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Ventilation and Lung Volume During Sleep and in Obstructive Sleep Apnea

BY

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Abstract

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Obstructive sleep apnea (OSA) appears to affect up to 5% of the population. The extent to what pulmonary function awake and during sleep relates to obstructive breathing and hypoxemia during sleep in these patients is unclear. The aim of this study was to investigate respiratory function in patients with varying degree of snoring and OSA and to analyse regional lung aeration during sleep.

In all, 35 healthy subjects and 90 patients with snoring and OSA were studied. The ventilatory response to CO₂ (VRCO₂) was measured. Lung function tests were performed. A technique based on computed tomography was developed to study lung aeration during sleep.

Patients with OSA displayed a higher VRCO₂ in comparison to healthy subjects and snorers ($p < 0.01$). Increased closing volume and reduced expiratory reserve volume (ERV) were found in patients with OSA ($p < 0.001$). In a multiple regression analysis, ERV was an independent predictor of nocturnal apnea ($R^2 = 0.13$; $p = 0.001$) and desaturation frequency ($R^2 = 0.11$; $p < 0.01$). In both healthy subjects and OSA patients, lung aeration was reduced during sleep by 0.10 ml gas/g tissue in the dorsal lung region ($p < 0.05$ and $p < 0.01$). OSA patients had a significantly lower gas/tissue ratio in comparison to healthy subjects both awake (-23%; $p < 0.04$) and during sleep (-25%; $p < 0.04$). In a univariate analysis, functional residual capacity (FRC) correlated with the change in lung aeration from wakefulness to sleep ($r = -0.78$; $p < 0.001$). In patients with OSA, ERV ($r = -0.69$; $p < 0.05$) and sleep time ($r = 0.69$; $p < 0.05$) correlated with the fall in lung aeration.

In conclusion, patients with OSA display an increased ventilatory response to CO₂, reduced ERV and increased closing volume. ERV predicts nocturnal apnea and desaturation frequency to a similar extent as obesity. Lung aeration is reduced in the dorsal region during sleep and patients with OSA display a lower amount of gas in comparison to healthy subjects. Decrease in lung volumes, promoting airway closure, and loss of muscle tone contributed to the altered lung function during sleep.

Keywords: Sleep, Ventilation, Sleep apnea syndromes, Snoring, Lung volume, Respiration, Computed tomography, Ventilatory response, Ventilation-perfusion, Airway closure

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To Maria, Erik and Josefin
To my parents

"Vad vore tillvaron utan oss människor, utan vår fantasi och våra drömmar och vår förmåga att höra havet sjunga? Det är ju vi som med vår lilla skärv av kunskap ger universum hela dess mening, vi som har blivit till genom samma krafter som frambringat havet, rymden och stjärnorna.

Eller tog jag fel som så ofta annars? Tillhör jag inte en ung och yrvaken art som nyss öppnat ögonen i ett universum som vi knappt ens börjat utforska?"

Peter Nilsson, Stjärnvägar, 1991

Free translation –

What would life be without human beings, without our imagination and our dreams and our ability to hear the sea sing? It is, after all, we, with our tiny amount of knowledge, that give the universe its meaning, we who were created by the same forces that produced the sea, space and the stars

Or am I wrong as I have so frequently been before? Am I not a member of a young, newly-awakened species that recently opened its eyes in a universe we have hardly started to explore.

"Sömnen är ett tillstånd av dvala, i vilket människan, skild från den yttre världen genom sina sinnens tvungna verksamhet, endast mekaniskt fortlever.

Liksom natten föregås sömnen av en skymning och efterföljes av gryning. Den förra leder till fullkomlig slöhet, den senare till liv och rörelse."

"....snart försvinner allt, varje rörelse upphör och man faller i fullkomlig sömn. Vad gör själen under denna tid? Den lever i sig själv, den är såsom lotsen under stiltje, eller som en spegel i ett mörkt rum, såsom en luta, vars strängar ingen anslår. Den avbildar nya väckelser."

Anthelme Brillat-Savarin (1755-1826), Smakens fysiologi, svensk översättning, 1924

Free translation –

Sleep is a state of trance in which man, divorced from the external world by the compulsory lack of activity in his senses, only exists mechanically.

Like the night, sleep is preceded by dusk and followed by dawn. The first leads to total lethargy, the second to life and movement.

...soon everything disappears, every movement ceases and you fall into a total sleep. What happens to the soul during this time? It lives in itself, it is like a pilot in the doldrums or like a mirror in a dark room, like a lute whose strings no one strums. It reflects new awakenings.

