

Laboratory Department, Division of  
Clinical Physiology and Nuclear Medicine  
and  
Department of Medicine, Division of Pulmonary Medicine,  
Helsinki University Central Hospital, Helsinki, Finland

**PULMONARY MECHANICS AND GAS EXCHANGE  
IN OBESITY**

**Effects of weight reduction and body position**

Katri Hakala

Academic Dissertation

To be publicly discussed, by the permission of the Medical Faculty of the  
University of Helsinki, in Lecture Room 2, Meilahti Hospital,  
Haartmaninkatu 4, Helsinki, on October 20<sup>th</sup>, 2000, at 12 o'clock

Helsinki 2000

## **SUPERVISED BY:**

Anssi R. A. Sovijärvi  
Professor of Clinical Physiology  
University of Helsinki  
Helsinki, Finland

Brita Stenius-Aarniala  
Professor of Pulmonary Medicine  
University of Helsinki  
Helsinki, Finland

## **REVIEWED BY:**

Ritva Tammivaara  
Docent of Clinical Physiology  
University of Uppsala and  
Docent of Pulmonary Medicine  
University of Turku  
Turku, Finland

Hannu Puolijoki  
Docent of Internal Medicine  
University of Tampere  
Tampere, Finland

## **OPPONENT AT THE DISSERTATION:**

Jaakko Hartiala  
Docent of Clinical Physiology  
University of Turku  
Turku, Finland

ISBN 952-91-2599-2 (nid.)  
ISBN 952-91-2600-X PDF (pdf)  
<http://ethesis.helsinki.fi>  
Yliopistopaino, Helsinki

*To my family*

# CONTENTS

<b>LIST OF ORIGINAL COMMUNICATIONS.....</b>	<b>7</b>
<b>ABBREVIATIONS.....</b>	<b>9</b>
<b>INTRODUCTION.....</b>	<b>11</b>
<b>REVIEW OF THE LITERATURE.....</b>	<b>12</b>
1. OBESITY.....	12
1.1. Definition and classification of obesity.....	12
1.2. Prevalence of obesity.....	13
1.3. Respiratory complications of obesity.....	13
1.4. Weight loss and pulmonary function .....	18
2. POSTURAL CHANGES IN RESPIRATORY FUNCTION.....	21
2.1. Normal subjects.....	21
2.2. Obesity.....	22
3. OBSTRUCTIVE SLEEP APNEA AND OBESITY.....	23
3.1. Obesity and upper airways.....	24
3.2. Obesity induced hypoxemia in OSAS.....	25
3.3. Obesity and ventilatory responsiveness in OSAS.....	25
3.4. The effect of posture on OSAS.....	26
3.5. Treatment of OSAS and daytime oxygenation.....	26
3.6. The effect of weight loss on OSAS.....	26
4. ASTHMA.....	27
4.1. Mechanical factors regulating airway caliber.....	27
4.2. Small airway disease in asthma.....	28
4.3. Lung volumes .....	29
4.4. Peak flow variability.....	30
4.5. Airways size and bronchial hyperresponsiveness....	31
5. ASTHMA AND OBESITY .....	31
5.1. Association between asthma and obesity.....	32
5.2. Weight loss in obese asthmatics .....	33

## CONTENTS

---

<b>AIMS OF THE STUDY.....</b>	<b>34</b>
<b>PATIENTS AND METHODS.....</b>	<b>35</b>
1. Patients.....	35
2. Methods.....	38
3. Study designs.....	41
4. Statistical methods.....	43
5. Ethical considerations.....	43
<b>RESULTS.....</b>	<b>44</b>
1 Body fat distribution and pulmonary function.....	44
2. Weight loss and pulmonary function.....	46
3. Arterial oxygenation.....	49
4. Weight loss and PEF variability .....	52
5. Respiratory gas exchange.....	53
<b>DISCUSSION.....</b>	<b>56</b>
1. Study population and methods.....	56
2. Lung volumes and obesity.....	58
3. Arterial oxygenation and obesity.....	59
4. Respiratory gas exchange and obesity.....	60
5. Asthma and obesity.....	60
<b>SUMMARY.....</b>	<b>64</b>
<b>CONCLUSIONS.....</b>	<b>66</b>
<b>ACKNOWLEDGEMENTS.....</b>	<b>67</b>
<b>REFERENCES.....</b>	<b>69</b>
<b>ORIGINAL COMMUNICATIONS.....</b>	<b>83</b>

## LIST OF ORIGINAL COMMUNICATIONS

- I            Hakala K, Mustajoki P, Aittomäki J, Sovijärvi ARA.  
Effect of weight loss and body position on pulmonary function  
and gas exchange abnormalities in morbid obesity.  
Int J Obes 1995;19:343-346
- II            Hakala K, Mustajoki P, Aittomäki J, Sovijärvi ARA.  
Improved gas exchange during exercise after weight loss in  
morbid obesity.  
Clin Physiol 1996;16:229-238
- III           Hakala K, Maasilta P, Sovijärvi ARA.  
Upright body position and weight loss improve respiratory  
mechanics and daytime oxygenation in obese patients with  
obstructive sleep apnoea.  
Clin Physiol 2000; 20: 50-55
- IV           Hakala K, Stenius-Aarniala B, Sovijärvi ARA.  
Effects of weight loss on peak flow variability, airways  
obstruction, and lung volumes in obese patients with asthma.  
Chest 2000; In press
- V            Hakala K, Stenius-Aarniala B, Sovijärvi ARA.  
Breathing pattern and gas exchange in obese asthmatics.  
Submitted

The original communications are reproduced with permission of the copyright holders. In addition some unpublished data have been included in the study.



## ABBREVIATIONS

- BMI = Body mass index  
 BF = Breathing frequency  
 CV = Closing volume  
 CC = Closing capacity = CV+RV  
 ERV = Expiratory reserve volume  
 FETCO<sub>2</sub> = End expiratory tidal CO<sub>2</sub> fraction  
 FEV<sub>1</sub> = Forced expiratory volume in one second  
 FIV<sub>1</sub> = Forced inspiratory volume in one second  
 FRC = Functional residual capacity  
 FVC = Forced vital capacity  
 MMEF = FEF<sub>25-75</sub> = Flow rate at the middle part of FVC  
 MEF<sub>50</sub> = Maximal flow at a volume of 50% of FVC  
 MEF<sub>25</sub> = Maximal flow at a volume of 25% of FVC  
 MVV = Maximal voluntary ventilation  
 ODI<sub>4</sub> = The number of 4 percent or greater desaturation events per hour in bed  
 PaO<sub>2</sub> = Arterial oxygen tension  
 PaCO<sub>2</sub> = Arterial carbon dioxide tension  
 P(A-a)O<sub>2</sub> = Alveolar arterial O<sub>2</sub> difference  
 PEF = Peak expiratory flow  
 PIF = Peak inspiratory flow  
 Raw = Airways resistance  
 RR = Respiratory rate  
 RV = Residual volume  
 SGaw = Airways conductance  
 TLC = Total lung capacity  
 VAS = Visual analogue scale  
 VE = Minute ventilation  
 $\dot{V}E/\dot{V}CO_2$  = Ventilatory equivalent for CO<sub>2</sub>  
 $\dot{V}E/\dot{V}O_2$  = Ventilatory equivalent for O<sub>2</sub>  
 VLCD = Very-low-calorie-diet  
 $\dot{V}O_2$  = oxygen uptake, oxygen consumption  
 $\dot{V}CO_2$  = carbon dioxide output, carbon dioxide production  
 VT = Tidal volume



## INTRODUCTION

Obesity is one of the most frequently found health risks and the prevalence of obesity appears to be increasing all over the world (Seidell et al. 1998, WHO: Obesity, 1998). In Finland, as in most European countries, one-fifth of adults are obese, with body mass index (BMI) more than 30 kg/m<sup>2</sup> (Pietinen et al. 1996). Health risks increase with increasing degree of obesity (Bray et al. 1998).

Obesity is associated with increased risks of respiratory symptoms, including shortness of breath and wheezing (Lean et al. 1999). The most characteristic changes in pulmonary function in obese persons are decreased functional residual capacity (FRC) and expiratory reserve volume (ERV) (Luce 1980, Ray et al. 1983). Pulmonary function abnormalities are more common in central obesity (Collins et al. 1995, Lazarus et al. 1997 and 1998). Recently, it has been questioned whether the effect of obesity on pulmonary function is simply a mechanical one or if it is one more consequence of central obesity (Sue 1997).

Obesity is regarded as a major risk factor for obstructive sleep apnea syndrome (OSAS) (Guilleminault et al. 1988, Douglas et al. 1994). In weight loss studies, a significant improvement in both symptoms and objective findings of OSAS after weight reduction has been demonstrated (Strobel et al. 1996, Lojander et al. 1998). Recently, increasing epidemiological evidence has suggested that there is an association between asthma and obesity (Shaheen 1999a, Wilson et al. 1999). At present, it is not possible to say whether obesity has contributed to the rise in asthma prevalence or whether asthma patients gain weight as a result of activity limitations or some other reasons.

The isolated effects of obesity on respiratory function must be known in order to evaluate the contribution of obesity to the dysfunction seen in different respiratory diseases. The studies in this thesis were designed to evaluate the effects of dietary induced weight loss on respiratory complications of obesity and further to determine the impact of obesity on respiratory function in OSAS patients and in asthmatics. Especially, gas exchange in response to standing up and during exercise was studied in order to find characteristic features of hypoxemia associated with obesity.

# REVIEW OF THE LITERATURE

## 1. OBESITY

### 1.1. Definition and classification of obesity

Obesity is defined as an excessive accumulation of fat that causes a generalized increase in body mass. Several definitions and cutoff points have been used to define overweight and the degree of obesity. The most commonly used indicator of general adiposity is body mass index (BMI), calculated as weight in kilograms divided by the square of the height in meters. World Health Organization (WHO) (1995) and National Institutes of Health (NIH) (1998) have recommended the classification of BMI using cutoff points of 25 kg/m<sup>2</sup> and 30 kg/m<sup>2</sup>, i.e. overweight BMI 25-30 kg/m<sup>2</sup>, and obesity BMI of 30 kg/m<sup>2</sup> or higher.

The risks of morbidity and mortality seem to increase with increasing BMI. Classification of obesity based on BMI and health risk described by Bray (1985)(Table 1) is widely used in Europe.

**Table 1.** Classification of obesity (Bray, 1985).

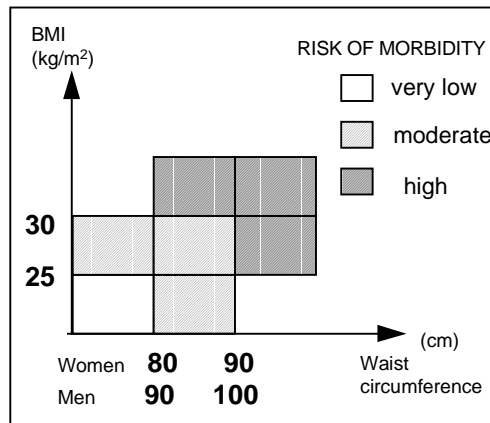
BMI (kg/m <sup>2</sup> )	Class	Health risk
BMI < 25	normal weight	very low
25 ≤ BMI < 30	overweight	low
30 ≤ BMI < 35	moderate obesity	moderate
35 ≤ BMI < 40	severe obesity	high
40 ≤ BMI	morbid obesity	very high

In addition to the degree of obesity, the distribution of excess fat affects the health risks of obesity. Several cardiovascular and metabolic complications are related to abdominal visceral obesity (Björntorp 1996, Seidell et al. 1999). A commonly used measure of body fat distribution is the waist-to-hip ratio (WHR). WHR over 0.95 in men and over 0.80 in women indicates increased

risk of cardiovascular and metabolic disturbances (Björntorp 1996, Seidell et.al 1999). Poulriot et al. (1994) reported that waist circumference better than WHR correlates with the amount of visceral fat, especially in women. The use of BMI and waist circumference together as a measure for the assessment of health risks of obesity is illustrated in Figure 1.

**Figure 1.**

The association of BMI and waist circumference with the risk of morbidity (Fogelholm et al. 1998).



### 1.2. Prevalence of obesity

Obesity is an increasing health problem all over the world (Seidell et al. 1998, WHO: Obesity, 1998). In ten years the prevalence of obesity has increased by 10 - 40 % in most European countries. In 1997 in Finland the prevalence of obesity (BMI > 30 kg/m<sup>2</sup>) was 19 % in adult population (Lahti-Koski et al. 1999). The prevalence of overweight (BMI > 25 kg/m<sup>2</sup>) was 48 % among men and 32 % among women aged 30 - 59 years.

In terms of medication, provision of health services, and absences from work, the overall costs of obesity are considerable. The estimated health care costs of obesity in 1997 in Finland were 0.9 - 3.2 billion marks, representing 1.4 -7.0 % of the total costs of health care (Pekurinen et al. 2000).

### 1.3. Respiratory complications of obesity

The most common medical problems attributed to obesity include non-insulin dependent diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and osteoarthritis (Rissanen et al. 1990, Manson et al. 1990 and 1995). Less known, but no less important, are the effects of obesity on respiratory

physiology (Strohl et al. 1998). Body fat distribution may have simple mechanical effects on lung volumes. Fat stored within the abdominal cavity, abdominal wall and chest wall is likely to directly compress the thoracic cage, diaphragm, and lung and reduce lung volumes (Sue 1997). Conversely, it has been postulated that adipose tissue added to the lower body would be too distant to affect lung volumes. Overall obesity and the pattern of fat distribution may have independent effects on ventilatory function (Lazarus et al. 1997). Collins et al. (1995) reported that high WHR was inversely related to spirometric and static lung volumes. But is the effect of abdominal body fat distribution on lung function simply a mechanical one? While mechanisms connecting cardiovascular and metabolic risks of abdominal obesity to pulmonary function are not known, adverse effects on pulmonary function may be one more consequence of central obesity (Sue 1997).

### *Respiratory symptoms*

Overweight and obesity are associated with increased risks of respiratory symptoms (Sahebji 1998). The prevalence of symptoms increases with increasing BMI (Lean et al. 1999) or waist circumference (Lean et al. 1998). In the cross-sectional survey of 5887 men and 7018 women aged 29 to 59 years from the Netherlands there were 45 % men and 31 % women with a BMI 25 - 30 kg/m<sup>2</sup>, and 11 % men and 11 women with a BMI  $\geq$  30 kg/m<sup>2</sup>. The prevalence of wheezing and shortness of breath when walking uphill / upstairs increased with increasing BMI. The odds ratios in those with a BMI over 30 kg/m<sup>2</sup> or higher were 3.5 (95% CI, 2.8-4.4) in men and 3.3 (95% CI, 2.8-3.9) in women for shortness of breath compared with the reference group of BMI below 25 kg/m<sup>2</sup>. The odds ratios for wheezing were 1.5 (95% CI, 1.13-2.0) in men and 1.99 (95% CI, 1.55-2.57) in women respectively (Lean et al. 1999).

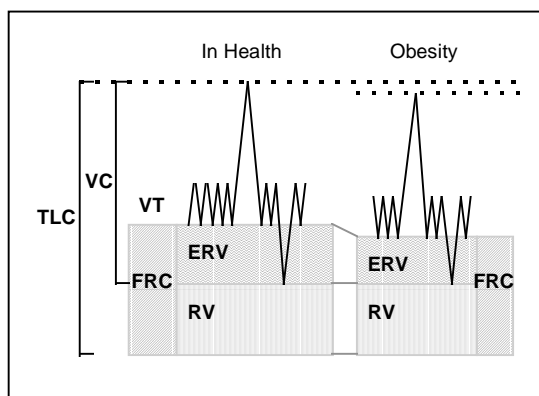
### *Lung volumes and expiratory flow rates*

The most common abnormality in pulmonary function recognized in obesity is a decrease in expiratory reserve volume (ERV) and functional residual capacity (FRC) (Ray et al. 1993, Sahebji et al. 1996, Biring et al. 1999). In mild to moderate obesity VC and TLC are usually within normal range, but in morbid obesity they may be reduced by 20-30 % compared to predicted values (Zerah et al. 1993). Ray et al. (1983) emphasized that only in extreme obesity TLC and VC may be reduced. According to some other studies, however, the decrease in lung volumes has been in proportion to the degree of obesity (Zerah et al. 1993, Strohl et al. 1998). In addition, Zerah et al. (1993) showed

that changes in FRC, ERV, VC and TLC correlated with each other. In general, residual volume (RV) is not reduced in obesity. It has been assumed (Sharp et al. 1964a) that mass loading of chest wall with limited function of expiratory muscles as well as high closing volume in relation to ERV help to maintain residual volume even in morbid obesity. RV related to TLC (RV/TLC) may even be higher than normal in morbid obesity (Ray et al. 1983).

**Figure 2.** Summary of the effects of obesity on lung volumes.

VC = Vital Capacity  
 TLC = Total Lung Capacity  
 FRC = Functional Residual Capacity  
 ERV = Expiratory Reserve Volume  
 RV = Residual Volume  
 VT = Tidal Volume



Recently, the longitudinal relationship between adiposity and  $FEV_1$  was investigated in a national study of British adults (Carey et al. 1999). The follow-up period was 7 years. Changes in weight or BMI were related to changes in  $FEV_1$ . The authors concluded that increase in body mass is a predictor of  $FEV_1$  decline, especially in older and heavier men. Several studies have reported that with increasing BMI the decrease in  $FEV_1$  is in proportion to the change in FVC (Rubinstein et al. 1990), so that the  $FEV_1 / FVC$  ratio usually remains normal (Thomas et al. 1989).

Expiratory flow rates at low lung volumes ( $FEF_{25-75}$ ) may decrease with increasing obesity suggesting narrowing of the small airways (Rubinstein et al. 1990). It is possible that narrowing of the peripheral airways is associated with increased bronchial responsiveness. While using  $FEF_{25-75} / FVC$  ratio as a measure of airways size related to lung size, Litonjua et al. (1999) found a significant association between  $FEF_{25-75} / FVC$  and methacholine airway responsiveness. Exercise induced bronchospasm (EIB) has been studied in obese children aged 6 to 10 years (Kaplan et al. 1993). The degree and frequency of EIB was higher in obese compared to non-obese children. The

causal relationship between obesity and bronchial hyperresponsiveness has not yet been proved. Whether EIB leads to exercise avoidance and obesity, or whether obesity increases bronchial responsiveness needs further studies.

### *Closing volume, air trapping, and gas exchange*

Closure of peripheral airways within dependent lung regions occurs in normal subjects during a maximal expiration. Closing volume (CV) is defined as the lung volume at which this closure occurs (Leblanc et al. 1970). The relationship of closing volume to ERV is important when we evaluate the tendency to increased small airway closure in obesity (Farebrother et al. 1974). When ERV is reduced, closing volume approaches or exceeds ERV so that small airways may close within tidal breathing (Craig et al. 1971). Don et al. (1971) have demonstrated regional gas trapping when CV was equal to or greater than ERV. A further decrease in CV / ERV ratio has been observed in supine position, and with age (Collins et al. 1973). Airways closure is an important mechanism capable of impairing gas exchange (Craig et al. 1971, Douglas et al. 1972). In early studies of Holley et al. (1967), a significant pulmonary ventilation and perfusion abnormality was reported in obese patients with low ERV ( $< 0.4$  l or 21% predicted). The distribution of tidal breathing in upright position was mainly to the upper lung zones, whereas perfusion was maximal to the lung bases (Holley et al. 1967, Barrera et al. 1973). Farebrother et al. (1974) demonstrated that hypoxemia in obese patients was related to the closure of dependent airways within the range of tidal breathing.

### *Respiratory and airways resistance*

Several studies have demonstrated the influence of lung volume on the resistance of respiratory system (Rrs). With the reduction in lung volume induced by different methods i.e. supine position or rib cage strapping, increase in Rrs has been observed (Van Noord et al. 1986, Navajas et al. 1988, Lorino et al. 1992). Zerah et al. (1993) showed increase in respiratory resistance as well as in airways resistance (Raw) with increasing obesity. A linear relationship was found between airways conductance (Gaw) and FRC. The authors suggested that obesity is associated with an increased respiratory resistance resulting from the reduction in lung volumes.

The dependence of pharyngeal area on lung volumes has been observed in healthy subjects (Brown et al. 1986a). The dilating effect of lung inflation on

intrapulmonary airways has been established (Series et al. 1990). On the contrary, pharyngeal size decreases with decreasing lung volumes (Brown et al. 1986b). By this mechanism reduced FRC found in obesity may cause pharyngeal narrowing contributing to increased airways resistance.

