for her incredible contribution to respiratory science.

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Obesity-Mediated Alterations in Immune Function, Host Defense, and Lung Disease

2

Anna Reichenbach, Silvia Cabrera Guerrero, and Deepa Rastogi

Contents

Introduction

Obesity is one of the foremost chronic conditions affecting the human race globally [1]. Its burden has worsened due to the COVID-19 pandemic [2]. Myriad diseases have been associated with obesity, which influences all systems in the body [3]. Although its effects on the cardiovascular and endocrine systems were among the initial ones to be described, there is abundant literature on the adverse effects of obesity on the respiratory system [4].

Obesity influences organ function through many different mechanisms [5], one of which is via its effects on the immune system. Immune responses are classified as either "innate" or "adaptive," in which the former are nonspecific defense mechanisms utilized early on following exposure to various environmental antigens, while

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A. E. Dixon, E. Forno (eds.), *Obesity and Lung Disease*, Respiratory Medicine,
https://doi.org/10.1007/978-3-031-52696-1_2