A short personal reflection

In 1989, I was presented with the task of setting up new equipment and establishing a clinical routine for investigating patients with snoring and suspected sleep apnea at the Department of Clinical Physiology, Sundsvall Hospital. At that time, no one at the department had heard much about obstructive sleep apnea and we had no idea about how to interpret the different respiratory patterns seen during sleep. When studying physiological methodology, and especially respiratory centre functionality, at the University of Umeå in 1994, it became apparent to me that malfunction at different levels in the respiratory system could play an important role in the pathophysiology of snoring and obstructive sleep apnea. This insight inspired me to sit down with Gunnar Sundström, head of the Department of Clinical Physiology, and sketch out a project I initially called “Project sleep apnea”. The years of research education have truly been like riding a roller coaster. I clearly remember the total feeling of emptiness when my first manuscript was rejected and the true happiness when it was accepted. Over the years, I have met people from all over the world and learned to work with people from a variety of specialities in the field of medicine and science. When I started my research studies, it was not that common for biomedical scientists to enter research education, but happily the number is increasing. It has been a privilege to meet all the people involved in my work and I am truly honoured that, over the years, they have taken the time to support my ideas and work in numerous ways. It has also been a real privilege to work in the field of sleep medicine. A field that is growing rapidly when it comes to developments in health care and science. A good night’s sleep is truly essential for life!

And so, finally, he stepped into his study, opened the window, turned off the lights and sat down on his chair. Carefully, he placed a book on his desk and gazed out of the window and into the dark, deep, starfilled night. A fresh, cool breeze entered the room through the window and he took a deep breath and filled his lungs with the finest of winter cooled air, exhaled and felt more relaxed than he had ever done before.

Jonas Appelberg, Sundsvall, March 2003

List of papers

The present doctoral thesis is based on the following original studies, which will be referred to in the text by their Roman numerals.

- I Appelberg J and Sundström G. Ventilatory response to CO₂ in patients with snoring, obstructive hypopnoea and obstructive apnoea. Clin Physiol 1997; 17:497-507
- II Appelberg J, Nordahl G, Janson C. Lung volume and its correlation to nocturnal apnoea and desaturations. Respir Med 2000; 94:233-239
- III Appelberg J, Pavlenko T, Bergman H, Rothen HU, Hedenstierna G. Lung aeration during sleep. Submitted
- IV Appelberg J, Janson C, Lindberg E, Pavlenko T, Weisby-Enbom L, Hedenstierna G. Lung aeration during sleep in patients with obstructive sleep apnea. Manuscript

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ABBREVIATIONS

AI	Apnea index
AHI	Apnea-hypopnea index
BMI	Body mass index
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CT	Computed tomography
CV	Closing volume
EEG	Electroencephalography
EMG	Electromyogram
EOG	Electro-oculogram
ERV	Expiratory reserve volume
F _{et} CO ₂	End-tidal fraction of carbon dioxide
FEV ₁	Forced expiratory volume in one second
FEV ₁ /VC	Forced expiratory volume in one second/vital capacity
FRC	Functional residual capacity
Nc	Neck circumference
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
O ₂	Oxygen
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
P0.1	Mouth occlusion pressure at first 100 ms of inspiration
PCO ₂	Arterial carbon dioxide tension
PO ₂	Arterial oxygen tension
REM	Rapid eye movement
RV	Residual volume
SaO ₂	Arterial oxygen saturation
TLC	Total lung capacity
VC	Vital capacity
V _E	Ventilation
VE/F _{et} CO _{2hy}	Ventilatory response to CO ₂ during hyperoxic conditions
VE/F _{et} CO _{2ho}	Ventilatory response to CO ₂ during hypoxic conditions
Wc	Waist circumference

INTRODUCTION

Produced during (or even by) the inspiratory phase of respiration (1), snoring is clearly a respiratory phenomenon and the obstructive sleep apnea syndrome (OSA) could thus be addressed as a respiratory disease.