### *Oxygen cost of breathing and breathing pattern*

Morbidly obese patients are known to have increased metabolic demands because extra muscle work must be performed to move an obese body (Dempsey et al. 1966, Luce 1980). Rates of total oxygen consumption ( $\dot{V}O_2$ ) and carbon dioxide production ( $\dot{V}CO_2$ ) are increased even at rest in obesity (Zavala et al. 1984, Refsum et al. 1990). To meet these increased requirements, minute ventilation has to be increased. Minute ventilation at rest is high in obese patients compared with normal subjects (Burki et al. 1984). To maintain augmented ventilation, extra work has to be done because oxygen cost of breathing is high in obesity (Kress et al. 1999). It has been assumed that reduced chest wall compliance associated with the accumulation of fat increases ventilatory load thereby increasing the work of breathing (Luce 1980). There are also several studies on respiratory muscle dysfunction in obesity (Wadström et al. 1991, Weiner et al. 1998). Reduced chest wall compliance in obesity or low lung volumes may cause inefficiency of respiratory muscles (Luce 1980). Recently, Weiner et al. (1998) demonstrated a significant improvement in respiratory muscle performance after weight loss in patients with morbid obesity. The predominant change was improvement in respiratory muscle endurance.

In non-obese persons oxygen cost of breathing ( $\dot{V}O_{2\text{RESP}}$ ) as a percentage of total body  $\dot{V}O_2$  at rest is estimated to be less than 3% (Robertson et al. 1977). Results of the study of Sharp et al. (1964b) suggested that obese subjects have total respiratory work values up to twice normal. Kress et al. (1999) studied the impact of morbid obesity on resting oxygen cost of breathing. The study group consisted of 18 morbidly obese patients with the mean BMI of 53.4 (13.9)  $\text{kg/m}^2$ . When  $\dot{V}O_{2\text{RESP}} / \dot{V}O_2$  was assumed as 3% in normal subjects, obese patients exhibited a fivefold increase in  $\dot{V}O_{2\text{RESP}} / \dot{V}O_2$ .

Tendency to rapid shallow breathing pattern has been observed in morbid obesity (Kaufman et al. 1959, Salvadori et al. 1993). It has been assumed that for a given  $\dot{V}E$ , breathing with high frequency (BF) and lower tidal volume (VT) may decrease oxygen cost of breathing (Luce 1980). However, with

increasing ventilation when BF rises and dead space (VD/VT) increases, rapid breathing may become unfavorable (Misuri et al. 2000).

Increased ventilatory responsiveness to hypoxia has been observed in morbidly obese patients who maintain adequate alveolar ventilation and are eucapnic (Burki et al. 1984, Chapman et al. 1990, Babb et al. 1991). It is now well recognized that in obesity hypoventilation syndrome (OHS), patients fail to meet the increased demands for ventilation associated with obesity. Ventilatory responsiveness to hypercapnia has been observed to decrease in OHS (Rochester et al. 1974, Gold et al. 1993). There are studies suggesting that this diminished responsiveness is acquired. Hypoventilation may be an adaptive process sparing O<sub>2</sub> for non-ventilatory demands (Luce 1980).

#### **1.4. Weight loss and pulmonary function**

The aim of the studies evaluating the effect of weight loss on pulmonary function in obesity has been on one hand to demonstrate the effect of obesity on pulmonary function and to clarify pathophysiological mechanisms behind these disturbances. On the other hand respiratory complications increase the risks of obesity and should be improved or abolished if the treatment of obesity is regarded as effective. Most of the weight loss studies have been made in patient groups with morbid obesity. Conservative treatment of morbid obesity has demonstrated limited success and the maintenance of the weight loss results have been poor (Pekkarinen 1999, Mustajoki et al. 1999). Therefore, morbidly obese patients are often candidates for surgical treatment of obesity. However, patients may be reluctant to undergo surgery and all are not eligible for surgery.

Very-low-calorie diet (VLCD) has appeared to be more effective than conventional diets (Anderson et al. 1992). Combining VLCD with behavior therapy (BT) has improved the long term maintenance (Pekkarinen et al. 1997, Pekkarinen 1999). VLCDS are defined as diets that contain energy of 3.36 MJ (800kcal) or less and high quality of protein 0.8-1.5 g/kg of ideal weight daily (National Task Force 1993). The carbohydrate content is 50-100 g daily and minerals, vitamins, electrolytes and essential fatty acids are according to the Recommended Dietary Allowances. The patients drink a minimum of two liters of non-caloric beverages daily (National Task Force 1993). Normally VLCDS replace food for 4 to 16 weeks, followed by a structured refeeding period. Side effects during VLCD are usually minor and transient. Weakness, dizziness, constipation, dry skin, hair loss and cold intolerance may occur, but

when used for carefully selected patients under professional supervision VLCDs are usually safe and effective. VLCDs are often combined with behavior therapy.

According to National Institutes of Health Consensus Conference 1991 candidates for the surgical treatment of obesity are: patients with BMI > 40 kg/m<sup>2</sup>; BMI > 35 kg/m<sup>2</sup> together with severe comorbidity; unsuccessful conservative weight loss efforts; well motivated patients; commitment to a long-term follow-up, and understanding the operative risks and eating limitations after surgery. Gastric bypass (GBP) and vertical banded gastroplasty (VBG) are the two procedures recommended for the treatment of the severe to morbid obesity. They have turned out to be safe and effective in long term.

#### *Improvement in pulmonary function and gas exchange after weight loss*

The most striking effect of weight loss in morbid obesity has been the increase in lung volumes, particularly in ERV or FRC (Table 2). Several studies have reported a significant increase in maximal voluntary ventilation (MVV) (Ray et al. 1983, Refsum et al. 1990, Wadström et al. 1991). RV usually remains unchanged, or only a slight increase has been observed. Consequently, changes in FRC reflect changes in ERV. The improvement in oxygenation is assumed to result from the increase in ERV. However, several studies have not been able to show improvement in oxygenation despite a remarkable increase in ERV. Farebrother et al. (1974) reported that improvement in PaO<sub>2</sub> occurred if the final weight was within 30% in excess of the ideal. Respiratory muscle performance, i.e. muscle strength and endurance, improves with weight loss. Weiner et al. (1998) studied morbidly obese patients before and six months after bariatric surgery (VBG) (Table 2). Maximal inspiratory mouth pressure (P<sub>I</sub>max) and expiratory pressure (P<sub>E</sub>max) were measured as well as inspiratory muscle endurance. The improvement in respiratory muscle performance correlated with weight loss. Refsum et al. (1990) (Table 2) have studied the effect of weight loss on ventilation and pulmonary gas exchange at rest. Minute ventilation ( $\dot{V}E$ ) and resting metabolic rate ( $\dot{V}O_2$ ) declined after weight loss.  $\dot{V}O_2$  related to body weight was low before weight loss and increased with weight reduction. The change in  $\dot{V}E$  was first of all due to a fall in tidal volume (VT). This data gave no support to the concept that obesity leads to rapid shallow breathing.

**Table 2.** The effect of weight loss on pulmonary function and gas exchange

Study	No	Age years	Sex F / M	Smoking	Weight (kg) Before w.l. After w.l.	BMI (kg/m <sup>2</sup> ) Before w.l. After w.l.	Weight loss (kg)	% Change from baseline	Treatment
<b>Emirgil et al, 1973</b>	4	26-48	2 / 2	-	<u>155 (114-192)</u> 106 (85-133)	<u>49.1 (40.5-57.5)</u> 33.7 (30.5-40.0)	49.1(28.1-68.0)	ERV + 157 * PaO <sub>2</sub> + 7 ns	Diet
<b>Farebrother at al, 1974</b>	8	24-56	4 / 4	8 / 8	<u>120 (107-143)</u> 86 (68-101)	<u>42.1 (36.5-45.7)</u> 30.9 (25.4-34.9)	33.6 (18.1-74.8)	ERV + 65 * PaO <sub>2</sub> + 11 ns	Diet
<b>Vaughan et al, 1981</b>	11	21-51	34 / 3	0 / 37	<u>139 (4)SEM</u> 88 (5)SEM	<u>50 (1)SEM</u> 31 (1)SEM	52 (2)SEM	ERV + 71 * PaO <sub>2</sub> + 5 ns	Surgery
<b>Ray et al, 1983</b>	29	19-32	21 / 8	-	<u>160 (5) SEM</u> 106 (6) SEM	<u>56.7 (1.8) SEM</u> 37.4 (2.1) SEM	54	ERV + 48 * MVV + 10 *	Diet
<b>Thomas et al, 1989</b>	29	18-56	?	14 / 29	<u>126 (92-174)</u>	-	34.2	ERV + 54 * TLC + 14 * PaO <sub>2</sub> + 23 *	Surgery
<b>Refsum et al, 1990</b>	34	20-59	34 / 0	-	<u>113.2 (84-156)</u> 81.7 (60-110)	<u>40.9 (33-50)</u> 29.7 (22-38)	31.5	ERV + 71 * TLC + 6 * MVV + 10 * PaO <sub>2</sub> + 6 * VO <sub>2</sub> - 23 * VE - 17 * VT - 10 *	Surgery
<b>Wadström et al, 1991</b>	16	27-49	13 / 3	-	125 (17)	42.8 (6.2)		FRC + 16* TLC + 4* MVV + 14 *	Surgery
<b>Weiner et al , 1998</b>	21	25-52		-	-	<u>41.5 (1.3) SE</u> 31.7 (1.1) SE		ERV + 16 * RV + 11 * TLC + 9 * PImax + 23 * PEmax + 15 *	Surgery

\* statistically significant

## 2. POSTURAL CHANGES IN RESPIRATORY FUNCTION

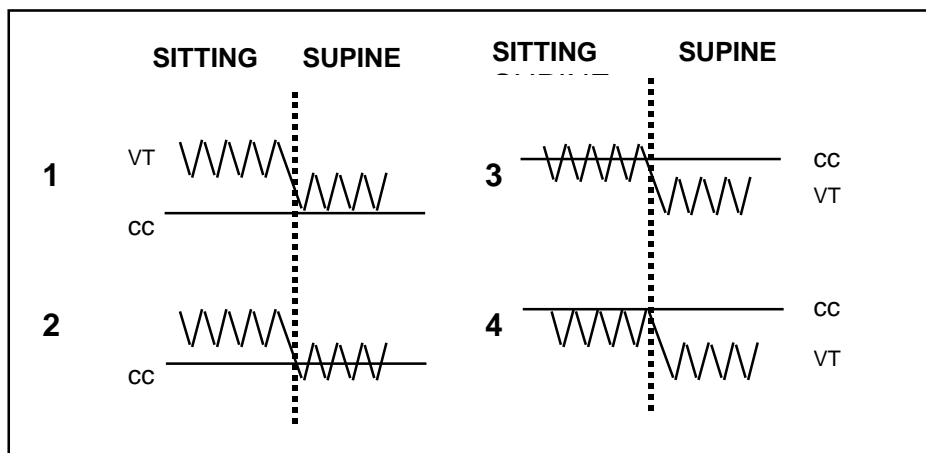
### 2.1. Normal subjects

Lung volumes are slightly but significantly higher in standing position (Townsend et al. 1984, Appel et al. 1986). American Thoracic Society (1995) and European guidelines (Quanjer et al. 1993) recommend that measurements of lung volumes and forced ventilatory flows are made in seated upright body position; other positions should be noted. In normal subjects there is a reduction in FRC and an increase in airways resistance in response to changing posture from sitting to supine. It has been assumed that most of this reduction results from gravitational effects on the abdominal pressure (Moreno et al. 1961). Lung compliance decreases in supine body position probably reflecting increased pulmonary blood volume and small airways closure (Behrakis et al. 1983). Body position can modify the generation of maximal inspiratory ( $PI_{max}$ ) and expiratory ( $PE_{max}$ ) pressures. Reductions in pressures have been observed in response to change of posture from sitting to supine (Fiz et al. 1990 and 1991).

As early as forty years ago, Moreno et al. (1961) studied the effect of body position on breathing pattern and  $O_2$  consumption in normal subjects. A significant decrease in tidal volume was demonstrated when changing posture from sitting to supine. The respiratory rate remained unchanged, while minute ventilation decreased in supine position. A decrease in  $O_2$  consumption was found in response to change of posture from sitting to supine. The relationship of FRC to closing capacity ( $CV + RV$ ) is an important determinant of airway closure and consequent hypoxemia. The change of posture from sitting to supine is associated with the decrease in FRC, CV may remain unchanged or decrease only slightly (Don et al. 1971). In those subjects in whom this decrease places FRC below CC, the volume of trapped gas increases (Don et al. 1971).

Craig et al. (1971) examined the hypothesis that increase in CC above FRC would result in a shunt-like effect and increase in alveolar arterial oxygen difference  $P(A-a)O_2$ . Measurements were done in sitting and supine positions (Figure 3). In those subjects (**1**, in Figure 3) in whom CC did not exceed FRC in either position  $P(A-a)O_2$  decreased in supine position. When closing capacity occurred in the breathing range in supine position (**2**, in Figure 3)  $P(A-a)O_2$  was elevated in this position. As CC exceeded FRC in both

positions (4, in Figure 3),  $P(A-a)O_2$  increased and was higher than in the other groups. It changed only slightly with posture in this group. When subjects in this study were grouped only according to age, weight, or smoking history, no postural change in gas exchange was observed.



- |   |  |
|---|--|
| <p>1. <math>FRC &gt; CC</math> in both positions;</p> <p>2. <math>CC &gt; FRC</math> in supine position</p> | <p>3. <math>CC &lt; FRC + VT</math> in sitting position &amp;<br/><math>CC &gt; FRC + VT</math> in supine position</p> <p>4. <math>CC &gt; FRC + VT</math></p> |
|---|--|

**Figure 3.** Relationship of closing capacity to tidal breathing (Craig et al. 1971).  
VT = tidal volume CC = closing capacity.

Closing capacity increases with age (Leblanc et al. 1970, Collins et al. 1973, Estenne et al 1985). Leblanc et al. (1970) have reported that in normal subjects CC exceeds FRC by about 40 years of age in the supine position, and by 65 years of age in the sitting position. These studies indicate the importance of evaluating the results of blood gas analysis with reference to posture, especially in elderly subjects.

## 2.2. Obesity

In obese subjects reduction in FRC and ERV measured in sitting position would be expected to increase in supine position because of the cranial movement of diaphragm that is enhanced by increased mass of abdomen. Yap et al. (1995) failed to demonstrate any further fall in ERV in supine position.

In this study, however, ERV was very low both in supine and standing positions when compared to control subjects in whom adoption of supine posture caused a significant reduction in ERV.

There are few studies of respiratory compliance (Crs) in obese subjects. Naimar and Cherniack (1960) found reduced Crs in seated obese subjects and a small further fall when supine. The major component appeared to be the changed chest wall properties in obesity. Respiratory resistance (Rrs) may be increased in sitting position and may further increase in supine position (Yap et al. 1995). The overall effect of supine body position on respiratory mechanics in obesity seems to be the enhancement of changes found in sitting position.

An early study of Farebrother et al. (1974) determined the effect of posture on arterial oxygenation in obesity. Arterial oxygen tension ( $\text{PaO}_2$ ), ERV and CV/VC were measured in sitting and supine positions. A significant reduction in  $\text{PaO}_2$  was demonstrated in supine position.  $(\text{ERV}-\text{CV})/\text{VC}\%$  as well as ERV alone were related to  $\text{PaO}_2$  both sitting and supine.

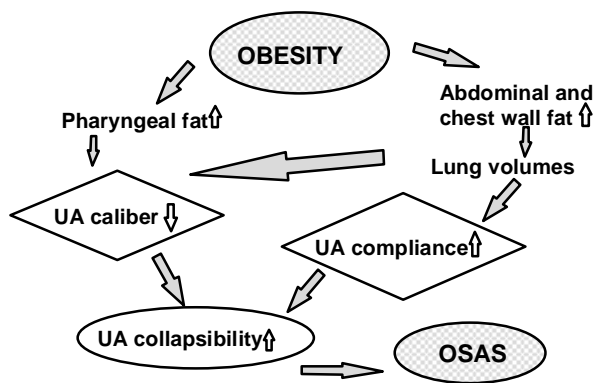
The effect of posture on  $\text{O}_2$  consumption has been studied in morbidly obese patients (Paul et al. 1976). Change of posture from sitting to supine was associated with the increase in  $\text{O}_2$  consumption. The authors suggested that increased  $\dot{\text{V}}\text{O}_2$  in the supine position reflects increased work of breathing. Small airway closure and increased congestion of the lungs in supine position may increase airway resistance and decrease pulmonary compliance.

### **3. OBSTRUCTIVE SLEEP APNEA AND OBESITY**

Obesity is considered as a major risk factor for the obstructive sleep apnea syndrome (OSAS) (Guilleminault et al. 1988, Douglas et al. 1994, Strobel et al. 1996). Although a close association between obesity and OSAS has been observed in clinical and epidemiological studies, the causal relationship between obesity and OSAS has been difficult to prove. Several mechanisms have been proposed including alterations in upper airways structure and function, changes in ventilatory drive, and obesity induced hypoxemia or abnormalities in pulmonary function (Appelberg et al. 2000)(Figure 4). In addition, there are recent studies referring to indirect mechanisms connecting obesity and OSAS. The development of OSAS has been reported to relate to the profile of body fat distribution. Shinohara et al. (1997) reported that

visceral obesity is a risk indicator for OSAS in obese subjects. Conversely, treatment of OSAS by nasal continuous positive airway pressure (nCPAP) reduced visceral fat accumulation and leptin levels (Chin et al. 1999, Saarelainen et al. 1997, Ip et al. 2000). Recently, Marik (2000) proposed that both obesity and OSAS could be due to leptin resistance. Ip et al. (2000) demonstrated that obese subjects with OSAS have significantly higher levels of leptin than weight-matched controls. NCPAP could restore leptin receptor sensitivity (Marik 2000).

**Figure 4.** The relationship between obesity and OSAS. Modified from Strobel et al. (1996).



### 3.1. The effect of obesity on upper airways (UA) structure and function in OSAS

Obesity and deposition of fat may alter upper airways structure. The increase in size of upper airways soft tissue structures has been demonstrated with increasing obesity (Partinen et al. 1988, Horner et al. 1989). Recently, results of two cephalometric studies in OSAS patients (Brander et al. 1999 and Sakakibara et al. 1999) confirmed that the main difference in upper airways size between obese and non-obese subject is the enlargement of upper airway soft tissue. In addition to alterations in UA structure, differences in UA function have been observed in patients with OSAS. It has been assumed that fat surrounding UA may alter soft tissue properties more compliant or fat infiltrating UA muscles may interfere with their function increasing collapsibility of the pharynx (Suratt et al. 1985). Reduced lung volumes associated with obesity may also decrease UA size or make the pharynx more susceptible to collapse. The patency of the upper airways is influenced by lung volume. The cross sectional area of the upper airways decreases as lung

volume decreases from total lung capacity to residual volume (Hoffstein et al. 1984, Strobel et al. 1996). Similarly the upper airways resistance varies with lung volumes, the lower the lung volumes the higher the resistance (Series et al. 1990). The results of animal studies suggest that tracheal traction may decrease pharyngeal resistance (Van de Graaff 1988).

May obstructive sleep apnea then be reversed by increase in lung volumes? Brown et al. (1986b) and Series et al. (1988 and 1989a) have studied the effect of pulmonary inflation on sleep apnea and oxygen saturation. They reported that the increase in FRC induced a significant reduction in rate and depth of the fall in SaO<sub>2</sub>. Through the increase in lung volume weight loss may affect pharyngeal geometry and function.

### **3.2. Obesity induced hypoxemia in OSAS**

Obesity induced hypoxemia may increase ventilatory instability which may facilitate UA occlusion (Strobel et al. 1996). Supporting this finding Onal et al. (1982) observed that genioglossus activity decreased with decreasing ventilation during periodic breathing. Supplemental oxygen may have beneficial effects on ventilatory stability. In obese patients with OSAS and hypoxemia, supplemental oxygen reduces mean apnea index and time (Martin et al. 1982, Smith et al. 1984, Gold et al. 1985). It is controversial whether OSAS may cause pulmonary hypertension without hypoxemic lung disease. Recently, Sajkov et al. (1999) reported that some patients with OSAS may develop pulmonary hypertension without lung disease and its development was associated with small airway closure during tidal breathing.