Respiration during sleep – a brief historical overview

It is easy to understand that respiration and sleep are essential for our biological functions and therefore also for life itself. The importance of the phenomenon of respiration was very accurately described in ancient times, by the physician and philosopher Anaximenes of Miletus, Asia Minor (around, 570 BC) for example, who wrote: “As our soul, being air, sustains us, so pneuma (*breath*) and air pervade the whole world (2). Most physiological functions are under the control of regions in the brain and brainstem. It can be read that, long ago, Galen (AD 130–199) observed different effects on respiration when studying animals in experimental models and gladiators wounded in the neck at tournaments. If the injury was located high up in the neck (below the second vertebra) breathing ceased totally while it persisted due to diaphragmatic breathing if the injury was located below the sixth vertebra (2). This may very well have been the first actual step in the understanding of the regulation of breathing and the localisation of the respiratory centre. Today, we know that respiration is regulated and modulated in a complex manner from the brainstem and possibly also from the spinal cord (3;4). In exactly the same way as for respiration, it can be assumed that a centre for sleep regulation exists. In fact, as mentioned by Magnussen, early in the 20th century, Economo suggested that a “Schlafsteuerungszentrum” exists in the brain (5).

In the awake state breathing is influenced by many things and, as stated above, is co-ordinated from the respiratory centre within the brain stem (3;4). When we fall asleep, the situation changes and the regulation of breathing is determined on a more autonomic level – “Sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension” (6). Before the beginning of the 20th century respiration during sleep was difficult to study in a standardised way.

Needless to say, several abnormal breathing patterns had already been described in the literature such as Cheyne-Stoke's respiration and breathing patterns resembling obstructive sleep apnea (7;8). A milestone was therefore passed when Hans Berger published a work on the recording of EEG in which different types of EEG patterns were observed during wakefulness and sleep (9). Another important step was the recognition of rapid eye movement (REM) sleep. Nathaniel Kleitman and Eugene Aserinsky used what they called an electro-oculogram (EOG) in order to study eye movement during sleep (10). This discovery identified a sleep stage termed rapid eye movement (REM) sleep and it became very important for understanding not only the normal sleep pattern but also for respiratory physiology during sleep, as REM sleep reduces muscle tone, which could involve the risk of producing different negative effects on respiratory function (see below). This identification of differences in EEG rhythm between wakefulness and sleep was a turning point when it came to understanding different sleep stages as we know and classify them today, comprising stages I, II, III and IV as the non-rapid eye movement sleep stages (NREM) and the rapid eye movement (REM) stage (11).

Obstructive sleep apnea (OSA) is classified as a respiratory sleep disorder and is thus characterised by a malfunction in breathing during sleep. However, the actual cause of OSA is still unclear even though the amount of research in this area has increased dramatically the last few decades. There are many cases in the historical literature that describe subjects or patients most probably suffering from obstructive sleep apnea or hypoventilation syndrome and creditable reviews of this area have been published (12;13). One of the most famous and perhaps also the most often quoted historical descriptions of snoring and sleepiness is probably that by Charles Dickens in the Posthumous Papers of the Pickwickian Club (14). Dickens' description of Joe, the fat boy, definitely creates an impression of a patient with OSA as we would meet him in the sleep laboratory today. Dickens' fairly detailed description of Joe's physical characteristics and problems consequently inspired both William Osler (15) and Sidney Burwell (16) to coin the expression "Pickwickian syndrome" in their early case descriptions of patients with awake hypoventilation and daytime sleepiness. However, at that time, no connection was made between daytime sleepiness, disturbances in nocturnal breathing and sleep architecture. The tendency to fall asleep in patients with Pickwickian syndrome was instead attributed to hypercapnia and hypoxemia caused by hypoventilation. Almost a decade after Burwell's publication, Gastau and colleagues presented the hypothesis that the drowsiness and sleepiness seen in patients with Pickwickian syndrome without pulmonary hypertension and awake hypoventilation might be caused by insufficient sleep during the night (17). In the same year, another publication by Richard Jung and Wolfgang Kuhlo also presented detailed

descriptions of frequent apneas in three cases of Pickwickian syndrome (18). In the early 1970's diagnostic expressions such as sleep-induced apnea syndromes (19) and sleep apnea syndrome were coined (20) and since then the definition and recognition of the disease has continued to develop (21-23).

In what way could the respiratory system be of importance in relation to snoring and obstructive sleep apnea? The respiratory centre is the motor of breathing. In order to succeed with this task, thereby generating the overall respiratory drive, it is dependent on several different sensory inputs. The respiratory system consists of several components, all well known in basic physiology and each of importance for the total function of the system. The lungs act as air containers and as an air reservoir. Within the lungs there are alveoli which are permeable to the gases O_2 and CO_2 . Pulmonary capillaries deliver blood containing CO_2 to the lungs and in return receive O_2 . The respiratory muscles comprise the diaphragm, intercostal muscles, and the upper airway muscles. Finally, the respiratory centre in the brain stem acts as a co-ordinator using chemo receptors as well as receptors sensitive to pressure-, and temperature and stretch to maintain the breathing and ventilation needed in different physical situations. Malfunction in any of these different components could predispose the subject to upper airway collapse and thus lead to the snoring phenomenon.