### **3.3. Obesity and ventilatory responsiveness in OSAS**

Ventilatory load compensation is defined as a sufficient ability to maintain adequate ventilatory output despite a mechanical hindrance to breathing. Imbalance between mass loading and central ventilatory drive in obese patients with OSAS has been observed (Strobel et al. 1996, Hudgel et al. 1998). A reduction in central respiratory drive coupled with increased elastic loading has been demonstrated in obesity-hypoventilation syndrome (Rochester et al. 1974). Similar abnormalities have been observed in eucapnic patients with OSAS (Gold et al. 1993). Sleep apnea patients had lower hypercapnic ventilatory response and higher waking PaCO<sub>2</sub> compared with normal obese controls (Burki et al. 1984, Gold et al. 1993). It is possible, that disturbances in

ventilatory control in obese sleep apnea patients are a continuum from normal obesity to the pickwickian syndrome (Gold et al. 1993).

### **3.4. The effect of posture on OSAS**

The upper airways resistance in OSAS decreases while moving from the lying to the sitting position (Anch et al. 1982). Body position during sleep affects the frequency and severity of breathing abnormalities in OSAS patients (Oksenberg et al. 1997). It has been demonstrated that a sitting sleep posture (60-degree angle) abolished obstructive sleep apnea in some patients without simultaneous disturbance in sleep architecture (McEvoy et al. 1986). The effect was most pronounced in patients with marked obesity and hypoxemia. The mechanisms proposed were the effects of posture on upper airways and improved oxygenation with increasing FRC in sitting position. Neill et al. (1997) reported that in patients with severe OSAS the elevation of upper body to 30 degree improved upper airways stability during sleep better than lateral positioning.

### **3.5. Treatment of OSAS and daytime oxygenation**

Treatment of OSAS with nasal CPAP may improve daytime oxygenation in patients with OSAS (Sforza et al. 1990, Leech et al. 1992). The improvement in PaO<sub>2</sub> has been more pronounced in patients who were hypoxemic prior to treatment (Sforza et al. 1990). In OSAS patients with hypercapnia a significant improvement in blood gas values has been demonstrated with nocturnal nasal positive pressure ventilation (NIPPV), but not on CPAP (Piper et al. 1994). In obese patients with OSAS a significant improvement in daytime oxygenation after dietary induced weight loss has been demonstrated (Suratt et al. 1992).

### **3.6. The effect of weight loss on OSAS**

Over the past decade several studies have been conducted on the effects of surgical and dietary weight loss in patients with OSAS (Strobel et al. 1996). A consistent trend has been observed towards improvement in sleep disordered breathing (SDB) (Smith et al. 1985, Sugarman et al. 1986, Suratt et al. 1987, Pasquali et al. 1990, Rajala et al. 1991, Lojander et al. 1998, Kansanen et al. 1998). The amount of weight loss needed to achieve significant improvement

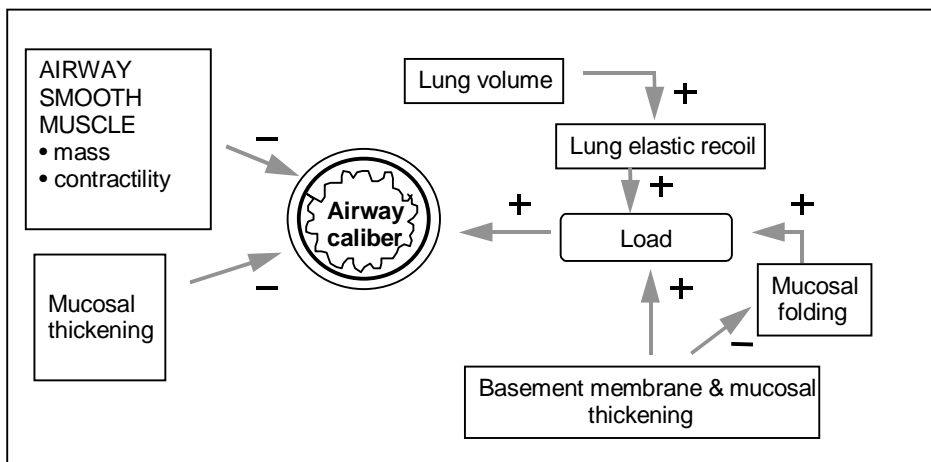
in SDB is not clear. Another issue not resolved has been the poor long term maintenance of weight loss results.

## 4. ASTHMA

### 4.1 Mechanical factors regulating airway caliber

Asthma is associated with a variable airflow limitation and airway closure. In addition to reversible airway obstruction some individuals with chronic asthma may show an irreversible component of airflow obstruction. The mechanisms leading to this fixed airflow limitation are unknown. It may be associated with structural changes in the airways resulting from inflammation in the airways (Fabbri et al. 1998).

In obesity, narrowing of the airway lumen that is responsive to bronchodilators has been reported (Unger et al. 1990, Fredberg et al. 1997). To evaluate the impact of obesity on airway narrowing and bronchial responsiveness in obese patients with chronic asthma, it is important to deal with the pathophysiological mechanisms of airway narrowing. Forces that tend to contract the airways and those that prevent narrowing determine the caliber of the intrathoracic airways (Fredberg et al. 1997). When a contractile stimulus is applied to the airway smooth muscle, the airway lumen decreases depending on how much the airway smooth muscle shortens and on the thickness of airway wall (Figure 5) (Brusasco et al. 1999).



**Figure 5.** Mechanical factors regulating airway caliber. + : mechanism increasing a given effect; - : mechanism decreasing a given effect. Modified from Brusasco et al. (1999).

The maximum extent to which smooth muscle can shorten is determined by the force developed by smooth muscle and by the magnitude of opposing factors. In asthma the airway smooth muscle may be thicker than normal. Assuming that muscle hypertrophy and hyperplasia are associated with an increased capacity to generate force, increased thickness of airway smooth muscle layer may be the major determinant of airway narrowing in asthma (Lambert et al. 1994). On the other hand abnormalities of smooth muscle contractility may contribute to the increased airway narrowing in asthma. The forces opposing airway narrowing include elastic elements of the airway (internal load) and of the surrounding lung parenchyma (external load). The magnitude of internal load depends on the stiffness of the airway wall as well as on the changes in geometric configuration that airway mucosa undergoes upon airway smooth muscle shortening. The thickening of the basement membrane in asthma may increase load on airway smooth muscle, thus opposing airway narrowing (Lambert 1991).

Mucosal folding provides a further load to smooth muscle (Lambert et al. 1994). Modelling studies have shown that the greater the number of folds, the less the obstruction (Lambert et al. 1994). However, the number of folds may decrease when mucosa is thick (Wiggs et al. 1997). In this regard, basement membrane thickening may increase airway narrowing. The external load the airway smooth muscle of intraparenchymal airways has to overcome during shortening, includes lung elastic recoil and forces of interdependence between airways and lung parenchyma (Macklem 1996). As lung elastic recoil pressure changes with lung volume, airway narrowing induced by constrictor agents is expected to be less at high than at low lung volumes (Ding et al. 1987). The interdependence between airways and lung parenchyma is produced by the parenchymal attachments to the airway external wall. The forces of interdependence tend to make the airways follow the movements of the lung.

#### **4.2. Small airway disease in asthma**

Every part of the airways can be involved in asthma. Thus airway narrowing in asthma may occur in both central and peripheral airways. The same individual may show evidence of predominantly central obstruction on one occasion and mainly peripheral obstruction on another (Pride et al. 1986). The small airways, defined as those airways of less than 2 mm internal diameter, provide a far greater cross-sectional area for airflow than the large airways. It is generally considered that the resistance in the small peripheral airways of the

lung constitutes less than 20% of the total airways resistance (Macklem 1998). In clinical practice, the changes in function of the small airways are difficult to demonstrate (Evans et al. 1998). Expiratory flows measured at low lung volumes ( $MEF_{50}$ ,  $MEF$ ,  $FEF_{25-75}$ ), i.e. in the terminal part of forced expiration, have been regarded as a measure of peripheral airway narrowing. As a measure of airway size related to lung size  $FEF_{25-75} / FVC$  has been used (Litonjua et al. 1999).

However, the flow at low lung volumes is not a specific or sensitive measure for detecting peripheral airways obstruction. A concave flow -volume curve and low flow rates during the last part of the volume can be considered as a profile of narrowing of small airways if the elastic recoil of the lungs and airways resistance (excluding narrowing of the large airways) are normal (Cherniack 1995). In asthma the involvement of the large airways can make it difficult to evaluate the narrowing of the small airways from the tests of forced expiration.

### **4.3. Lung volumes**

The alterations in airway mechanics occurring in asthma, particularly airway closure, may affect lung volumes. The early studies have shown that asthma is often characterized by a reduction in VC and increased residual volume (RV). These changes reflect increased air trapping, which results from closure of the airways (Woolcock et al. 1971). Airway closure may occur with airways smooth muscle contraction as well as occlusion of the airways by mucus, or mucosal thickening (Roche 1998).

FRC is also increased in patients with asthma for several reasons. Because the static volume-pressure curve is shifted upward and to the left in asthma, equilibrium between the elastic recoil of the chest wall and that of the lungs occurs at a higher lung volume (Cherniack 1995). Also, the increased inspiratory muscle activity is regarded as an important cause of increased FRC. Activation of inspiratory muscles effectively brakes the expiration and causes the end-expiratory lung volume to increase (Cornier et al. 1990). Finally, FRC is likely to be elevated because the increased flow resistance prolongs the overall time constant of the respiratory system, so that the time available for the lung to deflate is inadequate and equilibrium between the elastic forces is not achieved (Cherniack 1995). Because the flow resistance depends on the size of the airways, it is influenced by the lung volume and the lung elastic

recoil pressure. Thus, a correction must be made for the lung volume at which resistance ( $R_{aw}$ ) is measured. The relationship between lung volume and airways resistance is almost parabolic, but the reciprocal of  $R_{aw}$ , which is called airways conductance ( $G_{aw}$ ) is linearly related to lung volume. Measurements of  $R_{aw}$  or  $SG_{aw}$  predominantly reflect the resistance to airflow in the larger airways.

#### **4.4. Peak flow variability**

Exaggeration of the endogenous circadian variation of airways patency is a particular feature of asthma. Other pulmonary function measures, specifically  $FEV_1$  and airways resistance ( $R_{aw}$ ) show strong circadian patterns with lowest periods nocturnally, but PEF has the strongest circadian rhythm (Lebowitz et al. 1997). Related biochemical cycles include plasma histamine maxima and plasma cyclic adenosine monophosphate (cAMP) and epinephrine minima when PEF is at its minimum. The nocturnal reduction in function in asthma is related to bronchial responsiveness. Inflammation is closely related to the bronchial responsiveness. Broncho alveolar lavage have shown nocturnal increase in inflammatory cells in asthmatic with the nocturnal worsening (Martin et al. 1991). The fall in PEF was correlated with the cellular changes. Diurnal variability of PEF has been used as a marker of airway responsiveness, particularly in epidemiological studies. Daily PEF variation has been reported to correlate with the severity of bronchial hyperreactivity (BHR) (Brand et al. 1991, Higgins et al. 1993, Boezen et al. 1996, Kolbe et al. 1996). Yet, there are studies suggesting that PEF variability and BHR reflect different pathophysiological mechanisms (Boezen et al. 1998). In children, diurnal PEF variation correlated with exercise-induced bronchoconstriction but not with histamine or metacholine challenges (Sekerel et al. 1997).

Several alternative equations may be used to express PEF variation. The most common for diurnal PEF variability are the amplitude percentage mean ( $(\text{maximum} - \text{minimum})/\text{mean}$ ) or the amplitude percentage maximum ( $(\text{maximum} - \text{minimum})/\text{maximum}$ ), calculated for each day, and then averaged over a period of 1 or 2 weeks. Standard deviation (SD) percent mean morning PEF or coefficient of variation is generally used to express day-to-day PEF variability. For normal clinical practice these calculations are regarded as too time consuming. Recently, a simpler index of PEF variation such as the lowest morning peak flow, expressed as percentage of the patients personal best PEF, has been introduced to be included in new asthma guide lines (Reddel et al.

1999). As nine different PEF indices were evaluated, minimum morning PEF (expressed as percent recent best PEF) was recommended as the best index of airway lability in patients with stable asthma. It correlated strongly with BHR (Reddel et al. 1995).

#### **4.5. Airway size and bronchial hyperresponsiveness**

It has been suggested that the factors that can increase airway wall thickness or reduce airways size could influence airways responsiveness (Wiggs et al. 1992). Moreno et al. (1986) have suggested that with the increase in airway wall thickness the reactivity may increase with a modest or even without any increase in airways resistance. This is supported by studies reporting increased airways responsiveness in subjects with heart failure (Cabanes et al. 1989). It is possible that airway size also affects airway responsiveness (Brusasco et al. 1998 and 1999). Brusasco et al. (1998) reviewed studies on airway inflammation and airway hyperresponsiveness in asthma. The authors concluded that airway hyperresponsiveness and airway narrowing in asthma are not just a matter of airway inflammation. Boulet et al. (1995) have studied the relationship between bronchial wall thickness and airway responsiveness. Correlation between wall thickness and airway responsiveness was demonstrated only in asthmatic patients with fixed airway obstruction. Bronchial diameter correlated with bronchial reactivity in normal subjects but not in asthmatics. They suggested that in asthmatics other factors than airway narrowing may be more significant in determining the degree of airway responsiveness.

### **5. ASTHMA AND OBESITY**

The rise in asthma prevalence in children and adults has been accompanied by an increase in the prevalence of obesity. Increasing epidemiological evidence suggests that there is an association between obesity and asthma (Gennuso et al. 1998, Luder et al. 1998, Camargo et al. 1999, Shaheen et al. 1999a). However, the nature of the association needs to be clarified (Shaheen 1999b, Wilson et al. 1999). At present it is not possible to say whether obesity has contributed to the rise in asthma prevalence. The direction of the association is difficult to determine from cross-sectional studies.

### **5.1. Association between asthma and obesity**

Population based cross-sectional studies have found positive associations between BMI and wheeze or asthma in children (Gennuso et al. 1998, Huang et al. 1999). Luder et al. (1998) have reported that children with moderate to severe asthma are more likely to be obese than their controls from the same environment. An association between obesity and asthma symptoms was also demonstrated. In the large Nurses' Health Study II in the USA, a strong positive association between BMI and risk of adult-onset asthma was observed in women aged 27-44, who were followed for four years (Camargo et al. 1999). Again, the prevalence of asthma increased with increasing body mass index in females aged 12-24 years but not in males according to the Canadian National Population Health Survey in 1994-1995 (Chen et al. 1999). In a British Cohort Study (BCS70) BMI was associated with the prevalence of asthma at 26 years of age (Shaheen et al. 1999a). The results of the study suggested that impaired fetal growth as well as adult obesity were risk factors for adult asthma. Dixon et al. (1999) reported a high prevalence of asthma (24.6%) among morbidly obese adults, compared to overall prevalence of 12-13% in Australian community.

Is this association a real one? Firstly, a low level of physical activity, which is clearly associated with higher BMI (Gortmacher et al. 1996), was not taken into account in all these studies. Low physical activity with reduction in deep breathing may lead to airway narrowing by reducing the extent to which bronchial muscle is stretched (Platts-Mills et al. 1997, Shaheen et al. 1999a). In the absence of deep inspirations healthy persons may develop bronchoconstriction with methacholine inhalation (Skloot et al. 1995). Recently, Kapsali et al. (2000) demonstrated that deep inspiration with lung inflation has a potent bronchoprotective effect in normal healthy subjects but not in patients with asthma. Secondly, the dietary factors may explain the association between asthma and obesity. For example, salt intake and a low intake of antioxidants are proposed as risk factors for asthma (Weiss 1997). Thirdly, there may exist humoral and physiologic effects between asthma and obesity. For example, obesity increases gastroesophageal reflux (Wilson et al. 1999), which may trigger latent asthma. Varner (2000) proposed immunologic mechanisms based on biological activity of adipose tissue. Production of interleukin 6 (Mohamed-Ali et al. 1997) and cyclooxygenase-2 (Williams et al. 1997) from human adipose tissue may increase the risk of asthmatic inflammation. Recently the association between polymorphism in the human beta<sub>2</sub>-adrenoceptor gene and obesity has been reported in French men

(Meirhaeghe et al. 2000). At present there are many questions that remain to be answered.

## **5.2. Weight loss in obese asthmatics**

In morbid obesity a significant improvement in asthma has been observed after surgical weight loss (Dixon et al. 1999). The effect of weight loss on asthma was evaluated by using a questionnaire about the effects of asthma on sleep, exercise, asthma treatment required, and admissions to hospital due to asthma. The asthma score decreased significantly with weight reduction. The authors suggested that mechanisms other than direct weight loss including prevention of gastroesophageal reflux may play a part in this improvement.

Recently, a significant increase in FEV<sub>1</sub> and FVC as well as decrease in symptoms was demonstrated in obese asthmatics after dietary induced weight loss (Stenius-Aarniala et al. 2000). During weight reduction program, no changes in serum or urine cortisol or urinary excretion were observed. The one year maintenance of weight loss results and improvement in lung function was good.

## **AIMS OF THE STUDY**

The purpose of this study was to evaluate the effects of obesity on pulmonary function with special reference to asthmatics and patients with obstructive sleep apnea. The specific aims were:

1. To study the effectiveness of very-low-calorie-diet (VLCD) in improving pulmonary mechanics and gas exchange at rest and during exercise in morbid obesity
2. To evaluate the effects of weight loss and body position on daytime lung function and arterial oxygenation in obese patients with obstructive sleep apnea
3. To study the relation between asthma and obesity by comparing changes in peak flow variability and airways obstruction in response to weight reduction with simultaneous changes in lung volumes in obese asthmatics
4. To investigate the effects of weight reduction and body position on breathing pattern and gas exchange in obese asthmatics

## PATIENTS AND METHODS

### 1. Patients

The anthropometric and lung function data as well as the diagnoses of the patient groups are given in Table 3.

#### *Study I*

The study population in Study I consisted of patients with morbid obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) who were referred to the Metabolic Unit of Helsinki University Central Hospital for conservative treatment of obesity. They were initially examined by an endocrinologist. The criteria for referral to the University clinic were body mass index greater than 40 kg/m<sup>2</sup> and age less than 60 years. The weight reduction program included a very-low-calorie diet period combined with behavior therapy modification. Among the patients enrolled to start the weight reduction program 15 consecutive patients were selected to participate this study. Patients with a history of obstructive sleep apnea, obstructive lung disease or other serious illness were excluded. Current smokers were not included. Ex-smokers were included only if they had quit smoking at least two years earlier. Four patients dropped out the weight reduction program. Thus the study population consisted of 11 patients. The baseline pulmonary function and body fat distribution data presented in Table 6 include results of all 15 patients who started the study. This data has not been published before.

#### *Study II*

Seven patients from study I who had lost weight at least 10 kg (n = 7) were selected for further evaluation. Exercise testing with continuous analysis of expired air and arterial blood sampling was carried out. The mean weight loss in this study group had been 25.7 kg (range 10 to 50 kg).

#### *Study III*

Thirteen obese patients with obstructive sleep apnea were studied. The study population consisted of patients who were referred to the Helsinki University

**Table 3.** Diagnoses, anthropometric and lung function data of the study populations. Values are means (SD).

	Age (years)	Sex F/M	Weight (kg)	BMI (kg/m <sup>2</sup> )	FEV <sub>1</sub> (% pred)	FVC (% pred)	FRC (% pred)	Raw (% pred)
<b>Study I</b>								
Morbid obesity (N = 11)	40.7 (8.2)	6/5	133 (24)	45.4 (5.8)	95 (10)	101 (15)	65 (20)	201 (88)
<b>Study II</b>								
Morbid obesity (N = 7)	44.1 (7.5)	3/4	140 (22)	46.6 (6.3)	96 (17)	90 (9)	70 (24)	197 (102)
<b>Study III</b>								
OSAS (N = 13)	48.8 (8.8)	1/12	109 (10)	35.2 (2.5)	101 (7.3)	96 (7.3)	71 (7)	149 (30)
<b>Study IV</b>								
Asthma (N = 14)	51.8 (9.1)	11/3	101 (14)	37.2 (3.7)	77 (14)	88 (13)	86 (21)	329 (166)
<b>Study V</b>								
Asthma (N = 14)	51.8 (9.1)	11/3	101 (14)	37.2 (3.7)	77 (14)	88 (13)	86 (21)	329 (166)
Healthy controls (N = 11)	35.6 (11)	8/3	68 (12)	22.4 (2.6)	110 (14)	109 (10)		

Central Hospital due to symptoms suggestive of obstructive sleep apnea, excessive daytime somnolence and snoring, being the most common. The diagnosis of OSAS was based on oximetry with the static-charge-sensitive bed method validated previously (Svanborg et al. 1990). Moderately to severely obese patients (BMI 30-40 kg/m<sup>2</sup>) were evaluated for the weight reduction program. Patients who were at risk from somnolence at work, e.g. lorry drivers were excluded. Further exclusion criteria included asthma and chronic obstructive pulmonary disease, unstable angina pectoris and symptomatic liver or biliary disease. Altogether 61 patients with OSAS (mean age 49 years; mean BMI 32 kg/m<sup>2</sup>) were evaluated at the outpatients' department of pulmonary medicine, as described by Lojander et al. 1998. Current smokers were excluded from our study. The study population consisted of the first thirteen OSAS patients who started the weight reduction program.