Ventilation and lung volume – some aspects of normal physiology

Ventilation and lung volume during wakefulness and sleep

The total lung capacity (TLC) is the maximum volume of air that the lungs contain and it is traditionally divided into different sub-volumes. The vital capacity (VC) is the amount of air from maximum end expiration to maximum end inspiration. The functional residual capacity (FRC) is the amount of air in the lung after a normal quiet expiration. FRC is composed of the residual volume (RV) and the expiratory reserve volume (ERV). The FRC is normally around three to four litres and varies with weight, gender and age (24).

It is important briefly to state that lung volumes are sensitive to position (25) and to obesity and the most pronounced effect is seen on the sub-divisions FRC and ERV (26). The FRC is reduced in the obese subject. Obesity also

reduces the ERV because it increases the closure of peripheral airways (27). When ERV is reduced the alveolar surface tension increases (28). As a result, lung mechanics are affected by a reduction in lung compliance and this phenomenon is enhanced as the respiratory frequency increases (27). As this is not seen in non-obese subjects, it might imply a delay in ventilation and appears to be most pronounced in the lower (dependent) lung region (27;29). Severe obesity, due to a reduction in ERV, therefore carries a risk of causing ventilation-perfusion mismatch and impeding arterial oxygenation (30).

As mentioned above, experiments on the function of breathing have been performed for many years. However, systematic studies of respiration during sleep appear to have a much shorter history. According to Bülow (31), quantitative changes in ventilation during sleep were first reported by Sharling in 1843, followed by Smith (1860) and Mosso (1878). Periodic breathing is a common finding at sleep onset and the phenomenon called “Periodische Athmung und Luxusathmung” was reported back at the end of the 19th century (32). However, Bülow perhaps best describes the phenomenon of periodic breathing in his classic work from 1963 (31). Periodic breathing is characterised by an irregular or “undulatory” breathing pattern, often similar to Cheyne-Stoke’s respiration, or to Biot’s breathing (31). However, the normal periodic breathing pattern seen at sleep onset is comparable to Cheyne-Stoke’s respiration, where the irregularity seen when we fall asleep is probably caused by changes in controller gain and system gain (33).

Ventilation is affected by sleep (34). A significant reduction in tidal volume and inspiratory drive has been shown, together with minute falls in ventilation of approximately 5–16% depending on sleep stage, where the most pronounced drop is seen during REM sleep (34). Lung volume is also reduced during sleep and this is manifested by a reduction in the functional residual capacity (FRC) during NREM sleep (7%) (35;36). The decrease is most profound during REM sleep where the change amounts to approximately 0.3 litres or 10% (36). The reduction in FRC occurs almost immediately after sleep onset and reaches a maximum during NREM sleep, approximately within the first 30 minutes of sleep, but it then remains constant, except during the REM phase, where it is further reduced, as mentioned previously (37). Several factors, such as the central pooling of blood, reduction in lung compliance and reduced respiratory muscle tone, have been suggested as potential causal factors in the reduction in FRC (36-38). A significant reduction in muscle tone occurs especially during the REM sleep phase. The diaphragm is the largest respiratory muscle. It is made up of ordinary striated muscle fibres but, as mentioned by Bryan and Muller (38), it differs from other respiratory muscles in the sense that the

number of muscle spindles is low. As a result, the tone of the diaphragm muscle is not reduced during sleep to the same extent as that of other muscles. Nevertheless, the decreased muscle tone appears large enough to affect the distribution of ventilation during sleep, and especially during REM sleep (38).

It has been hypothesised that reduced FRC during sleep may induce the closure of airways within the regular breath, causing a ventilation-perfusion mismatch, contributing to the small but yet significant changes in arterial saturation seen especially during REM sleep (35;39). However, it is not known whether and in what way the lungs are affected in terms of the regional distribution of air and ventilation during sleep.

Control of breathing

As mentioned above, the respiratory centre, localised in the brain stem, controls and regulates breathing. It does so via a complex feedback system involving several different receptor types (central and peripheral, located in the brain stem, carotid, and aortic bodies). Acting through chemo-receptors in the brain stem, the centre is sensitive to changes in H^+ in the cerebrospinal fluid. It is therefore able to sense the concentration of CO_2 in the blood and thereby modulate ventilation.