#### *Study IV*

The study population consisted of fourteen obese asthmatics. They were selected from the 19 patients who participated as a control group in the study of Stenius-Aarniala et al. (2000). The recruitment of the patients to that study has been described elsewhere (Stenius-Aarniala et al. 2000). The control patient group took part in educational sessions concerning asthma and allergy and their spirometric and serial PEF values were carefully followed up every two months during one year. Two to five months after closing that trial, 14 obese asthmatics out of 19 patients volunteered to start the weight reduction program including a 8-week VLCD period. Current smokers were excluded. 4 of 14 patients were ex-smokers with the mean smoking history of 12 pack years. The diffusing capacity was within normal range in all patients. The mean duration of asthma was 12.7 years (range 1 to 27 years). The anti-asthmatic medication included regular use of inhaled corticosteroids in all 14 patients, sustained-release theophylline compounds in 2 patients and regular long-acting beta<sub>2</sub>-agonists in 3 patients.

#### *Study V*

The study population consisted of fourteen obese asthmatics and eleven healthy control subjects. The obese patients with asthma are the same as in Study IV. Eleven healthy non-obese (BMI < 27 kg/m<sup>2</sup>) non-smoking subjects without any cardiorespiratory symptoms or signs were volunteered as controls. They all showed normal findings in physical examination and in flow volume spirometry.

## 2. Methods

### *Pulmonary function tests*

Flow- volume spirometry was performed using a rolling seal spirometer (CPI 220, Cardiopulmonary Instruments, Houston, USA) connected to a microcomputer system (Medikro 202, Medikro Oy, Kuopio, Finland). The results from the envelope curve of at least three forced expiratory flow-volume loops were recorded. The highest values of forced expiratory volume in one second ( $FEV_1$ ) and forced vital capacity (FVC) were determined with the patient in the sitting position (Study I-V). In Study III flow rate at a volume of 50% of FVC ( $MEF_{50}$ ) and in Study IV flow rate at the middle part of FVC ( $FEF_{25-75}$ ) as well as area under the expiratory flow volume curve (AFV) were reported. The peak inspiratory flow (PIF), forced inspiratory volume in one second ( $FIV_1$ ) and forced inspiratory vital capacity (FIVC) were recorded in Study III. Maximal voluntary ventilation (MVV) was measured from a period of 15 s of maximal breathing to the spirometer (Study I).

A single breath method (Master Lab, Jaeger, Wurtzburg, Germany) was used for measuring diffusing capacity of the lungs for carbon monoxide (DLco) in Studies I, III and IV. Lung volumes were determined using a single breath helium dilution method ( $VC_{He}$ ,  $TLC_{He}$  and  $FRC_{He}$ ) and body plethysmograph ( $VC_B$ ,  $RV_B$ ,  $TLC_B$  and  $FRC_B$ ). The evaluation of non-ventilated lung compartment was based on the difference between  $TLC_B$  and  $TLC_{He}$  (Study I and IV). Airways resistance (Raw) as well as airways conductance (SGaw) were measured during tidal breathing timed with a metronome (30/min) using a constant volume body plethysmograph (Bodyscreen, Erich Jaeger GmbH, Wurtzburg, Germany). The mean value of 3-5 determinations was recorded for analysis.  $ERV_B$  was calculated from the difference between  $FRC_B - RV_B$ .

In Study I closing volume CV was measured with the patients in sitting position by using a nitrogen single breath method (Buist et al. 1973). At least three measurements were performed; the mean value was recorded for the analysis. Closing capacity CC was then calculated as  $CC = CV + RV_B$ . In Study III closing volume was measured with the patient in supine and sitting positions. Otherwise the method used was identical with the one described above.

*Arterial blood gases*

A brachial or a radial artery was cannulated for arterial blood samples in Studies I-II. After the cannulation patients rested at least for 10 min in supine position. That was followed by an orthostatic tolerance test lasting for 8 min according to Thulesius (1970). Arterial blood samples for blood gas analysis were drawn in supine position and during orthostatic tolerance test in standing position at 8 min. In Study II arterial blood samples were also drawn during exercise testing at the end of each work load, at the peak exercise, and 10 min following the exercise phase. Arterial blood PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, and base excess were analyzed using an automatic acid-base analyzer (ABL 30, Radiometer, Copenhagen, Denmark). Alveolar-arterial oxygen tension difference was obtained from the following equation:

$$P(A-a)O_2 = PAO_2 - PaO_2 ;$$

$$PAO_2 = F_iO_2 \times (P_B - P_{H_2O}) - \frac{PaCO_2}{RQ}$$

where P<sub>B</sub> is the actual barometric pressure, P<sub>H<sub>2</sub>O</sub> is water vapor tension at 37°C, F<sub>i</sub>O<sub>2</sub> is oxygen content of inspired air and RQ the respiratory quotient (VCO<sub>2</sub>/VO<sub>2</sub>) assumed to be 0.8 at rest. In study II actual measured RQ values during exercise were used for calculations.

*Exercise test with respiratory and blood gas analyses*

In Study II, before orthostatic and exercise testing, a brachial or radial artery was cannulated under local anaesthesia. After 10 min rest in supine position an orthostatic tolerance test described above (Thulesius 1970) was carried out. This was immediately followed by exercise test using an electrically braked bicycle ergometer (Bosch ERG 220, Robert Bosch GmbH, Berlin, Germany) with the patient in sitting position. The initial work load was 40 W for women and 50 for men. It was then increased at 3 min intervals in steps of 40 W and 50 W, respectively, until exhaustion (grade 19-20 according to Borg 1962). A twelve lead (Mason-Likar) electro-cardiogram (ECG) was continuously monitored and recorded during the test using a computerized ECG device (Marquette, Case12, Marquette Inc, USA). Blood pressure was measured stethoscopically by a sphygmomanometer (Erkanieter, Germany) from the left arm.

For the collection of respiratory gases a tightly attached face mask (Rudolph series 7910, Hans Rudolph Inc, Kansas City, USA) with a dead space of 185 ml was used. Continuous measurement of minute ventilation ( $\dot{V}E$ ), oxygen and carbon dioxide partial pressures of the mixed expired air was carried out and the ventilatory variables (all in BTPS) were calculated at 30 s intervals using a microcomputer assisted equipment (Ergo-Oxyscreen, Erich Jaeger GmbH, Wurzburg, Germany). Minute ventilation ( $\dot{V}E$ ), breathing frequency (BF), oxygen consumption ( $\dot{V}O_2$ ), carbon dioxide outflow ( $\dot{V}CO_2$ ), respiratory exchange ratio (RQ), ventilatory equivalent for  $O_2$  ( $\dot{V}E/\dot{V}O_2$ ) and for  $CO_2$  ( $\dot{V}E/\dot{V}CO_2$ ), and end expiratory tidal  $CO_2$  fraction (FETCO<sub>2</sub>) were recorded. Breathing reserve was defined as  $(MVV - \text{peak}\dot{V}E) \times 100/MVV$ , where MVV represents maximal voluntary ventilation.  $O_2$ -pulse ( $\dot{V}O_2$  related to heart rate,  $\dot{V}O_2/HR$ ) was also calculated.

#### *Orthostatic test with respiratory gas analyses*

In Studies III and V, respiratory gas exchange and ECG (HR) were continuously monitored during orthostatic tolerance test (Thulesius 1970). The method used for collection and analyses of respiratory gases was identical to that used during exercise testing (Study II). After the patient had rested for 10 minutes in supine position, respiratory gas exchange was monitored for ten minutes in supine position. Steady state ventilation was achieved within five minutes. The initial five minutes of data were discarded and data from subsequent five minutes were used for calculation of ventilatory gas exchange variables as in Study II. After this resting period, patients were asked to rise up and stand still and unsupported for 8 minutes. Gas exchange and ventilation were continuously monitored during standing. The data from the last five minutes were used for calculations as in supine position.

#### *Sleep studies*

In Study III the diagnosis and follow-up of OSAS was based on oximetry with the static-charge-sensitive bed method (Svanborg et al. 1990). Transcutaneous arterial oxygen saturation was continuously monitored with a Biox 3700e Pulse oximeter using a finger probe (Ohmeda, Boulder, Colorado, USA). Airflow through the nose and mouth were monitored by thermistors. Respiratory and body movements were recorded with a SCSB methods (Biomat, Biorec Inc., Finland) (Salmi et al. 1989). The frequency of oxygen desaturation events ( $ODI_4$  = desaturation by 4% or more per hour in bed and  $ODI_{10}$  = desaturation by 10% or more, respectively) was calculated to

characterize the amount of respiratory disturbances during the night. ODI<sub>4</sub> indices of greater than 10 were considered abnormal. Daytime somnolence was recorded on a 100 mm linear visual analogue scale, where 0 represented "none" and 100 mm "very severe".

#### *Peak expiratory flow variability*

The highest of three measurements of peak expiratory flow (PEF) by mini-Wright peak flow meter was recorded by the patients themselves every morning and evening during 14 successive days before and after the weight loss period. If patients were taking bronchodilator, PEF values were measured before its use. PEF variability was expressed in three ways: as the diurnal PEF variation (highest PEF - lowest PEF / mean value of the two, x 100%), the mean difference between the highest and lowest morning PEF values measured over a follow-up period of 14 days, and the day-to-day PEF variation (SD percent mean morning PEF).

#### *Histamine challenge*

A rapid dosimetric method with controlled tidal breathing was used for histamine challenge of the airways (Sovijärvi et al. 1993). Patients with a FEV<sub>1</sub> ≤ 70 % predicted were excluded from histamine provocation testing . If FEV<sub>1</sub> decreased from the baseline by 15 percent or more after any dose, further administration of histamine was discontinued. The PD<sub>15</sub>FEV<sub>1</sub> was calculated from logarithmically transformed histamine doses.

### **3. Study designs**

#### *Study I-II*

In Studies I and II patients with severe to morbid obesity were treated with weight reduction program that included VLCD period for 6 weeks and behavioral therapy (BT) for 16 weeks (Pekkarinen et al. 1999). VLCD period started before group BT. The VLCD used was Dietta Mini (MediFood, Finland). It provided 2100 kJ daily and consisted of 50g high-quality protein, 65g of carbohydrate, and 2g of fat, and vitamins, trace elements, and minerals according to the recommended dietary allowances. It was in powdered form and mixed with water. A moderate amount of low-energy vegetables was allowed during the VLCD period. The 16-week behavior therapy program had been developed in the Metabolic Unit of the Department of Medicine in

Helsinki University Hospital (Pekkarinen et al. 1997) and was partly based on the LEARN Program for Weight Control by Brownell (Brownell 1985). The 16-week-program consisted of weekly group sessions that lasted for 1 hour and were led by a trained nurse. Issues discussed in sessions included recording of eating behavior, control of eating stimuli, slowing of eating rate, planning ahead, eating in only one place, discussions of the energy and nutrient content of foods and low-energy shopping and cooking. VLCD and BT program lasted for 5 months. Pulmonary function tests and exercise testing were done before and after VLCD+BT program. Six to eight months after the start of the weight reduction program the lung function tests were repeated. This was also the end point of the weight loss in this study. Pulmonary function tests were done in sitting position. In order to study the postural changes in pulmonary gas exchange, arterial blood gases were measured in supine and standing positions before and after weight reduction.

### *Study III*

The weight reduction program consisted of VLCD for the first 6 weeks. The VLCD used was Dietta Mini as in Studies I-II. Prior to the 6-week VLCD period and after that patients were weighed. Overnight polygraphic recording, VAS, pulmonary function tests and arterial blood gas analyses were carried out before starting VLCD and six weeks later at the end of VLCD. Arterial blood samples for blood gas analysis were taken in supine and standing positions. Alveolar-arterial oxygen tension differences were calculated in both body positions. Closing volume was measured in supine and sitting positions. Other pulmonary function tests were done with the patients in sitting position.

### *Studies IV- V*

All patients participated in a weight reduction program starting with a VLCD period of eight weeks. The VLCD preparation used was Nutrilett (Nycomed Pharma AS, Oslo, Norway). The daily dose was five sachets that contains 429 kcal/1760 kJ of energy, 60g of protein, 7g of fat, 30,5 g of carbohydrate of which 17.5 g is fiber. The VLCD preparation is in powder form and is mixed with water. In addition to the powder preparation, the VLCD includes one daily tablet containing the recommended daily amounts of vitamins, minerals and trace elements and one capsule containing essential fatty acids. The end point of weight reduction was the time of repeating lung function tests and gas exchange measurements two to three months after starting weight reduction

program with VLCD. In atopic patients measurements were done out of pollen season.

In Study IV patients measured their daily morning and evening peak flows for two weeks and recorded the use of rescue medication and symptoms on VAS scale. Diurnal and day-to-day pulmonary peak flow variability was calculated. In Study V respiratory gas exchange was measured in supine and standing positions during orthostatic tolerance test.

#### **4. Statistical methods**

In Study I paired t-test was used in comparisons of test results before and after weight loss and between body positions. For correlation analysis the Pearson correlation coefficient was calculated. Wilcoxon signed rank test was used for comparisons of repeated measurements of lung function and gas exchange data in Study II and Study III. Spearman's correlation coefficient was calculated to determine relationships between variables. In Studies IV-V Wilcoxon signed rank test was used in paired comparisons of test results between body position and before and after weight reduction. The Mann-Whitney U-test was used to compare the active group to controls in Study V. Linear regression analysis was used for correlation analysis. A p-value of less than 0.05 was considered to indicate statistical significance.

The data are expressed as mean (SD), mean (range) or median (range). Mean or median difference with 95 % confidence limits are shown in Study V.

#### **5. Ethical considerations**

Studies I-V were approved by the Ethics Committee of the Department of Pulmonary Medicine at Helsinki University Hospital. Before entering the study protocol, all patients and control subjects gave their informed consent.

## RESULTS

### 1. Body fat distribution and pulmonary function in patients with morbid obesity (I)

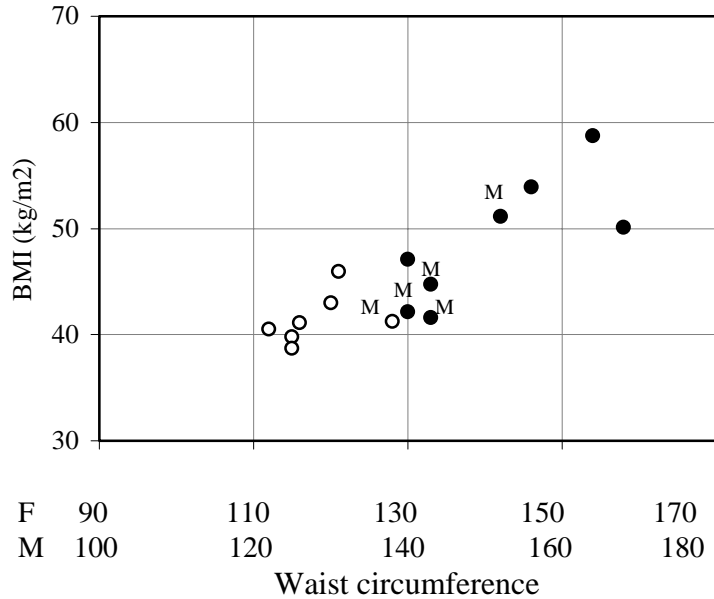
The baseline results of waist circumference and waist to hip ratio (W/H) of 15 morbidly obese patients, who started the weight reduction program in Study I, are shown in Table 4. The patients who later dropped out of the weight loss trial (n = 4) are included here.

**Table 4.** Waist hip ratio (WHR) and waist circumference (WC) in patients with morbid obesity in Study I.

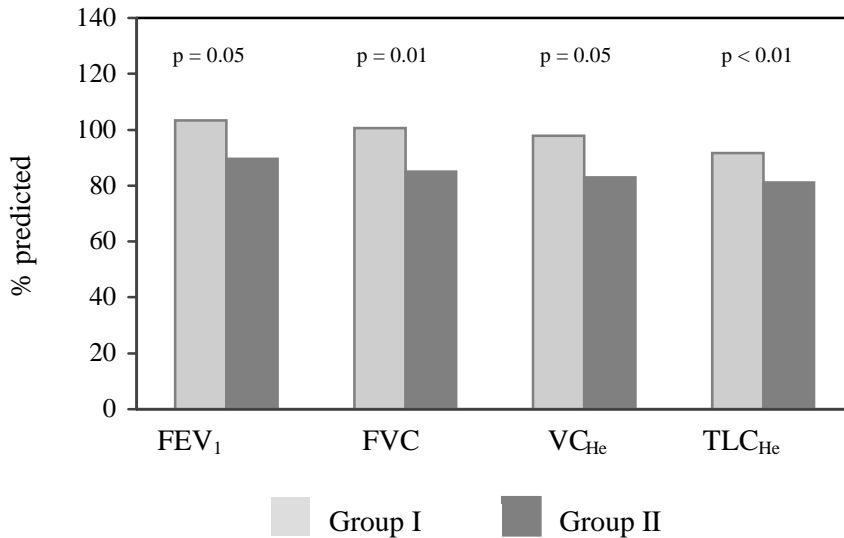
Patients	WHR	Weight (kg)	BMI (kg/m <sup>2</sup> )	WC (cm)
Female (n = 10)	0.94 (0.05)	118.8 (21.9)	45.9 (6.6)	128.7 (17.5)
Male (n = 5)	1.05 (0.04)	148.6 (11.3)	44.1 (4.1)	133.2 (5.4)
All (n = 15)	0.97 (0.07)	128.7 (23.6)	45.3 (5.8)	130.2 (14.5)

Based on BMI and waist circumference patients were divided into two groups, as shown in Figure 6. Group II consisted of 8 patients, who had higher BMI or waist circumference than in group I. Four male patients were included in group II, whereas in group I there was only one male patient. Waist to hip ratio was significantly higher in Group II (1.01 (0.05)) than in Group I (0.97(0.07))(p < 0.05) referring to more central distribution of fat in these patients. Pulmonary function test results between these two groups were compared (Figure 7). Forced expiratory flows (FEV<sub>1</sub> and FVC) and lung volumes measured, using helium dilution method (VC<sub>He</sub> and TLC<sub>He</sub>), were significantly lower (Figure 7) in patients with higher waist circumference or BMI (Group II), whereas FRC and TLC measured by bodyplethysmograph (FRC<sub>B</sub> and TLC<sub>B</sub>) were not different in these groups.

RESULTS



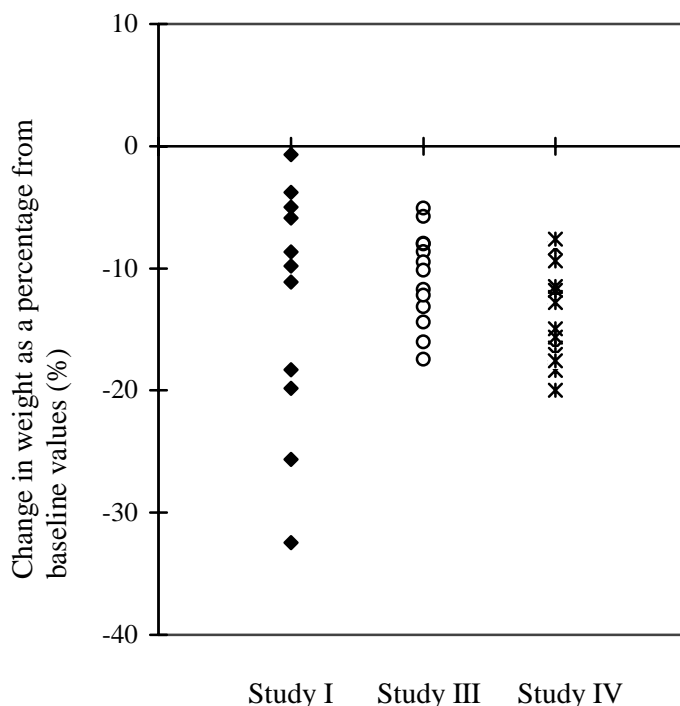
**Figure 6.** Patients with morbid obesity (n = 15) were divided into two groups based on body mass index (BMI) and waist circumference (WC), o = Group I; ● = Group II; F = female, M = male



**Figure 7.** Spirometry and lung volumes in patients with less central obesity (Group I, n = 7) compared to patients with more central obesity (Group II, n = 8). Mann-Whitney U test was used for comparisons between groups.

## 2. The effect of weight reduction on pulmonary function (I, III, IV)

The mean weight loss in Study I (morbid obesity) was - 12.8% (range from - 0,7 to - 32.5%), -10.8% (range from -5,1 to 17.5%) in OSAS patients, and - 13.7% (range from -7.6 to -18.4%) among obese asthmatics, Figure 8.



**Figure 8.** Weight change (%) from baseline at the time of repeating pulmonary function tests. Study I: Patients with morbid obesity, n = 11; Study III: Obese patients with OSAS, n = 13; Study IV: Obese asthmatics, n = 14.

The results of the pulmonary function tests before and after weight loss are summarized in Table 5. Forced expiratory flow rates (FEV<sub>1</sub>, FVC, MMEF and MEF<sub>25</sub>) were within the 95% confidence limits for the predicted values in patients with morbid obesity and in OSAS patients. Still, a significant increase in the flow rates was observed with weight reduction. Initially the mean FEV<sub>1</sub> as well as MMEF and MEF<sub>25</sub> were low in asthma patients, but normalized after weight loss. FRC and ERV were markedly reduced in patients with morbid obesity. With weight reduction the mean FRC and ERV increased significantly

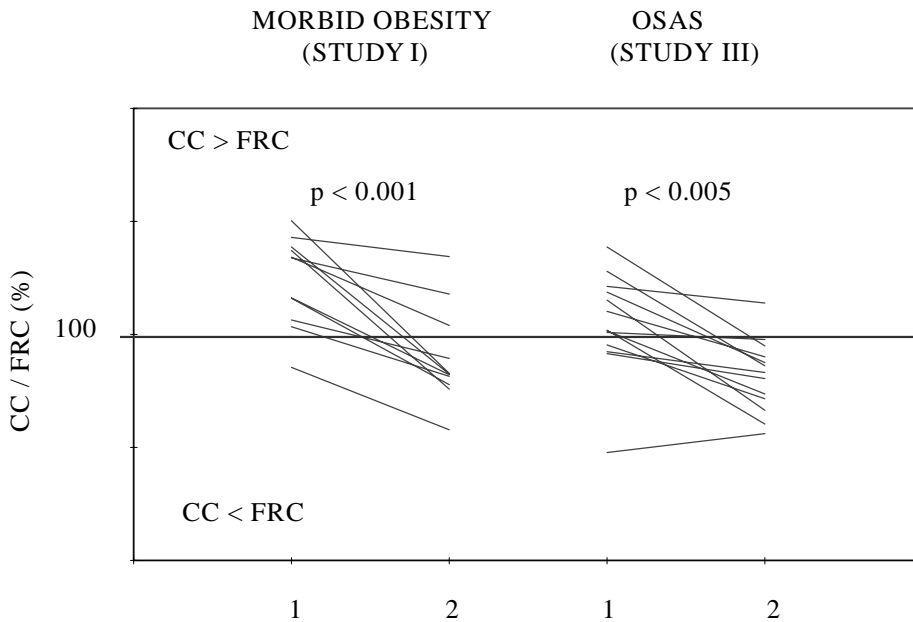
**Table 5.** Pulmonary function data before and after weight reduction. Data are expressed as mean (SD).

	<b>Study I: Morbid obesity</b>			<b>Study III: OSAS</b>			<b>Study IV: Asthmatics</b>		
	Before weight loss	After weight loss	p-value	Before weight loss	After weight loss	p-value	Before weight loss	After weight loss	p-value
<b>FEV<sub>1</sub> (% pred)</b>	95 (10)	101 (15)	<0.05	101 (7)	105 (6)	<0.05	77 (14)	83 (13)	<0.05
<b>FVC (% pred)</b>	91 (10)	97 (13)	<0.01	96 (7)	100 (9)	<0.05	88 (13)	93 (13)	<0.01
<b>FEV<sub>1</sub>/FVC (%)</b>	86 (4)	85 (4)	ns	85 (6)	85 (5)	ns	71 (9)	73 (8)	ns
<b>MMEF (% pred)</b>	91 (20)	97 (20)	ns	98 (27)	105 (26)	<0.05	45 (18)	54 (22)	<0.01
<b>FIV<sub>1</sub> (L)</b>	4.2 (1.2)	4.4 (1.4)	ns	4.9 (0.4)	5.1 (0.4)	<0.01			
<b>DLco (% pred)</b>	99 (15)	106 (14)	<0.05	100 (11)	106 (12)	<0.05	103 (11)	103 (13)	ns
<b>TLC<sub>He</sub> (L)</b>	5.5 (1.4)	5.8 (1.5)	ns	6.3 (0.7)	6.8 (0.8)	<0.05	4.9 (1.2)	5.0 (1.4)	ns
<b>TLC<sub>B</sub> (L)</b>	5.8 (1.4)	5.9 (1.6)	ns	6.5 (0.8)	6.8 (0.8)	<0.05	5.3 (1.2)	5.6 (1.4)	<0.01
<b>FRC<sub>B</sub> (% pred)</b>	65 (20)	81 (24)	<0.005	71 (7)	85 (12)	<0.01	86 (21)	90 (19)	ns
<b>ERV (L)</b>	0.4 (0.3)	0.9 (0.7)	<0.01	0.8 (0.3)	1.3 (0.4)	<0.005	0.4 (0.2)	0.7 (0.5)	<0.005
<b>RV<sub>B</sub> (% pred)</b>	87 (22)	87 (19)	ns	79 (17)	83 (13)	ns	116 (26)	113 (25)	ns
<b>VC<sub>B</sub> (% pred)</b>	90 (10)	93 (12)	ns	94 (8)	96 (8)	<0.05	86 (11)	91 (13)	<0.01
<b>Raw (% pred)</b>	201 (88)	154 (50)	ns	149 (30)	115 (23)	<0.005	329 (166)	252 (112)	<0.05
<b>SGaw (% pred)</b>	108 (40)	96 (24)	ns	105 (22)	114 (25)	ns	52 (31)	61 (40)	ns

p- values refer to the Wilcoxon signed rank test

in all study groups. Airways resistance ( $R_{aw}$ ) was within normal range in all OSAS patients, but was high in patients with asthma. Weight loss induced a significant decrease in  $R_{aw}$  in OSAS group and asthma group but not in patients with morbid obesity.

The mean value of CV as well as closing capacity ( $CC = CV + RV$ ) were within normal range, but because of low FRC closing capacity exceeded FRC ( $CC/FRC > 100\%$ ) in 10 patients out of 11 with morbid obesity. The mean  $CC/FRC$  was 119 (16%). After weight reduction  $CC$  was higher than  $FRC$  only in three patients, Figure 9. The mean  $CC/FRC$  decreased to 92 (17%) after weight reduction. In OSAS patients with less severe obesity (III), initial  $CC/FRC$  was 104 (18%) and after weight reduction 85 (13%).



**Figure 9.** Closing volume ( $CC$ ) compared to  $FRC$  in patients with morbid obesity (I) and in obese patients with OSAS (III). 1 = before weight reduction; 2 = after weight reduction. The p-values refer to Wilcoxon signed rank test.

In obese patients with OSAS (III), closing volume was measured also in supine position both before and after weight loss. A slight decrease in closing volume was demonstrated in sitting position compared to supine values ( $p = 0.06$  before weight loss;  $p = 0.01$  after weight loss). In response to weight loss, a significant decrease in closing volume was found in OSAS group ( $p < 0.05$ )(III) but not in patients with morbid obesity (I).

### 3. Postural and weight loss induced changes in arterial oxygenation (I-IV)

Results of arterial blood gas analysis are shown in Table 6. In Studies I-III arterial blood samples were first taken at rest in supine position and after that in standing position. In Study IV blood samples were taken only in supine position. In patients with morbid obesity and in OSAS patients the mean arterial oxygen tension (PaO<sub>2</sub>) was slightly reduced in supine position. Standing up induced a significant increase in PaO<sub>2</sub>. PaCO<sub>2</sub> and pH were within normal range in all patients in both body positions.

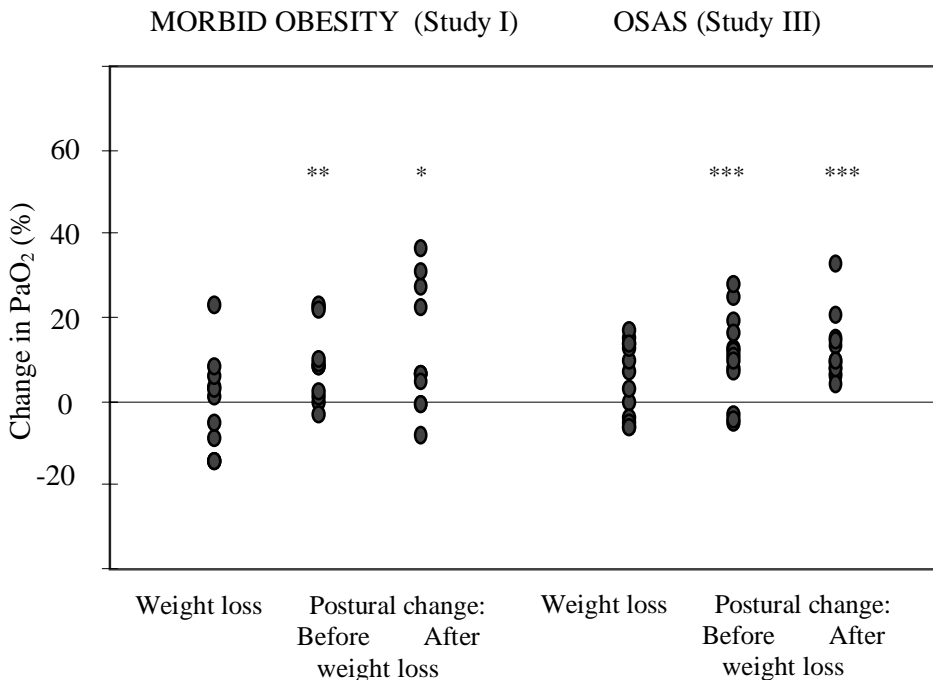
**Table 6.** Results of arterial blood gas analyses in different patient groups. Data are mean (SD).

	Morbid obesity; Study I		OSAS; Study III		Asthma; Study IV	
	Before weight loss	After	Before	After	Before	After
<b>PaO<sub>2</sub> (kPa)</b>						
Supine	10.6 (1.4)	10.4 (1.0)	10.3 (0.8)	10.9 (1.1)	11.4 (0.9)	11.9 (1.4)
Standing	11.6 (1.3)	11.6 (1.3)	11.4 (1.4)	12.1 (1.0)		
	**	*	***	***		
<b>PaCO<sub>2</sub> (kPa)</b>						
Supine	5.0 (0.4)	5.0 (0.3)	5.4 (0.4)	5.3 (0.3)	5.2 (0.3)	5.2 (0.6)
Standing	4.7 (0.4)	4.7 (0.5)	5.2 (0.4)	5.1 (0.5)		
	*	**				
<b>pH</b>						
Supine	7.42 (0.02)	7.41 (0.01)	7.40 (0.02)	7.41 (0.03)	7.42 (0.01)	7.42 (0.03)
Standing	7.43 (0.02)	7.42 (0.02)	7.41 (0.02)	7.43 (0.05)		
<b>P(A-a)O<sub>2</sub></b>						
Supine	3.5 (1.3)	3.1 (1.1)	3.2 (0.9)	2.6 (0.9)	2.6 (0.7)	2.5 (1.2)
Standing	2.9 (1.0)	2.2 (1.1)	2.3 (1.4)	1.6 (0.7)		
			*	**		

\* p<0.05, \*\*<0.01, \*\*\*p<0.005. Comparisons were made between standing and supine body positions, and also values after weight loss were compared with the values before weight loss. P-values refer to the paired t-test in Study I and the Wilcoxon signed rank test in Study III and IV.

## RESULTS

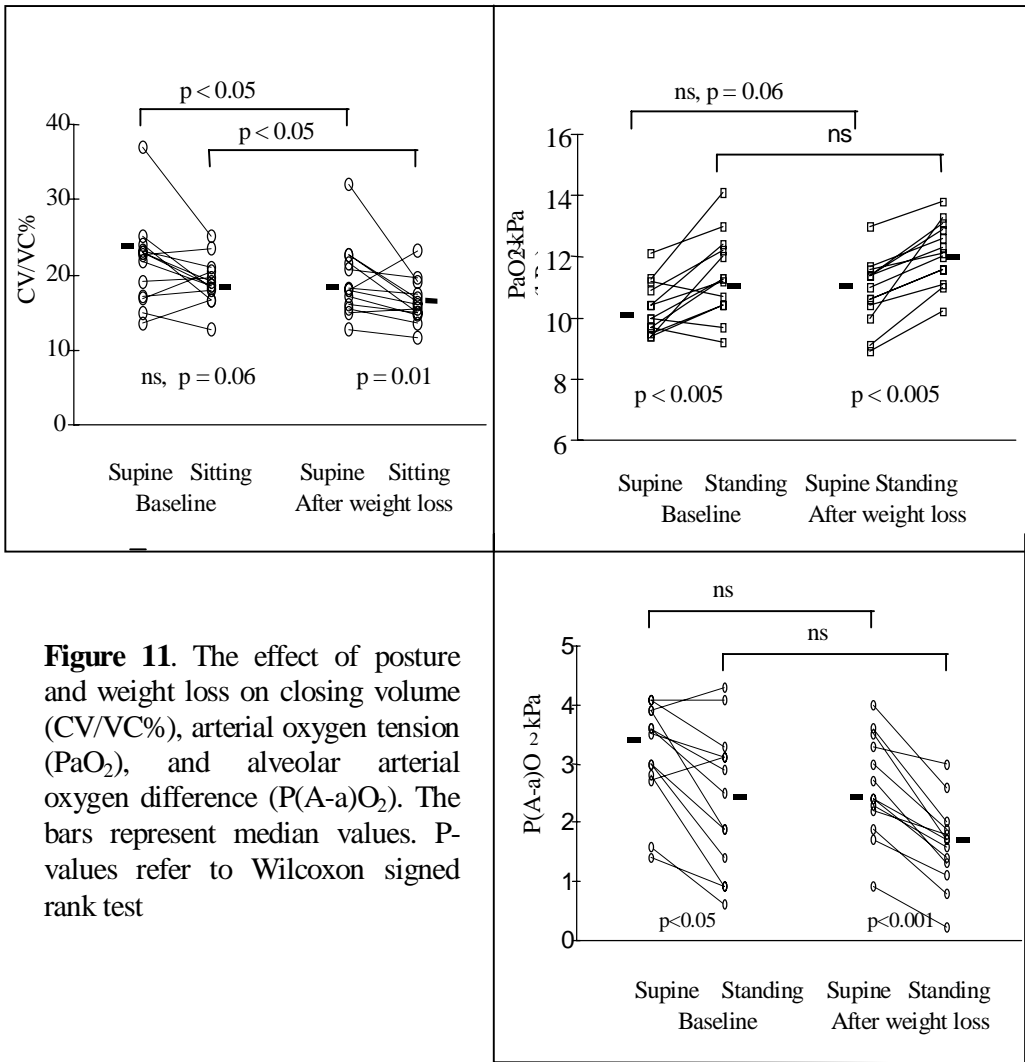
The effects of weight reduction and standing up on PaO<sub>2</sub> as a percentage from baseline values are shown in Figure 10. With weight reduction no change in the mean PaO<sub>2</sub> in patients with morbid obesity was observed. In OSAS group the change as a percentage from baseline was +5.5% (p = 0.07). In Study I there were four patients, who had moderate hypoxemia with PaO<sub>2</sub> 8.7 – 9.5 kPa. In all these patients, PaO<sub>2</sub> increased with weight reduction.



**Figure 10.** Changes in arterial oxygen tension (PaO<sub>2</sub>) in response to standing up and with weight reduction, expressed as a percentage from baseline. PaO<sub>2</sub> measured in standing position was compared with PaO<sub>2</sub> measured in supine position, and supine values after weight loss were also compared with supine values before weight loss \*p<0.05, \*\*p<0.01, \*\*\*p<0.005

In obese OSAS patients the postural changes in PaO<sub>2</sub> and P(A-a)O<sub>2</sub>, together with simultaneous changes in closing volume are shown in Figure 11. Closing volume was recorded in supine and sitting positions before and after weight reduction. CV/VC% showed a tendency to decrease in sitting position. The mean CV/VC% was significantly lower in sitting position, compared to supine values when measurements were done after weight loss. Although the mean PaO<sub>2</sub> increased in standing position before and after weight loss, a rise in PaO<sub>2</sub>

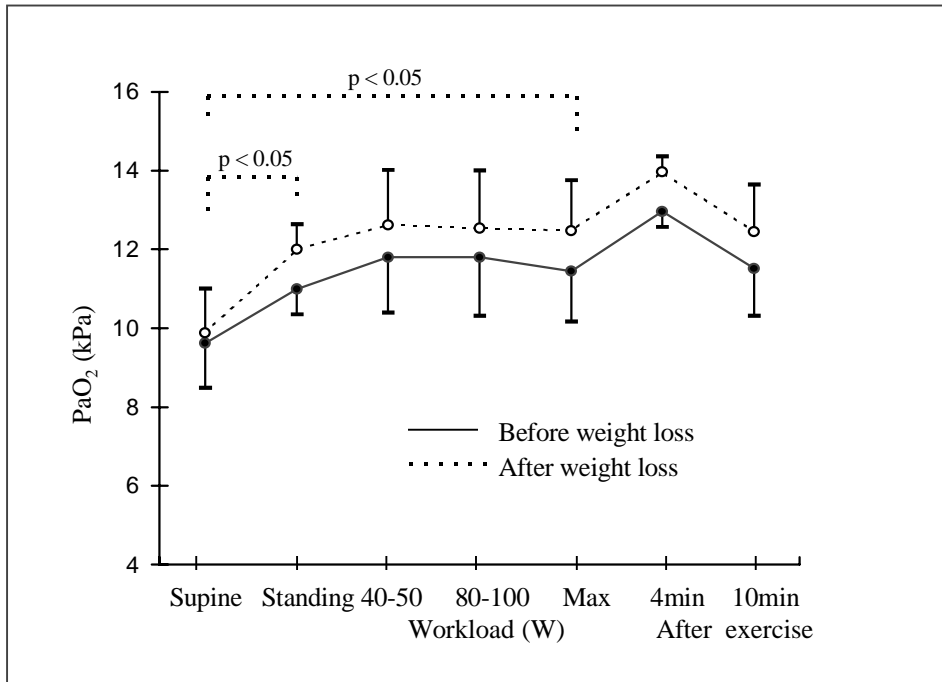
RESULTS



in all patients was observed only after weight reduction, Figure 10 and 11. The postural increase in the mean PaO<sub>2</sub> was accompanied by the decrease in P(A-a)O<sub>2</sub>

In morbidly obese patients arterial blood gas values were analyzed during exercise testing (II), Figure 12. At peak exercise, PaO<sub>2</sub> was significantly higher than at rest in supine position. The improvement in PaO<sub>2</sub> was observed in response to standing up. During exercise testing this higher level was maintained but no further change was demonstrated, Figure 12. Standing up and light exercise resulted in a significant decrease in P(A-a)O<sub>2</sub> ( $p < 0.05$ )

when compared to supine values. With weight reduction blood gases during exercise did not change. In response to weight loss a significant decrease in  $P(A-a)O_2$  was observed at peak exercise.



**Figure 12.** Arterial oxygen tension ( $PaO_2$ ) in response to standing up from supine position and during exercise testing in morbidly obese patients.  $N = 7$ . P-values refer to the Wilcoxon signed rank test.

#### 4. The effect of weight loss on PEF variability in obese asthmatics (IV)

A significant improvement in the mean morning and evening PEF values with weight loss was demonstrated. The difference between the daily highest and lowest PEF did not change. Diurnal PEF variation decreased from 5.5% (2.4) to 4.5% (1.5) ( $p = 0.01$ ). PEF indexes over a follow-up period of 14 days before and after weight loss are shown in Table 7. Calculated from the morning PEF values over two weeks, the mean difference between the highest and lowest morning PEF values fell by 38% with weight reduction. Day-to-day PEF variation decreased from 5.3% (2.6) to 3.1 % (1.1) ( $p < 0.005$ ).

## RESULTS

**Table 7.** PEF indexes before and after VLCD period of eight weeks in obese patients with asthma. Values are means (SD).