According to Magnussen, the first attempt to study CO_2 sensitivity awake and during sleep was made by Loewe in the late 19th century and, according to Read (40), Leusen (1950) and Loeschke (1958) later located and further examined specific chemo-sensitive areas within the brain stem. When arterial CO_2 rises, it results in an increased hydrogen ion concentration in the cerebrospinal fluid surrounding respiratory neurons in the brain stem and, as a result, ventilation increases. In order to test the sensitivity to CO_2 , a hypercapnic ventilatory response test has been described (40), for details see the method section.

It was suggested long ago that the sensitivity to CO_2 is reduced during anaesthesia and during sleep (5;41). Subsequent studies have indicated a decrease in alveolar ventilation due to reduced sensitivity to CO_2 (42), as well as reduced hypoxic and hypercapnic ventilatory responses to CO_2 sleep, which are lower in both NREM and REM sleep in comparison to wakefulness (31;43-46). Even though others have failed to demonstrate this during slow-wave sleep (47), the consensus appears to be that ventilatory responses are reduced during sleep by approximately 30–40%, depending on the sleep stage (48).

Several things influence the ventilatory response to CO_2 and the inter-individual variation is obvious (49). In patients with chronic respiratory failure, the ventilatory response to CO_2 is often lower than normal due to central chemo-receptor adaptation to higher CO_2 and H^+ concentrations in

cerebrospinal fluid over time, leading to reduced sensitivity to CO₂ and thereby to a diminished capability to ventilate (50;51). Some variation in CO₂ sensitivity may occur over the day, but the most marked difference is the day-to-day variability in the ventilatory response to CO₂, mainly due to variations in arterial pH (52). Men have been shown to have higher CO₂ responsiveness than women (53;54). The hypoxic but not the hypercapnic ventilatory response to CO₂ is influenced (increased) by testosterone (55). The hypercapnic ventilatory response is also more pronounced when hypoxemia is present (56).

The sensitivity to CO₂ may vary with age (53). However, the variation in young and middle-aged subjects appears to be small and insignificant (49) and also appears to be abolished when airway resistance is accounted for (57). There is some controversy regarding the influence of obesity on CO₂ responsiveness. Patrick and Howard did not find any association between body size and ventilatory response to CO₂, while the opposite was suggested in the results presented by Hirshman and co-workers (49) and by Miyamura et al. (58).

Snoring and obstructive sleep apnea (OSA)

Some general aspects relating to patients with snoring and OSA

When, during sleep, air is sucked in and passes through the upper airway and the unstable local areas of the upper airway, such as the uvula and soft palate, and the pharyngeal wall starts to vibrate, the sound of snoring is produced (1;59). Needless to say, snoring is the main feature of OSA, but it is not always necessarily the most prominent symptom (60). Surprisingly, however, quantifying the amount and severity of snoring itself in an objective manner is difficult and there is a lack of standardisation. Microphones or other vibration-detecting sensors placed of the larynx area on the neck are frequently used, but they are not always accurate in determining the severity of snoring. The most comprehensive way to quantify snoring is probably by validated questionnaires (61-63). As a result of snoring, the upper airway sometimes collapses totally so that no air can pass through it even though breathing attempts persist. When this happens and if it continues for at least 10 seconds, it is called an obstructive apnea (20), see below.

Definitions and registration techniques

The definition of apnea, which is used for the diagnosis of OSA in clinical routine as well as in sleep research, is a total cessation of oral/nasal airflow for 10 seconds or more (20). The most common technique used to detect and register apneas during sleep is the thermistor technique with the sensor positioned at the nostrils. The thermistor measures flow indirectly by responding to temperature shift when breathing in and out. It is a good, albeit somewhat slow, detector of apneas, but as described by Berg et al., it is less sensitive when detecting hypopneas (64). Newer techniques, such as a nasal cannula pressure sensor, which permits the detection of *airflow limitation*, have also recently been described (65) and it appears that they will develop into a new standard in the future. To be able to distinguish between the different types of apnea, simultaneous recordings of chest and abdominal movements and oesophageal pressure are required. In patients with different degrees of snoring and OSA, apneas are mainly obstructive, but other types of apnea may also occur (17;20).

An *obstructive apnea* is caused by an obstruction of the upper airway so that no or very little air can pass. However, during the apnea, the respiratory drive is alert and active, as evidenced by polysomnographic recordings such as ongoing respiratory movements from the chest and abdomen. An apnea index (AI) is calculated by dividing the number of apneas by the calculated or estimated sleep time in hours.