	Before weight loss	After weight loss	p - value
Morning PEF (l/min)	399 (80)	418 (85)	p < 0.001
Evening PEF (l/min)	406 (86)	426 (88)	p < 0.005
Lowest morning PEF (l/min)	368 (66)	404 (84)	p < 0.001
Highest morning PEF (l/min)	437 (92)	452 (93)	ns
Highest - lowest morning PEF (l/min)	63 (35)	39 (10)	p < 0.005

p- values refer to the Wilcoxon signed rank test

### 5. Respiratory gas exchange in obese patients with OSAS and obese asthmatics (III, IV, V)

The results of pulmonary gas exchange at rest in supine position and during orthostatic test in standing position in obese OSAS patients, obese asthmatics, and in healthy subjects are shown in Table 8. Tidal volume was expressed as a percentage from actual FVC. Minute ventilation ( $\dot{V}E$ ) was related to predicted values of maximal voluntary ventilation (MVV) and oxygen uptake to predicted values of maximal  $\dot{V}O_2$ . Comparisons between patient groups and control subjects were based on percentage of predicted values in order to control the differences in gender, age, and height distribution between groups.  $VT/FVC\%$  and  $\dot{V}E/MVV\%$  at rest as well as  $\dot{V}O_2/\dot{V}O_{2max}\%$  were higher in obese asthmatics than in healthy controls. In obese OSAS patients these values were not different from the control group. In obese asthma patients minute ventilation ( $p < 0.01$ ) and tidal volume decreased after weight reduction (IV, V). When standardized to body weight, oxygen uptake ( $\dot{V}O_2/kg$ ) was low in obese asthmatics and in obese OSAS patients. In asthma group a significant correlation ( $r = 0.76$ ,  $p < 0.05$ ) between initial weight and oxygen consumption was observed. However, not a significant change in oxygen uptake after weight loss was demonstrated.

RESULTS

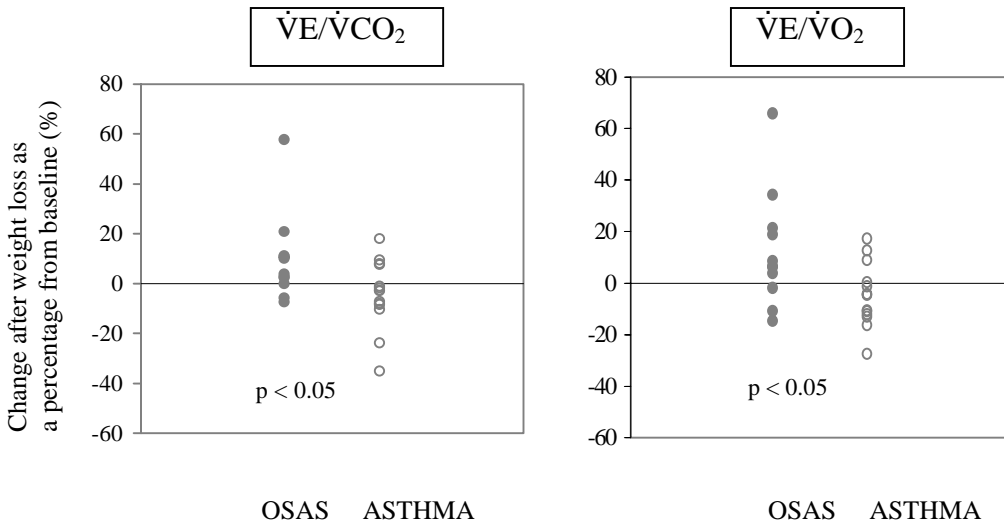
**Table 8.** Tidal volume expressed as a percentage from FVC (VT/FVC; %), minute ventilation as a percentage from predicted MVV ( $\dot{V}E/MVV$ ; %) and  $\dot{V}O_2/kg$  in OSAS patients (III), in obese asthmatics (V), and in healthy controls (V).

	OSAS; Study I		Asthma; Study V		Controls; Study V
	Before weight loss	After weight loss	Before weight loss	After weight loss	
<b>BF (1/min)</b>					
Supine	16.2 (3.3)	16.8 (3.4)	16.0 (2.3)	15.0 (3.3)	13.9 (3.1)
Standing	14.5 (3.2)	14.1 (3.9)	15.0 (3.1)	15.0 (3.3)	14.2 (3.2)
<b><math>\dot{V}E/MVV</math> (%)</b>					
Supine	6.8 (1.4)	6.6 (1.6)	9.0 (1.6)**	7.5 (1.8)	7.0 (1.2)
Standing	8.7 (5)	8.9 (5.4)	11.6 (3.4)**	9.9 (2.9)	8.1 (1.5)
<b>VT/FVC (%)</b>					
Supine	11.4 (2.1)	10.3 (1.8)	16.7 (4.1)**	14.1 (3.8)	12.1 (2.3)
Standing	14.2 (2.3)	15.5 (3.5)	23 (7.4)**	18.7 (5.2)	13.9 (2.4)
<b><math>\dot{V}O_2/kg</math> (ml/min/kg)</b>					
Supine	2.7 (0.5)***	2.7 (0.6)***	2.5 (0.6)****	2.8 (0.6)***	3.5 (1.0)
Standing	3.2 (0.6)**	3.2 (0.9)**	3.0 (0.6)***	3.3 (0.7)**	3.9 (0.7)
<b><math>\dot{V}O_2/\dot{V}O_{2max}</math> (%)</b>					
Supine	11.2 (1.9)	9.9 (2.1)	13.1 (3.2)*	12.3 (2.6)	10.4 (2.5)
Standing	13.2 (2.6)	11.6 (2.6)	15.7 (3.7)**	14.9 (3.1)*	11.5 (2.0)

$p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.005$ , \*\*\*\*  $p < 0.001$ ; P-values refer to the Mann-Whitney-U-test, which was used for comparisons between patient group and control subjects.

When ventilatory equivalents for  $O_2$  ( $\dot{V}E/\dot{V}O_2$ ) and  $CO_2$  ( $\dot{V}E/\dot{V}CO_2$ ) measured in supine body position were compared before and after weight loss in OSAS patients and patients with asthma, a significantly different response to weight loss was observed. OSAS patients showed tendency to increase ventilatory equivalents after weight loss, while in some asthma patients ventilatory

equivalents decreased after weight reduction. The individual changes in  $\dot{V}E/\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  are shown in Figure 13 (III, V).



**Figure 13.** The changes in ventilatory equivalents for  $O_2$  ( $\dot{V}E/\dot{V}O_2$ ) and  $CO_2$  ( $\dot{V}E/\dot{V}CO_2$ ) at rest in response to weight reduction.

During orthostatic test, however, ventilatory equivalents as well as end tidal  $CO_2$  while standing and change from supine to standing were not different from control patients, so that orthostatic response of respiratory gas exchange did not show tendency to hyperventilation in asthma group or in OSAS patients (III,V).

$\dot{V}E$  and  $\dot{V}O_2/kg$  were recorded every 30-second interval during orthostatic test and the mean values of  $\dot{V}E$  and  $\dot{V}O_2/kg$  for the asthma group over every interval were calculated. A close linear correlation between  $\dot{V}E$  and  $\dot{V}O_2/kg$  was found. The slope of the regression line in obese asthma patients was different from the control group ( $p < 0.001$ , asthmatics versus control group before weight loss;  $p < 0.005$  asthmatics versus control group after weight loss; Mann-Whitney U test was used for comparisons) (V).

## DISCUSSION

### 1. Study population and methods

In Study I-II, patients with morbid obesity were selected because we expected that the abnormalities in pulmonary function and gas exchange caused by obesity would be more clearly seen among patients with morbid obesity than with milder disease. Especially, we assumed to find hypoxemia in supine position. Most of the previous studies on weight reduction in morbid obesity have investigated the effects of surgically induced weight loss on respiratory function. The amount of weight loss following gastric surgery has been over 20 % from initial weight, whereas the mean weight loss after non-surgical treatments usually has been less than 20% (Pekkarinen 1999). One of the aims of this study was to find out, if treatment of obesity with the diet and behavioral therapy would induce weight loss enough to improve pulmonary function and gas exchange in short-term. In this study we did not follow up the long-term results. The maintenance of weight loss has been poor in some studies, but behavioral therapy combined with VLCD seems to improve long-term results (Pekkarinen et al. 1997).

Traditionally, the goal of the weight reduction has been the normalization of the weight. In most obese patients this is not realistic. Based on reports of medical benefits of moderate weight reduction, a weight loss of 5% of initial weight has been regarded as success in some studies (Pekkarinen 1999). In Study I, the mean weight loss was 12.8 % from initial, which is comparable with the average achieved using treatment programs including VLCD and behavior modification. However, the amount of weight loss achieved varied with a wide range between patients, Figure 8. The differences in initial weight and variation in weight loss results made it difficult to correlate changes in weight with improvement in pulmonary function. The mean values for the group, however, showed that even modest weight loss had significant effects on pulmonary function and respiratory gas exchange.

The postural effects on arterial blood gases were studied, because we expected that ventilation perfusion mismatch, which may mainly account for the hypoxemia of obesity, would be diminished in upright body position. It was hypothesized that the mechanisms of improvement in arterial oxygenation in standing body position would be similar to that expected with weight reduction.

Previous studies have suggested that the improvement in arterial oxygenation after weight loss has been demonstrated only if weight was reduced near to normal weight (Farebrother et al. 1974). With non-surgical treatment of obesity it seldom is possible to achieve normal or near normal weight, which may explain why improvement in arterial oxygenation with weight reduction was not observed in Studies I-II and IV.

There were four female patients who withdrew from the Study I, because they were not willing to repeat pulmonary function tests and exercise testing which they regarded as too demanding or they had dropped out the weight reduction program. The baseline characteristics of all 15 patients started have been presented in the results of this thesis.

For the studies III-V patients with less severe obesity were selected in order to achieve weight normalization at least in some patients. In these studies the follow up period was shorter than in Studies I-II. Pulmonary function tests and gas exchange analyses were repeated soon after the VLCD period, which in Study III was 6 weeks and in Study IV-V 8 weeks. The results of weight reduction were similar in both patient groups. With respect to the age and sex, groups were different from each other. Except for one female patient, OSAS patients were males, whereas in the asthmatic group there was a female preponderance. Asthmatic patients were older than OSAS patients, with the mean age of 51.8 (9.1) years. When comparing gas exchange data between these two groups these differences in study populations have to be taken into consideration.

In Study IV and V there were 7 patients who had history of allergy to pollen or skin prick tests had been positive to pollen. Allergic patients were studied out of pollen season. Asthmatic patients had been advised not to change their anti-asthmatic treatment other than short-acting  $\beta_2$  - agonists during the study, if the stability of asthma was clinically acceptable. When the follow-up period was only 2 months, no need to change the maintenance therapy was reported. The dose and timing of long-acting  $\beta_2$  - agonists and sustained-release theophylline compounds were identical at study visits before and after weight loss. Patients were advised not to use short-acting bronchodilators for 4 h before pulmonary function tests including serial PEF measurements at home.

In Studies IV-V asthmatic patients had been followed carefully for one year before this study so that their asthma could be classified as stable, although

their expiratory flow volumes were not normal when starting the weight reduction program in this study.

All patients and subjects in Studies I-V were non-smokers or ex-smokers. Only patients who had quit smoking at least two years earlier or more were enrolled. Diffusing capacity was within normal range in all patients including ex-smokers.

## **2. Lung volumes and obesity**

Ray et al. (1983) suggested that abnormal lung volumes in obese patients are usually caused by lung disease, not by obesity, except in patients with extreme obesity. Changes in lung volumes have been classified into two groups, those that change in proportion to degree of obesity, i.e. ERV and FRC and those reduced only in extreme obesity, i.e. VC and TLC. Patients with extreme obesity were then defined as patients whose weight (kg) exceeded height (cm). Several other studies have reported that the changes in FRV and ERV as well as VC, TLC and FEV<sub>1</sub> are in proportion to the degree of obesity (Rubinstein et al. 1990, Zerah et al. 1993).

The results of this study give support to the assumption that lung volumes in morbid obesity fall within the generally accepted 95% confidence limits for the predicted values. Also in the subgroup of patients with highest BMI and waist circumference (Group 2 in Figure 6) the mean values of lung volumes were within normal range. In spite of the normal initial lung volumes, a statistically significant increase in FEV<sub>1</sub>, FVC, TLC<sub>He</sub> as well as in maximal voluntary ventilation (MVV) was demonstrated after weight reduction among patients with morbid obesity.

Previous studies have shown reduced expiratory flow rates in nonsmoking patients with obesity, especially obese men may have low MEF<sub>50</sub> and MEF<sub>25</sub> values (Rubinstein et al. 1990, Zerah et al. 1993). In our study expiratory flows were not below normal in morbid obesity group or in OSAS patients. Still, a significant increase in the mean MEF<sub>50</sub> was demonstrated after weight reduction in OSAS patients.

Decreased FRC and ERV have been regarded as the most characteristic pulmonary function abnormalities in obesity. In this study the 95% confidence limits for the predicted values of FRC are from 71% to 142% in men and from 74% to 136% in women. The mean FRC was reduced in morbidly obese

patients and just below normal range in OSAS patients with moderate to severe obesity. In asthmatic patients with the same degree of obesity as in OSAS group, the mean initial FRC was within normal range. Individual FRC values varied in a wide range in asthma patients. With weight reduction FRC and ERV increased in all patient groups.

What is then the significance of low FRC in obese patients? The relationship of closing capacity to FRC is important when we evaluate the tendency to increased small airway closure in obesity. Closing capacity may approach or exceed the reduced FRC and further lead to a closure of small airways during tidal breathing and impairment of gas exchange. In studies I and III the CC / FRC ratio was high before weight loss and a significant decrease was demonstrated after weight loss, as shown in Figure 9.

The pharyngeal size, as well as the size of intrapulmonary airways, is dependent on lung volumes (Series et al. 1990). In OSAS patients pharyngeal size may decrease with decreasing lung volumes (Hoffstein et al. 1984). By this mechanism reduced FRC may cause pharyngeal narrowing and increase in airways resistance. Surprisingly, in Study III airways resistance ( $R_{aw}$ ) was within normal range in all OSAS patients. Also peak inspiratory flow (PIF) and forced inspiratory flow in one second ( $FIV_1$ ), which have been regarded as acceptable variables for detection of laryngeal obstruction (Hoijer et al. 1991) were normal. Despite the normal initial values, a significant decrease in airways resistance and increase in  $FIV_1$  was observed with weight reduction. Only in patients with asthma the mean initial  $R_{aw}$  was increased. In all patient groups  $R_{aw}$  showed tendency to decrease, which may reflect the changes in FRC, because airways conductance did not change with weight reduction.

### **3. Arterial oxygenation and obesity**

The improvement in arterial oxygenation in response to change of posture from supine to standing was observed in patients with morbid obesity and in sleep apnea patients. In asthmatics arterial oxygenation was measured only in supine position. When compared to obese OSAS patients, arterial oxygen tension ( $PaO_2$ ) was significantly higher in obese asthmatics (Table 6). In response to weight reduction improvement in  $PaO_2$  was not demonstrated.

In OSAS patients the changes in  $PaO_2$  in response to standing up before and after weight loss were compared with simultaneous changes in closing volume (CV) and alveolar arterial  $O_2$  difference  $P(A-a)O_2$ . The increase in  $PaO_2$  when

standing up coincided with the decrease in  $P(A-a)O_2$  and a slight decrease in CV. These findings give support to the assumption that the decrease in airways closure will improve ventilation and perfusion relationship and oxygenation in standing position.

Why then was weight reduction not effective in improving arterial oxygenation? Several previous studies on surgically induced weight loss have reported a significant increase in  $PaO_2$  with weight reduction, but then the mean weight loss has been over 30 kg (Vaughan et al. 1981, Thomas et al. 1989, Refsum et al. 1990), Table 2. Vaughan et al. (1981) reported a significant improvement in  $PaO_2$  only if change in BMI was more than 20  $kg/m^2$ . Our results showed that the mean change in BMI was 6.0  $kg/m^2$  in Study I, 3.8  $kg/m^2$  in Study III and 5.1  $kg/m^2$  in Study IV. Thus it seems that with moderate weight loss it is not possible to improve arterial oxygenation in spite of a significant increase in ERV or FRC. Our results give support to the conclusion Farebrother et al. (1974) stated: for severely obese subjects it seems not to be that "little is good, but more is better", but rather "little is no good, and much is essential".

#### **4. Respiratory gas exchange and obesity**

In morbidly obese patients respiratory gas exchange analysis showed that oxygen uptake ( $\dot{V}O_2$ ) at peak exercise did not change with weight reduction but a significant increase in  $\dot{V}O_2/kg$  was observed. Slight increase in  $\dot{V}E/\dot{V}CO_2$  and decrease in  $F_{ETCO_2}$  in morbid obesity after weight reduction suggested tendency to hyperventilation. When ventilatory equivalents during orthostatic test were compared between OSAS patients and asthmatics, a significant difference in changes after weight reduction was observed. OSAS patients tended to increase  $\dot{V}E/\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  while patients with asthma showed decreasing tendency in these variables (Figure 11).

#### **5. Asthma and obesity**

There are two previous studies on weight loss in obese asthmatics. Dixon et al. (1999) have reported a significant decrease in asthma score based on standard questionnaire one year after gastric banding. Decrease in asthma symptoms and use of rescue medication as well as improvement in pulmonary function (PEF, FEV1 and FVC) have been demonstrated after dietary treatment of obese asthmatics (Stenius-Aarniala et al. 2000). Increasing epidemiological

evidence suggests that there is an association between asthma and obesity. At present, it is not possible to say, whether obesity has contributed to the rise in asthma prevalence or whether asthma patients gain weight as a result of activity limitations or some other reasons. It could be assumed that impairment in pulmonary mechanics related to obesity, such as reduction in lung volumes, increased airways resistance and impairment in small airways function may contribute to an increase in asthma severity.

The mean FEV<sub>1</sub> was low before weight loss while the mean FVC was within normal range (Study IV). As in the study of Stenius-Aarniala et al. (2000) a significant increase in FEV<sub>1</sub> and FVC was observed in our study. FEV<sub>1</sub> / FVC ratio did not change. Thus the increase in FEV<sub>1</sub> may reflect overall improvement in lung volumes rather than decrease in airways obstruction. Flow rates at low lung volumes (MMEF = FEF<sub>25-75</sub>) were slightly reduced and showed a significant increase after weight loss also when related to forced vital capacity (MMEF/FVC). This finding suggests decreased peripheral airways obstruction. Also, an increase in FVC may indicate improvement in small airways obstruction.

The mean values of FRC, VC and TLC were within normal range before weight loss, but still a significant increase in lung volumes was demonstrated after weight reduction in morbid obesity group (Study I) as well as OSAS group (Study III). The most significant improvement in lung volumes was the increase in expiratory reserve volume (ERV). In chronic asthma RV and FRC can be elevated because of hyperinflation. In obese asthmatics weight reduction and a decrease in asthma severity with less inflation of the lungs may change FRC to opposite directions. This may explain why in our study individual changes in FRC varied with a wide range. The increase in ERV was more constant, so that in obese asthmatics changes in ERV better than FRC may reflect the effects of obesity or weight loss on lung volumes. Airways resistance was high in obese asthmatics. A significant decrease was demonstrated with weight reduction, but the mean Raw still remained above normal. The change in body mass index correlated with the increase in airways conductance (1/Raw).

In clinical practice, the changes in function of small airways are difficult to demonstrate. Expiratory flows measured at low lung volumes (MEF<sub>50</sub>, MEF<sub>25</sub>, and MMEF=FEF<sub>25-75</sub>) have been regarded as measures of peripheral airways narrowing. As a measure of airways size related to lung size the ratio MMEF/FVC has been used. Both obesity and asthma can cause excessive

small airway closure and increase in gas trapping. Of parameters that reflect small airway obstruction, MMEF was reduced and increased after weight loss as well as MMEF /FVC. Also increase in FVC and VC may reflect decreased small airways obstruction. On the other hand only slight if any gas trapping was observed based on our data of non ventilated lung compartment ( $TLC_B - TLC_{He}$ ).

Increased spontaneous variation in the airway caliber is considered as a hallmark of asthma. Diurnal variability of PEF has been used as a marker of airway responsiveness, particularly in epidemiological studies. Several alternative equations can be used to express PEF variation. In Study IV PEF variability was expressed in three ways: as diurnal PEF variation, the difference between the highest and lowest morning PEF values measured over a follow-up period of 14 days, and day-to-day variation. In obese asthmatics (Study IV) PEF variability decreased with weight loss, Table 7. The mechanism of these changes is not clear, but simply the simultaneous increase in morning and evening PEF could explain the reduction in diurnal variation. However, this mechanism will not explain the reduction in day-to-day variation or the decreased difference between lowest and highest morning PEF over follow-up period. An interesting finding was that the lowest morning PEF values increased with weight loss while the highest morning PEF remained unchanged. The mechanism of how weight loss affects PEF variation still remains unclear. It could be assumed that the decrease in airways obstruction and improved ventilatory mechanics after weight loss may contribute to a better control of airways obstruction.