A *central apnea* is characterised by the loss of respiratory drive and therefore by the absence of respiratory chest and abdominal movements. Central apneas may occur in OSA, but they are most commonly seen in normal subjects at sleep onset and during REM sleep, in congestive heart failure with Cheyne-Stoke's respiration or in some neurological disorders (66).

A *mixed apnea* is a combination of a central and an obstructive. It starts as a central apnea followed by respiratory efforts against an occluded upper airway (20).

Several different definitions for the term *hypopnea* exist, which unfortunately makes the term somewhat confusing. An early definition of hypopnea was a decrease in oral/nasal airflow, a reduction in chest movements and the occurrence of a desaturation of at least 4% from the preceding baseline (39). At a later stage, it was suggested that the best definition of a hypopnea was a 50% reduction in thoraco-abdominal movements lasting for a minimum of 10s (22). A more recent definition states that the hypopnea has an effect on sleep and thus causes an arousal

(67). A hypopnea index (HI) is calculated by dividing the number of apneas by the calculated or estimated sleep time in hours. More commonly however, the number of apneas and hypopneas are summarised and the apnea/hypopnea index (AHI) calculated.

In addition to causing arousals, both apneas and hypopneas may and often do cause *desaturations*. The term desaturation marks a significant drop in oxygen saturation level from the preceding baseline. The accuracy and sensitivity of the equipment and technique used to measure arterial saturation is of particular importance when determining what a significant decrease is. During sleep in healthy subjects and in patients with OSA, a level of desaturation of 4% (39;68) and of 3% (67) has been described. An oxygen desaturation index (ODI) is often calculated by dividing the number of desaturations by the calculated or estimated sleep time in hours.

Diagnosis

It was once suggested that when the number of apneas during sleep is five or more per hour of sleep, the snorer should be diagnosed as suffering from obstructive sleep apnea (OSA) (20;22). If, in addition, daytime sleepiness is present then the term/diagnose obstructive sleep apnea syndrome (OSAS) is used (20;67). International recommendations regarding the investigation and diagnosis of patients with snoring and suspected OSA have recently been published (67). Also in Sweden, national guidelines have been established (69).

Even though some of the clinical features, such as obesity and daytime sleepiness are obvious in patients with OSA, it has proved difficult to predict which patients among snorers suffer from OSA (70-72). This is most probably due to the fact that snoring (73;74) and upper airway resistance (23) may also alter sleep efficiency and may cause sleep fragmentation with daytime sleepiness as a result. In addition, other diseases such as gastro-oesophageal reflux and nocturnal asthma may also cause or contribute to daytime sleepiness (75;76). Nocturnal investigations (by limited nocturnal registrations of snoring, position, arterial oxygen saturation and respiratory variables or by full polysomnography) are therefore generally needed in order to establish a correct diagnosis.

Prevalence

The prevalence of OSA varies in different parts of the world. Several factors may contribute to the varying figures, such as time of the study, definition of the disease, study design and method used for diagnosis. According to Bixler

and co-workers, who studied sleep apnea activity in 100 healthy subjects using polysomnography, nocturnal apneas and desaturations during sleep are rare (< 30 apneas during one night's sleep) in healthy subjects without clinical symptoms of snoring and daytime sleepiness (77). Lavie estimated the prevalence of OSA among industrial workers in Israel at approximately 1% (78). Gislason and co-workers reported similar data in Sweden on sleep apnea syndrome obtained in a two-stage study (a postal survey followed by polysomnography in 61 men) where the prevalence was estimated to be 1.3% (79). Using postal questionnaires, Cirignotta et al. (80) found a prevalence of 10% for every-night snoring and reported a prevalence figure of 2.7% for OSA. In USA, the prevalence of OSA and OSAS has been estimated to 24 and 4% respectively (81). The prevalence of OSA was estimated. In a study by Ulfberg et al. comprising 908 patients (742 men and 166 women) with suspected OSAS a prevalence of 3.7% was found using a sleep apnea screening method for OSAS in men (62). Despite growing knowledge, it is still generally thought that snoring and OSA are primarily a male phenomenon. However, studies have established prevalence that the prevalence among postmenopausal women is similar to that of men (81-83).

Factors contributing to snoring and OSA

Back in 1983, Lugaresi et al. suggested that snoring is a progressive disease, which, over time leads to more severe obstruction of the upper airway during sleep, which develops into obstructive sleep apnea (21). This theory is supported by subsequent studies (84) and recently also by data reporting that the prevalence of snoring increases (mainly age dependent) when followed over a 10-year period (63). One possible effect of snoring is that it has a destructive impact on upper airway soft tissue. In fact, signs of neuropathy have been reported in OSA patients (85) and studies have revealed afferent and efferent nerve lesions in pharyngeal muscle tissue. Snoring thus appears to be self-aggravating in some way and the early treatment of snoring may be of the utmost importance when it comes to stopping this viscous circle (86).