Tendency to rapid shallow breathing pattern has been observed in morbid obesity (Kaufman et al. 1959), whereas symptomatic patients with chronic asthma may display increased minute ventilation with increased tidal volume while breathing frequency is normal (Tobin et al. 1983). Morbidly obese patients are known to have increased metabolic demands because extra muscle work must be performed to move an obese body (Dempsey et al. 1966, Luce 1980). Rates of total oxygen consumption ( $\dot{V}O_2$ ) and carbon dioxide production ( $\dot{V}CO_2$ ) are increased even at rest in obesity (Zavala et al. 1984, Refsum et al. 1990). To meet these increased requirements, minute ventilation has to be increased. To maintain augmented ventilation, extra work has to be done because oxygen cost of breathing is high in obesity (Sharp et al. 1964b). The main reason might be a decrease in chest wall compliance (Naimark et al. 1960).

In Study V, minute ventilation ( $\dot{V}E$ ), tidal volume (VT) and respiratory gases were continuously monitored during orthostatic tolerance test as described by Malmberg et al. (2000). The data from five minutes during stable phase in supine and standing positions was used for calculations of ventilatory gas exchange variables. The results of the study V showed that in obese asthmatics resting minute ventilation and tidal volume as a percentage of FVC were higher than in healthy controls. Thus the breathing pattern of obese asthmatics in Study V was similar to that previously described in symptomatic patients with chronic asthma. In response to standing up the increase in ventilation was in proportion to the changes in oxygen uptake and  $CO_2$  production so that ventilatory equivalents ( $\dot{V}E/\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$ ) were not elevated in standing position. When using cut-off levels for these parameters suggested by Malmberg and co-workers (2000), the mean values of  $\dot{V}E/\dot{V}O_2$  and  $\dot{V}E/\dot{V}CO_2$  in standing position or changes in ventilation equivalents from supine to standing ( $\Delta\dot{V}E/\dot{V}O_2$  and  $\Delta\dot{V}E/\dot{V}CO_2$ ) were not suggestive of tendency to hyperventilation. Increased oxygen cost of breathing associated with obesity or asthma or both may account for the high resting  $\dot{V}O_2$ . The change in ventilation related to change in oxygen consumption ( $\Delta\dot{V}E/\Delta\dot{V}O_2/kg$ ) declined in obese asthmatics after weight reduction.

## SUMMARY

The effects of obesity on respiratory function have been widely studied since the early 1960s. The characteristic changes in lung volumes i.e. reduction in FRC and ERV, as well as hypoxemia in supine position are well established. Most of the study populations, however, have been morbidly obese patients with many other complications of obesity. In these patients the rapid treatment of obesity is of vital importance and surgical procedures have been widely used. Recently, conservative treatment with very-low-calorie diets (VLCD) has turned out to be effective also in morbid obesity.

One of the aims of the study was to evaluate whether weight reduction program including VLCD and behavior therapy (BT) would be effective in improving respiratory complications of morbid obesity. Simultaneously, changes in pulmonary gas exchange in response to standing up and during exercise were studied. A significant improvement in lung volumes with weight reduction was observed, although lung volumes except FRC and ERV were within predicted values also before weight loss. The relationship between closing capacity (CC) and FRC was calculated. In ten patients out of eleven studied, CC exceeded FRC. Weight reduction converted this relationship in eight patients. This may suggest improved ventilation to perfusion relationship and improved arterial oxygenation. Although the mean PaO<sub>2</sub> for the study group did not increase with weight reduction, PaO<sub>2</sub> increased in those patients who had marked hypoxemia before weight loss (n = 4, PaO<sub>2</sub> < 9.5 kPa). In response to standing up, the mean PaO<sub>2</sub> increased both before and after weight loss. **(I)**

In morbidly obese patients arterial blood gases and respiratory gases were analyzed during exercise testing. At peak exercise PaO<sub>2</sub> was significantly higher than at rest in supine position. The improvement in PaO<sub>2</sub> was observed in response to standing up and it was maintained during exercise. The increase in PaO<sub>2</sub> was accompanied by decrease in alveolar arterial O<sub>2</sub> difference P(A-a)O<sub>2</sub> referring to improvement in ventilation to perfusion abnormalities. With weight reduction P(A-a) at peak exercise decreased. Respiratory gas analyses showed that oxygen consumption ( $\dot{V}O_2$ ) achieved at peak exercise did not change with weight reduction but a significant increase in oxygen consumption when related to body weight ( $\dot{V}O_2/\text{kg}$ ) was observed. **(II)**

In order to evaluate the impact of obesity on daytime pulmonary function and gas exchange, OSAS patients with moderate to severe obesity were studied before and after dietary induced weight loss. CV was measured in supine and sitting positions. CV values were significantly lower after weight reduction and in sitting position. The changes in PaO<sub>2</sub> and P(A-a)O<sub>2</sub> in response to standing up were parallel to those demonstrated in patients with morbid obesity. When changes in daytime arterial oxygen tension were compared to changes in nocturnal desaturation index (ODI<sub>4</sub>), a significant positive correlation was found. On the whole the abnormalities in daytime lung function and gas exchange were similar to those in morbid obesity. This similarity suggests that obesity may be the main factor in the pathogenesis of daytime gas exchange disturbances in obese OSAS patients. (III)

The relationship between asthma and obesity has been under discussion after several epidemiological studies reported association between asthma and obesity. In order to evaluate the relation between these two common diseases, the effects of weight loss on airways obstruction and PEF variability were compared to simultaneous changes in lung volumes and breathing pattern. The mean FEV<sub>1</sub> was low before weight loss while the mean FVC was within normal range. A significant increase in FEV<sub>1</sub> and FVC was observed, but FEV<sub>1</sub>/FVC ratio did not change. Thus the increase in FEV<sub>1</sub> may reflect improvement in lung volumes rather than decrease in airways obstruction. However, other findings such as increase in MMEF and MMEF/FVC as well as increase in FVC may reflect decrease in small airway obstruction. Also reduction in airways resistance (Raw) after weight loss suggests decrease in obstruction of larger airways. PEF variability expressed as diurnal PEF variation, day-to-day variation or difference between the highest and lowest morning PEF during the follow-up period declined with weight reduction. Bronchial reactivity measured by histamine challenge test did not change. (IV)

The resting minute ventilation and tidal volume are higher in obese asthmatics than in healthy controls. With weight reduction a significant decrease in minute ventilation was observed. As a response to change of posture from supine to standing the rate of increase in ventilation was greater in obese asthmatics than in non-obese subjects. The increase in ventilation was in proportion to the changes in  $\dot{V}O_2$  and  $\dot{V}CO_2$  so that ventilation equivalents were not elevated in standing position. When the change in  $\dot{V}E$  in response to standing up was related to simultaneous increase in  $\dot{V}O_2/kg$ , a significant decrease in  $\Delta\dot{V}E/\Delta\dot{V}O_2/kg$  was demonstrated with weight reduction. (V)

## CONCLUSIONS

The effects of obesity on pulmonary mechanics and gas exchange must be known in order to evaluate whether the abnormalities in lung function are caused by obesity or an existing lung disease. On the other hand, in different pulmonary diseases the impact of obesity on the severity of the disease should be considered.

The results of this study suggest that restrictive pattern in spirometry is seldom caused by obesity alone, except in patients with extreme obesity. Low FRC or ERV seem to be the most characteristic changes in lung volumes and even modest weight loss is effective in increasing FRC. The low FRC may be especially unfavorable in lung diseases with airway narrowing, such as different obstructive lung diseases and OSAS. In obese patients with low FRC, the airways obstruction as well as gas exchange abnormalities may be increased in supine position.

The characteristic features for hypoxemia induced by obesity are the worsening of hypoxemia in supine position and improvement in standing position. Hypoxemia that improves during exercise testing is typical for obesity. The results of this study confirm the previous findings that if the goal of the weight loss is to improve oxygenation then the criteria of successful treatment should be normalization of weight or at least near normal weight.

The causal relationship between asthma and obesity still remains unclear. It seems possible that obesity may trigger latent asthma with different mechanisms but it is unlikely that obesity could cause asthma. Our results suggest that obesity may worsen airways obstruction both in larger and small airways. Obesity with high ventilatory demands as well as increased work of breathing may be harmful in asthmatics with tendency to hyperventilation. In addition to these more or less mechanical effects of obesity on lung function, some indirect mechanisms or cofactors have been suggested. Further studies will be needed to explain the connection between obesity and respiratory complications.

## ACKNOWLEDGEMENTS

This study was carried out at the Laboratory of Clinical Physiology, Laboratory Department, and the Division of Pulmonary Medicine, Department of Medicine at the Helsinki University Central Hospital.

I wish to thank Professor Lauri A. Laitinen, MD, Chief Executive Officer of Helsinki and Uusimaa Hospital Federation and former Head of the Department of Medicine at the Helsinki University Central Hospital for providing me the opportunity to work at his department and perform this study, and for his kind interest in my work.

I owe my warmest thanks to my supervisor Professor Anssi Sovijärvi, MD., for introducing me to clinical physiology and for proposing the subject of this study. His interest in lung function and his remarkable ability to suggest ideas and solutions made this study possible.

I express my sincere thanks to my other supervisor, Professor Brita Stenius-Aarniala MD., for giving valuable advice and criticism. Especially, I wish to thank her for providing me the opportunity to study the patients with asthma and obesity.

I owe my gratitude to Docents Ritva Tammivaara and Hannu Puolijoki, the official experts appointed by the Faculty of Medicine, University of Helsinki, for reviewing the manuscript and giving me valuable suggestions and comments.

I am very grateful to Docent Pertti Mustajoki MD., Third Department of Medicine, Helsinki University Central Hospital and later the Head of the Department of Medicine at Peijas Hospital for his help and advice, as well as the contribution as a coworker. His wide knowledge of obesity and of the treatment of obesity were essential for accomplishing this study.

My heartfelt thanks go to my coworker Docent Paula Maasilta, MD., Division of Pulmonary Medicine, Helsinki University Central Hospital. She has always found time to offer her guidance and encouragement throughout the course of this work. Her optimism and emphatic attitude helped me to overcome difficult situations during these years. My special thanks go to my coworker Docent Juha Aittomäki, MD., Helsinki University Central Hospital for his

## ACKNOWLEDGEMENTS

---

practical assistance. Although busy at his daily routines, he kindly found time for this study.

I am most grateful to Niini Vartia, M. Sc., who revised the English language of this thesis.

My deepest thanks go to all the personnel of the Laboratory of Clinical Physiology, and Department of Pulmonary Medicine. Without their help and patience this work would not have been possible. I also wish to thank the personnel of the Metabolic Unit of Helsinki University Central Hospital, Soile Rönkä, R.N and Pirjo Mecklin R.N at the Division of Pulmonary Medicine, and Anne Nurmikumpu, R.N. and Marjaana Korpinen, R.N. at Helsingin Lääkärikeskus for conducting the weight reduction groups during the course of these studies.

I wish to thank all my colleagues at the Division of Pulmonary Medicine and Laboratory of Clinical Physiology for their kind support and cooperation.

I would also like to thank all the patients who participated in this study at Helsinki University Central Hospital.

Finally, I owe my warmest thanks to my dear husband Juha and our children Anna and Jaakko. Without their love and understanding, I could not have completed this long-term project. I also thank them for their practical assistance during the final phase of the work.

I am grateful for the financial support provided by grants from the Ida Montin Foundation and the Finnish Cultural Foundation.

Turenki, September 2000

*Katri Hakala*

---

## REFERENCES

American Thoracic Society. Standardization of Spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-1136

Anch AM, Remmers JE, Bunce H. Supraglottic airway resistance in normal subjects and patients with occlusive sleep apnea. *J Appl Physiol* 1982;53:1158-1163

Anderson JW, Hamilton CC, Brinkman-Kaplan V. Benefits and risks of an intensive very-low-calorie diet program for severe obesity. *Am J Gastroenterol* 1992;87:6-15

Appel M, Childs A, Healey E, Markowitz S, Wong S, Mead J. Effect of posture on vital capacity. *J Appl Physiol* 1986;61:1882-1884

Appelberg J, Nordahl G, Janson C. Lung volume and its correlation to nocturnal apnoea and desaturation. *Resp Med* 2000;94:233-239

Babb TG, Korzick D, Meador M, Hodgson JL, Buskirk ER. Ventilatory response of moderately obese women to submaximal exercise. *Int J Obes* 1991;15:59-65

Barrera F, Hillyer P, Ascanio G, Bechtel J. The distribution of ventilation, diffusion, and blood flow in obese patients with normal and abnormal blood gases. *Am Rev Respir Dis* 1973;108:819-830

Behrakis PK, Baydur A, Jaeger MJ, Milic-Emili J. Lung mechanics in sitting and horizontal body positions. *Chest* 1983;83:643-646

Biring MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. *Am J Med Sci* 1999;318:293-297

Björntorp P. The regulation of adipose tissue distribution in humans. *Int J Obes* 1996;20:291-302

Boezen HM, Postma DS, Schouten JP, Kerstjens HAM, Rijcken B. PEF variability, bronchial responsiveness and their relation to allergy markers in a random population (20-70 Yr). *Am J Respir Crit Care Med* 1996;154:30-35

Boezen M, Schouten J, Rijcken B, Vonk J, Gerritsen J, Van der Zee S, Hoek G, Brunekreef B, Postma D. Peak expiratory flow variability, bronchial responsiveness, and susceptibility to ambient air pollution in adults. *Am J Respir Crit Care Med* 1998;158: 1848-1854

Borg G. Physical performance and perceived exertion. Gleeurp, Lund 1962:162

## REFERENCES

---

- Boulet L-P, Belanger M, Carrier G. Airway responsiveness and bronchial-wall thickness in asthma with or without fixed airflow obstruction. *Am J Respir Crit Care Med* 1995;152:865-871
- Brand PL, Postma DS, Kerstjens HA, Koeter GH. and. Relationship of airway hyperresponsiveness to respiratory symptoms and diurnal peak flow variation in patients with obstructive lung disease. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1991;143:916-921
- Brander PE, Mortimore IL, Douglas NJ. Effect of obesity and erect/supine posture on lateral cephalometry: relationship to sleep-disordered breathing. *Eur Respir J* 1999;13:398-402
- Bray GA. Complications of obesity. *Ann Intern Med* 1985;103:1052-1062
- Bray GA. Classification and evaluation of the overweight patient. In: Bray GA, Bouchard C, James WPT, eds. *Handbook of obesity*. New York: Marcel Dekker, Inc. 1998:831-854
- Brown IG, Zamel N, Hoffstein V. Pharyngeal cross-sectional area in normal men and women. *J Appl Physiol* 1986a;61:890-895
- Brown I, Taylor R, Hoffstein V. Obstructive sleep apnea reversed by increased lung volume? *Eur J Respir Dis* 1986b;68:375-380
- Brownell RB. *The LEARN program for weight control*. Philadelphia: University of Pennsylvania; 1985.
- Brusasco V, Crimi E, Pellegrino R. Airway hyperresponsiveness in asthma: not just a matter of airway inflammation. *Thorax* 1998;53:992-998
- Brusasco V, Pellegrino R, Rodarte JR. Airway mechanics. *Eur Resp Mon* 1999;12:68-91
- Buist AS, Ross BB. Predicted values for closing volume using a modified single breath nitrogen test. *Am Rev Respir Dis* 1973;107:744-752
- Burki NK, Baker RW. Ventilatory regulation in eucapnic morbid obesity. *Am Rev Respir Dis* 1984;129:538-543
- Cabanes LR, Weber SN, Matran R, Regnard J, Richard MO, Degeorges ME, Lockhart A. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. *N Engl J Med* 1989;320:1317-1322

## REFERENCES

---

- Camargo CA, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159:2582-2588
- Carey IM, Cook DG, Strachan DP. The effects of adiposity and weight change on forced expiratory volume decline in a longitudinal study of adults. *Int J Obes* 1999;23:979-985
- Chapman KR, Himel HS, Rebuck AS. Ventilatory responses to hypercapnia and hypoxia in patients with eucapnic morbid obesity before and after weight loss. *Clinical Science* 1990;78:541-545
- Chen Y, Dales R, Krewski D, Breithaupt K. Increased effects of smoking and obesity on asthma among female Canadians: The National Population Health Survey, 1994-1995. *Am J Epidemiol* 1999;150:255-262
- Cherniack RM. Physiologic diagnosis and function in asthma. *Clin Chest Med* 1995;16:567-581
- Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999;100:706-712
- Collins J.V. Closing volume - A test of small airway function. *Brit J Dis Chest* 1973;67:1-18
- Collins L, Hoberty PD, Walker JF, Fletcher EC, Peiris AN. The effect of body fat distribution on pulmonary function tests. *Chest* 1995;107:1298-1302
- Cormier Y, Lecours R, Legris C. Mechanisms of hyperinflation in asthma. *Eur Respir J* 1990;3:619-624
- Craig DB, Wahba WM, Don HF, Couture JG, Becklake MR. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J Appl Physiol* 1971;31:717-721
- Dempsey JA, Reddan W, Balke B, Rankin J. Work capacity determinants and physiologic cost of weight-supported work in obesity. *J Appl Physiol* 1966;21:1815-1820
- Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine-induced bronchoconstriction in normal humans. *J Appl Physiol* 1987;62:1324-1330
- Dixon JB, Chapman L, O'Brien P. Marked improvement in asthma after Lap-Band surgery for morbid obesity. *Obesity Surgery* 1999;9:385-389

## REFERENCES

---

- Don HF, Craig DB, Wahba WM, Couture JG. The measurement of gas trapped in the lungs at functional residual capacity and the effects of posture. *Anesthesiology* 1971;35:582-590
- Douglas FG, Chong PY. Influence of obesity on peripheral airways patency. *J Appl Physiol* 1972;33:559-563
- Douglas NJ, Polo O. Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome. *Lancet* 1994;344:653-655
- Emirgil C, Sobol B. The effects of weight reduction on pulmonary function and the sensitivity of the respiratory center in obesity. *Am Rev Respir Dis* 1973;108:831-842
- Estenne M, Yernault J-C, de Troyer A. Rib cage and diaphragm-abdomen compliance in humans: effects of age and posture. *J Appl Physiol* 1985;59:1842-1848
- Evans DJ, Green M. Small airways: a time to revisit ? *Thorax* 1998;53:629-630
- Fabrizi LM, Caramori G, Beghe B, Papi A, Ciaccia A. Physiologic consequences of long term inflammation. *Am J Respir Crit Care Med* 1998;157:S195-S198
- Farebrother HJB; McHardy GJR, Munro JF. Relation between pulmonary gas exchange and closing volume before and after substantial weight loss in obese subjects. *BMJ* 1974;3:391-393
- Fiz JA, Texido A, Izquierdo J, Ruiz J, Roig J, Morera J. Postural variation of the maximum inspiratory and expiratory pressures in normal subjects. *Chest* 1990;97:313-314
- Fiz JA, Aguilar X, Carreres A, Barbany M, Formiguera X, Izquierdo J, Morera J. Postural variation of the maximum inspiratory and expiratory pressures in obese patients. *Int J Obes* 1991;15:655-659
- Fogelholm M. Lihavuuden arviointi. In: Fogelholm M, Mustajoki P, Rissanen A, Uusitupa M, eds. *Lihavuus*. Helsinki: Duodecim 1998:29-38
- Fredberg JJ, Inouye D, Miller B, Nathan M, Jafari S, Raboudi SH, Butler JP, Shore SA. Airway smooth muscle, tidal stretches, and dynamically determined contractile states. *Am J Respir Crit Care Med* 1997;156:1752-1759
- Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adol Med* 1998;152:1197-1200
- Gold AR, Bleecker ER, Smith PL. A shift from central and mixed sleep apnea to obstructive sleep apnea resulting from low-flow oxygen. *Am Rev Respir Dis* 1985;132:220-223