Other factors are also of importance in terms of snoring and OSA. The dominant clinical feature of OSA is probably obesity. This was already noted in early publications relating to OSA (20). Obesity has several consequences, which may contribute to snoring and OSA. Weight gains lead to an increase in neck and waist circumference (87-89), which may have a negative impact on upper airway stability. Another important factor that requires attention is the negative effect obesity has on lung volume, see the section below. Other factors, such as heredity (90-92), smoking causing inflammation and oedema in the upper airway (93), exposure to organic solvents (94) and anatomical factors (95;96) appear to be of importance in the development of snoring and OSA. In addition, supine posture may also

contribute to upper airway narrowing (97). Due to a reduction in muscle tone in the upper airway, alcohol is also believed to induce and worsen obstructive breathing during sleep (98) and, in the same way, sleep deprivation also appears to contribute to an increase in the number of obstructive apneas/hypopneas during sleep (99).

Risk factors

The negative effect of OSA obviously comprises a wide range of symptoms and negative medical effects (100). Increased daytime sleepiness is often present (20;78) and, according to Ferguson and Fleetham, cognitive function may be impaired (100). As a result, OSA patients run an increased risk of having car accidents while driving (101;102). Headache (62;103) and nocturia (104;105) are also common complaints which may be partly reduced when OSA is treated (104). In a recent study, it was also reported that snoring in combination with obesity might increase the risk of developing diabetes (106).

Constant discussions and research are in progress when it comes to the question of whether snoring and OSA may increase the risk of other diseases. Sleep apnea has been shown to be very common among hypertensive patients (107) and snoring has been suggested as an independent risk factor for the development of hypertension (108) and ischemic heart disease (109). The association between snoring, OSA and cardiovascular disease has been investigated in depth both in Sweden (108;110-112) and internationally in recent decades (82;113-119) and increased mortality as a consequence of the disease has been suggested (120-122). Obstructive breathing produces considerable pressure swings within the cardiovascular system (119;123), along with frequent and marked arterial hypoxemia. In fact, hypoxemia during sleep seems to be closely related to the degree in pressure swings (124) and also to nocturnal angina in patients with OSA (125). However, the causal relationship between sleep apnea and cardiovascular effects is complicated and has been extensively reported on elsewhere (126-128).

Pathophysiology – upper airway obstruction

Why do we snore and why do the upper airway sometimes collapse during sleep? According to Block et al., upper airway stability depends on several different factors, such as muscle properties, and on mechanical and neurological factors (129). Remmers et al. first presented some fundamental results relating to the pathogenesis of upper airway occlusion during sleep in patients with OSA (130). They measured pharyngeal and oesophageal pressure in 10 patients with OSA and located the site of occlusion in the

oropharynx and subsequent studies have also shown that the upper airway is narrower in OSA patients than in control subjects when studied awake (95;131). The lower cross-sectional area may be due to anatomical differences, but, according to Remmers et al., occlusion occurs whenever the contractile forces acting on the upper airway exceed the forces that are trying to keep it open. This observation in addition to the results presented by Brouillette et al. (132), is termed “the balance of pressures concept” and indicates that the area of the upper airway is determined by intra-luminal and surrounding tissue pressure. In fact, a critical factor for the maintenance of adequate tone in the upper airway muscles could be the existence of sufficient sensitivity to CO₂ in the respiratory centre. Since the upper airway muscles behave like a respiratory muscle and, like the diaphragm and the intercostal muscles, respond to hypercapnic and hypoxic stimulus (133;134), upper airway stability is partly dependent upon respiratory timing when it comes to the modulation of muscle tone. Interestingly, patients with OSA appear to have increased phasic activity in the genioglossus muscle group (135), and in spite of this, they also appear to have a increased collapsibility in the nasopharyngeal area (136). So, even though the increase in muscle activity indicates that efforts are being made, the upper airway appears to be unable to respond sufficiently to accommodate the increase in negative pressure generated in the upper airway during inspiration.

The upper airway may be affected by several factors. Patients with OSA have increased neck circumferences in comparison to non-apneic snorers (87). Fat deposits (137) and increased muscle tissue at different levels in the upper airway have been demonstrated in OSA patients (138). So, as suggested, the upper airway may be narrowed both by increased external pressure and by increased muscle tissue and fat within the soft tissue of the upper airway. The negative pressure that is generated in the upper airway during inspiration will increase which will tend to cause collapse of the upper airway (139).