## REFERENCES

---

- Gold AR, Schwartz AR, Wise RA, Smith PL. Pulmonary function and respiratory chemosensitivity in moderately obese patients with sleep apnea. *Chest* 1993;103:1325-1329
- Gortmacher SL, Must A, Sobol AM, Peterson K, Colditz GA, Dietz WH. Television viewing as a cause of increasing obesity among children in the United States, 1986-1990. *Arch Ped Adol Med* 1996;150:356-362
- Guilleminault C, Dement WC. Sleep apnea syndromes and related disorders. In: Williams R, Karacan I, Moore C, eds. *Sleep disorders: Diagnosis and treatment*. New York: Wiley, 1988:47-71
- Higgins BG, Britton JR, Chinn S, Lai KK, Burney PGJ, Tattersfield AE. Factors affecting peak expiratory flow variability and bronchial reactivity in a random population sample. *Thorax* 1993;48:899-905
- Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1984;130:175-178
- Hojjer U, Ejnell H, Bake B. The ability of noninvasive methods to detect and quantify laryngeal obstruction. *Eur Respir J* 1991;4:109-114
- Holley HS, Milic-Emili J, Becklake MR, Bates DV. Regional distribution of pulmonary ventilation and perfusion in obesity. *J Clin Invest* 1967;46:475-481
- Horner RL, Mohiaddin RH, Lowell DG, Shea SA, Burman ED, Longmore DB, Guz A. Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. *Eur Resp J* 1989;2:613-622
- Huang S-L, Shiao G-M, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999;29:323-329
- Hudgel DW, Gordon EA, Thanakitcharu S, Bruce EN. Instability of ventilatory control in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1998;158:1142-1149
- Ip MSM, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000;118:580-586
- Kansanen M, Vanninen E, Tuunainen A, Pesonen P, Tuononen V, Hartikainen J, Mussalo H, Uusitupa M. The effect of very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome. *Clin Physiol* 1998;18:377-385

## REFERENCES

---

- Kaplan TA, Montana E. Exercise-induced bronchospasm in nonasthmatic obese children. *Clin Pediatr* 1993;220-225
- Kapsali T, Permutt S, Laube B, Scichilone N, Togias A. Potent bronchoprotective effect of deep inspiration and its absence in asthma. *J Appl Physiol* 2000;89:711-720
- Kaufman BJ, Ferguson MH, Cherniack RM. Hypoventilation in obesity. *J Clin Invest* 1959; 38:500-507
- Kolbe J, Mercer-Fenwick J, Richards G, Rea H. Relationship of non-specific airway hyperresponsiveness (AHR) to measures of peak expiratory flow (PEF) variability. *Aust NZ J Med* 1996;26:59-65
- Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing ( $\dot{V}O_{2\text{RESP}}$ ) at rest. *Am J Respir Crit Care Med* 1999;160:883-886
- Lahti-Koski M, Pietinen P, Männistö S, Vartiainen E. Trends in body mass index and prevalence of obesity among adults in Finland from 1982 to 1997. National Public Health Institute. Helsinki 1999; Abstract
- Lambert RK. Role of bronchial basement membrane in airway collapse. *J Appl Physiol* 1991;71:666-673
- Lambert RK, Codd SL, Alley MR, Pack RJ. Physical determinants of bronchial mucosal folding. *J Appl Physiol* 1994;77:1206-1216
- Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function. *Chest* 1997;111:891-898
- Lazarus R, Gore CJ, Booth M, Owen N. Effects of body composition and fat distribution on ventilatory function in adults. *Am J Clin Nutr* 1998;68:35-41
- Lean MEJ, Seidell JC. Impairment of health and quality of life in people with large waist circumference. *Lancet* 1998;351:853-856
- Lean MEJ, Han TS, Seidell JC. Impairment of health and quality of life using new US Federal Guidelines for the identification of obesity. *Arch Intern Med* 1999;159:837-843
- Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on "airway closure" in man. *J Appl Physiol* 1970;28:448-451
- Lebowitz MD, Krzyzanowski M, Quackenboss JJ, O'Rourke MK. Diurnal variation of PEF and its use in epidemiological studies. *Eur Respir J* 1997;10: Suppl. 24:S49-S56

## REFERENCES

---

- Leech JA, Önal E, Lopata M. Nasal CPAP continues to improve sleep-disordered breathing and daytime oxygenation over long-term follow-up of occlusive sleep apnea syndrome. *Chest* 1992;102:1651-1655
- Litonjua AA, Sparrow D, Weiss ST. The FEF<sub>25-75</sub> / FVC ratio is associated with methacholine airway responsiveness. The Normative Aging Study. *Am J Respir Crit Care Med* 1999;159:1574-1579
- Lojander J, Mustajoki P, Rönkä S, Mecklin P, Maasilta P. A nurse-managed weight reduction programme for obstructive sleep apnoea syndrome. *J Intern Med* 1998;244:251-255
- Lorino AM, Atlan G, Lorino H, Zanditenas D, Harf A. Influence of posture on mechanical parameters derived from respiratory impedance. *Eur Respir J* 1992;5:1118-1122
- Luce JM. Respiratory complications of obesity. *Chest* 1980;78:626-631
- Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr* 1998;132:699-703
- Macklem PT. A theoretical analysis of the effect airway smooth muscle load on airway narrowing. *Am J Respir Crit Care Med* 1996;153:83-89
- Macklem PT. The physiology of small airways. *Am J Respir Crit Care Med* 1998;157: S181-S183
- Malmberg LP, Tamminen K, Sovijarvi ARA. Orthostatic increase of respiratory gas exchange in hyperventilation syndrome. *Thorax* 2000;55:295-301
- Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens CH. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J med* 1990;322: 882-889.
- Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. *N Engl J Med* 1995;333:677-685
- Marik PE. Leptin, Obesity, and obstructive sleep apnea. *Chest* 2000;118:569-571
- Martin RJ, Sanders MH, Gray BA, Pennock BE. Acute and long-term ventilatory effects of hyperoxia in the adult sleep apnea syndrome. *Am Rev Respir Dis* 1982;125:175-180
- Martin RJ, Cicutto LC, Smith HR, Ballard RD, Szeffler SJ. Airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1991;143:351-357

## REFERENCES

---

- McEvoy RD, Sharp DJ, Thornton AT. The effects of posture on obstructive sleep apnea. *Am Rev Respir Dis* 1986;133:662-666
- Meirhaeghe A, Helbecque N, Cottel D, Amouyel P. Impact of polymorphisms of the human beta<sub>2</sub>-adrenoceptor gene on obesity in a French population. *Int J Obes* 2000;24:382-387
- Misuri G, Lanini B, Gigliotti F, Iandelli I, Pizzi A, Bertolini MG, Scano G. Mechanism of CO<sub>2</sub> retention in patients with neuromuscular disease. *Chest* 2000;117:447-453
- Mohamed-Ali V, Goodrick S, Rawesh A. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Invest* 1997;82:4196-41200
- Moreno F, Lyons HA. Effect of body posture on lung volumes. *J Appl Physiol* 1961; 16:7-29
- Moreno RH, Hogg JC, Pare PD. Mechanics of airway narrowing. *Am Rev Respir Dis* 1986;133:1171-1780
- Mustajoki P, Pekkari T. Maintenance programmes after weight reduction-how useful are they? *Int J Obes Relat Metab Disord* 1999;23:553-555
- Naimark A, Cherniack RM. Compliance of the respiratory system and its components in health and obesity. *J Appl Physiol* 1960;15:377-382
- National Institute of Health Consensus Development Conference Statement. Gastrointestinal Surgery for Severe Obesity. *Ann Intern Med* 1991;115:956-961
- National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The Evidence Report. Bethesda, Md: National Institutes of Health; 1998
- National Task Force on the Prevention and Treatment of Obesity. Very-low-calorie diets. *JAMA* 1993;270:967-974
- Navajas D, Farre R, Rotger MM, Milic-Emili J, Sanchis J. Effect of body posture on respiratory impedance. *J Appl Physiol* 1988;64:194-199
- Neill AM, Angus SM, Sajkov D, McEvoy RD. Effects of sleep posture on upper airway stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1997;155:199-204
- Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropometric, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;112:629-639

## REFERENCES

---

Onal E, Lopata M. Periodic breathing and the pathogenesis of occlusive sleep apneas. *Am Rev Respir Dis* 1982;126:676-680

Partinen M, Guilleminault C, Quera-Salva MA, Jamieson A. Obstructive sleep apnea and cephalometric roentgenograms. The role of anatomic upper airway abnormalities in the definition of abnormal breathing during sleep. *Chest* 1988;93:1199-1205

Pasquali R, Colella P, Cirignotta F, Mondini S, Gerardi R, Buratti P, Rinaldi Ceroni A, Tartari F, Schiavina M, Melchionda N, Lugaresi E, Barbara L. Treatment of obese patients with obstructive sleep apnea syndrome (OSAS): effect of weight loss and interference of otorhinolaryngoiatric pathology. *Int J Obes* 1990;14:207-217

Paul DR, Hoyt JL, Boutros AR. Cardiovascular and respiratory changes in response to change of posture in the very obese. *Anesthesiology* 1976;45:73-78

Pekkarinen T, Mustajoki P. Comparison of behavior therapy with and without very-low-energy diet in the treatment of morbid obesity. *Arch Intern Med* 1997;157:1581-1585

Pekkarinen T. Behavioral therapy, very-low-calorie diet and gastroplasty in the treatment of severe and morbid obesity in adults. Doctoral thesis. Helsinki University 1999

Pekurinen M, Pokka-Vuento M, Salo H, Idänpään-Heikkilä U. Lihavuus ja terveystenot Suomessa 1997. *Suomen Lääkärilehti* 2000;55:11-16

Pietinen P, Vartiainen E, Männistö S. Trend in body mass index and obesity among adults in Finland from 1972 to 1992. *Int J Obes* 1996;20:114-120

Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. *Chest* 1994;105:434-440

Platts-Mills TAE, Sporik RB, Chapman MD, Heymann PW. The role of domestic allergens. *Ciba Found Symp* 1997;206:173-189

Pouliot M-C, Despres J-P, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;73:460-468

Pride NB, Macklem PT. Lung mechanics in disease. In: Macklem PT, Mead J, eds. *Handbook of Physiology. The respiratory system. Mechanics of breathing. Vol. 3, Part 2.* American Physiological Society, Bethesda: 1986:659-692.

## REFERENCES

---

- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993;6:Suppl 16:5-40
- Rajala R, Partinen M, Sane T, Pelkonen R, Huikuri K, Seppäläinen A-M. Obstructive sleep apnea syndrome in morbidly obese patients. *J Intern Med* 1991;230:125-129
- Ray CS, Sue DY, Bray G, Hansen JE, Wasserman K. Effects of obesity on respiratory function. *Am Rev Respir Dis* 1983;128:501-506
- Reddel HK, Salome CM, Peat JK, Woolcock AJ. Which index of peak expiratory flow is most useful in the management of stable asthma? *Am J Respir Crit Care Med* 1995;151:1320-1325
- Reddel H, Jenkins C, Woolcock A. Diurnal variability - time to change asthma guidelines? *BMJ* 1999;319:45-47
- Refsum HE, Holter PH, Lovig T, Haffner JFW, Stadaas JO. Pulmonary function and energy expenditure after marked weight loss in obese women: observations before and one year after gastric banding. *Int J Obes* 1990;14:175-183
- Rissanen A, Heliövaara M, Knekt P, Reunanen A, Aromaa A, Maatela J. Risk of disability and mortality due to overweight in a Finnish population. *BMJ* 1990;301:835-837
- Robertson CH, Pagel MA, Johnson RL. The relationship of respiratory failure to the oxygen consumption and distribution of blood flow among respiratory muscles during increasing inspiratory resistance. *J Clin Invest* 1977;59:31-42
- Roche WR. Inflammatory and structural changes in the small airways in bronchial asthma. *Am J Respir Crit Care Med* 1998;157:S191-S194
- Rochester DF, Enson Y. Current concepts in the pathogenesis of the obesity-hypo-ventilation syndrome: mechanical and circulatory factors. *Am J Med* 1974;57:402-420
- Rubinstein I, Zamel N, DuBarry L, Hoffstein V. Airflow limitation in morbidly obese, nonsmoking men. *Ann Int Med* 1990;112:828-832
- Saarelainen S, Lahtela J, Kallonen E. Effect of nasal CPAP treatment on insulin sensitivity and plasma leptin. *J Sleep Res* 1997;6:146-147
- Sahebjami H, Gartside PS. Pulmonary function in obese subjects with a normal FEV<sub>1</sub> / FVC ratio. *Chest* 1996;110:1425-1429
- Sahebjami H. Dyspnea in obese healthy men. *Chest* 1998;114:1373-1377

## REFERENCES

---

Sajkov D, Wang T, Saunders NA, Bune AJ, Neill AM, McEvoy RD. Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. *Am J Respir Crit Care Med* 1999;159:1518-1526

Sakakibara H, Tong M, Mantsushita K, Hirata M, Konishi Y, Suetsugu S. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. *Eur Respir J* 1999;13:403-410

Salmi T, Telakivi T, Partinen M. Evaluation of automatic analysis of SCSB, airflow and oxygen saturation signals in patients with sleep related apneas. *Chest* 1989;74:360-364

Salvadori A, Fanari P, Mazza P, Fontana M, Clivati A, Longhini E. Breathing pattern during and after maximal exercise testing in young untrained subjects and in obese patients. *Respiration* 1993;60:162-169

Seidell JC, Rissanen AM. Time trends in the worldwide prevalence of obesity. In: Bray GA, Bouchard C, James WPT, eds. *Handbook of obesity*. New York: Marcel Dekker, Inc. 1998:79-91

Seidell JC, Bouchard C. Abdominal adiposity and risk of heart disease. *JAMA* 1999;281:2284-2285

Sekerel BE, Saraclar Y, Kalayci Ö, Cetinkaya F, Tuncer A, Adalioglu G. Comparison of four different measures of bronchial responsiveness in asthmatic children. *Allergy* 1997;52:1106-1109

Series F, Cormier Y, Lampron N, La Forge J. Increasing the functional residual capacity may reverse obstructive sleep apnea. *Sleep* 1988;11:349-353

Series F, Cormier Y, Lampron N, La Forge J. Influence of lung volume in sleep apnoea. *Thorax* 1989a;44:52-57

Series F, Cormier Y, Desmeules M, La Forge J. Effects of respiratory drive on upper airways in sleep apnea patients and normal subjects. *J App Physiol* 1989b;67:973-979

Series F, Cormier Y, Desmeules M. Influence of passive changes of lung volume on upper airways. *J Appl Physiol* 1990;68:2159-2164

Sforza E, Krieger J, Weitzenblum E, Apprill M, Lampert E, Ratamaharo J. Long-term effects of treatment with nasal continuous positive airway pressure on daytime lung function and pulmonary hemodynamics in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1990;141:866-870

## REFERENCES

---

- Shaheen SO, Sterne JAC, Montgomery SM, Azima HA. Birth weight, body mass index and asthma in young adults. *Thorax* 1999a;54:396-402
- Shaheen SO. Obesity and asthma: cause for concern ? *Clin Exp Allergy* 1999b;29:291-293
- Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. The effects of mass loading on the respiratory system in man. *J Appl Physiol* 1964b;19:959-966
- Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. The total work of breathing in normal and obese men. *J Clin Invest* 1964b;43:728-739
- Shinohara E, Kihara S, Yamashita S, Yamane M, Nishida M, Arai T, Kotani K, Nakamura T, Takemura K, Matsuzawa Y. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *J Int Med* 1997;241:11-18
- Skloot G, Permutt S, Togias AG. Airway hyperresponsiveness in asthma: a problem of limited smooth muscle relaxation with inspiration. *J Clin Invest* 1995;96:2393-2403
- Smith PL, Haponik EF, Bleecker ER. The effects of oxygen in patients with sleep apnea. *Am Rev Respir Dis* 1984;130: 958-963
- Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med* 1985;103:850-855
- Sovijarvi ARA, Malmberg LP, Reinikainen K, Ryttilä P, Poppius H. A rapid dosimetric method with controlled tidal breathing for histamine challenge. *Chest* 1993;104:164-170
- Stenius-Aarniala B, Poussa T, Kvarnström J, Grönlund E-L, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;320:827-832
- Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. *Sleep* 1996;19:104-115
- Strohl KP, Strobel RJ, Parisi RA. Obesity and pulmonray function. In: Bray GA, Bouchard C, James WPT, eds. *Handbook of obesity*. New York: Marcel Dekker, Inc. 1998:725-739
- Sue DY. Obesity and pulmonary function: more or less ? *Chest* 1997;111:844-845
- Sugerman H, Fairman P, Baron PL, Kwentus JA. Gastric surgery for respiratory insufficiency of obesity. *Chest* 1986;90:81-86

## REFERENCES

---

- Suratt PM, McTier RF, Wilhoit SC. Collapsibility of the nasopharyngeal airway in obstructive sleep apnea. *Am Rev Respir Dis* 1985;132:967-971
- Suratt PM, McTier RE, Findley LJ, Pohl SL, Wilhoit SC. Changes in breathing and the pahrnx after weight loss in obstructive sleep apnea. *Chest* 1987;92:631-637
- Suratt PM, McTier RF, Fidley LJ, Pohl SL, Wilhoit SC. Effect of very-low-calorie diets with weight loss on obstructive sleep apnea. *Am J Clin Nutr* 1992;56:1825-1845
- Svanborg E, Larsson H, Carlsson-Nordlander B, Pirskanen R. A limited diagnostic investigation for obstructive sleep apnea syndrome. Oximetry and static charge sensitive bed. *Chest* 1990;98:1341-1345
- Thomas PS, Cowen ERT, Hulands G, Milledge JS. Respiratory function in the morbidly obese before and after weight loss. *Thorax* 1989;44:382-386
- Thulesius O. Orthostatic circulatory disturbances. *Triangle* 1970;9:258-264
- Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA. Breathing patterns.2. Diseased subjects. *Chest* 1983;84:286-294
- Townsend MC. Spirometric forced expiratory volumes measured in the standing versus the sitting position. *Am Rev Respir Dis* 1984;130:123-124
- Unger R, Kreeger L, Chistoffel KK: Childhood obesity: medical and familial correlates and age of onset. *Clin Pediatr* 1990;29:368-373
- Van Noord JA, Demedts M, Clement J. Effect of rib cage and abdominal restriction on total respiratory resistance and reactance. *J Appl Physiol* 1986;61:1736-1740
- Van de Graaff WB. Thoracic influence on upper airway patency. *J Appl Physiol* 1988;65:2124-2131
- Varner AE. An immunologic mechanism for the association between obesity and asthma. *Arch Intern Med* 2000;160:2395-2396
- Vaughan RW, Cork RC, Hollander D. The effects of massive weight loss on arterial oxygenation and pulmonary function tests. *Anesthesiology* 1981;54:325-328
- Wadström C, Muller-Suur R, Backman L. Influence of excessive weight loss on respiratory function. *Eur J Surg* 1991;157:341-346

## REFERENCES

---

- Weiner P, Waizman J, Weiner M, Rabner M, Magadle R, Zamir D. Influence of excessive weight loss after gastroplasty for morbid obesity on respiratory muscle performance. *Thorax* 1998;53:39-42
- Weiss ST. Diet as a risk factor for asthma. *Ciba Foundation Symposium* 1997;206:244-257
- Whipp BJ, Davis JA. The ventilatory stress of exercise in obesity. *Am Rev Respir Dis* 1984;129:Suppl S90-S92
- Wiggs BR, Bosken C, Pare PD, James A, Hogg JC. A model of airway narrowing in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;145:1251-1258
- Wiggs BR, Hrousis CA, Drazen JM, Kamm RD. On the mechanisms of mucosal folding in normal and asthmatic airways. *J Appl Physiol* 1997;83:1814-1821
- Williams JA, Shacter E. Regulation of macrophage cytokine production by prostaglandin E2: distinct roles of cyclooxygenase-1 and -2. *J Biol Chem* 1997;272:25693-25699
- Wilson MM, Irwin R. The association of asthma and obesity. *Arch Intern Med* 1999;159:2513-2514
- Woolcock AJ, Rebeck AS, Cade JF, Read J. Lung volume changes in asthma measured concurrently by two methods. *Am Rev Respir Dis* 1971;104:703-709
- World Health Organization (WHO). Physical status: The use and interpretation of anthropometry - Report of a WHO Expert Committee, Technical report series. Geneva, Switzerland 1995;854
- World Health Organization (WHO): Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva, Switzerland 1998
- Yap JCH, Watson RA, Gilbey S, Pride NB. Effects of posture on respiratory mechanics in obesity. *J Appl Physiol* 1995;79:1199-1205
- Zavala DC, Printen KJ. Basal and exercise tests on morbidly obese patients before and after gastric bypass. *Surgery* 1984;95:221-228
- Zerah F, Harf A, Perlemuter L, Lorino H, Lorino A-M, Atlan G. Effects of obesity on respiratory resistance. *Chest* 1993;103:1470-1476