Treatment

Tracheotomy was once the only suitable choice when it came to improving breathing during sleep in OSA patients. In the obese patient with OSA, weight reduction is perhaps the most effective, but not necessarily the easiest treatment (140;141), mainly due to improvement in upper airway stability and improved pulmonary function (142). At an early stage, snoring and even OSA were treated with uvulopalatopharyngoplasty (UPPP), first introduced by Fujita in 1981 (143). In all probability, the most effective treatment is nasal Continuous Positive Airway Pressure (nCPAP), introduced by Sullivan and co-workers in 1981 (144). They demonstrated that applying a low

positive pressure of air through the nose acts as a pneumatic splint and thereby prevents obstructive apneas during sleep. This has a very distinct and direct effect in the treatment of OSA and its credibility is widely documented (145). In recent years, oral appliances, such as the mandibular advancement device, have attracted increasing attention as the treatment of choice for heavy snoring and OSA. This treatment has a stimulating effect on the upper airway muscles and enlarges the upper airway by repositioning the mandible (146). Recent studies have indicated that treatment is most successful in patients with mild to moderate OSA (147;148) and especially in supine-dependent OSA (149).

Ventilation and lung volume in patients with snoring and OSA

As discussed above, the respiratory system appears to have play a crucial role in creating adequate stability in the upper airway and it is therefore natural to suspect that malfunction at some level within this system might contribute to or even be the single cause of upper airway collapse in patients with OSA. Isolating the individual factors that might contribute to this instability is, however, complicated, as several things may directly or indirectly interact in the upper airway. Respiratory function in patients with snoring and OSA has been studied by a number of researchers for several decades, but the fact that so many different things influence both snoring and OSA, as well as overall respiratory function, means that the results conflict.

Lung volume

As the lungs are a part of the respiratory system, they could also be suspected of playing an important role in OSA. This has actually been reported in several previous studies. Back in 1955, two interesting publications on ventilatory abnormalities as measured by lung function testing were published. In one of the first reports on obesity-hypoventilation syndrome (i.e. Pickwickian syndrome), Seiker and co-workers reported respiratory data in two patients with cardiopulmonary syndrome (150). They reported that the patients had Cheyne-Stokes' respiration with profound cyclical swings in arterial saturation during sleep. They had a 20% decrease in total lung volume and a 50% reduction in ERV. A further reduction (down to 17% of average normal value) was noted when the patients were studied in the supine position. The authors concluded that the reduction in lung volume

may contribute to the frequent desaturations and that obesity was the primary factor in this syndrome.

In a publication from 1956, Burwell and co-workers reported an interesting observation regarding lung volumes (16). “During weight reduction the total vital capacity increased from 1.6 to 4.2 l. However, the most striking change in lung volumes was in the expiratory reserve volume which increased during weight loss from 0.46 to 1.8 l”. It is notable that an increase in respiratory centre sensitivity also occurred. The case in question was a 51-year-old man who was so tired that he fell asleep during a game of poker and therefore failed to take advantage of the good hand of a full house!

In 1959, Howland Auchincloss and Robert Gilbert published a comprehensive review of 21 cases of obesity-hypoventilation syndrome (151). Several features were listed as being present or not present among these cases, when it came to lung volumes, it is interesting to note that, in the studies in which the ERV was measured, it was reduced.

In 1966, Gastaut and co-workers published a paper on a case in which they state that, when it came to spirometric investigation, “the majority of the results in our patient appeared to be normal”. However, they also reported that “The ERV showed a distinct diminution, attaining only 420 ml instead of 1000 ml” (17).

More recently, several studies have focused on the significance of reduced lung volume when it comes to the presence and severity of snoring and OSA (152-154). It has also been observed that the cross-sectional area of the upper airway is lung volume dependent and that OSA patients in the awake state have a smaller area in comparison with healthy non-snoring subjects (155;156). Several studies have also reported on the benefit of increased lung volume both experimentally (157) and as a result of weight reduction on the pulmonary function in OSA patients. This appears to improve or reduce obstructive breathing during sleep (140-142;158-160).

It is not at all clear whether lung volume changes in OSA actually cause or contribute to the severity of the disease. This is naturally due to the fact that both pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD) and restrictive lung disease may co-exist with OSA. Sleep-induced disordered breathing was reported several years ago in patients with COPD and it was suggested to be an important cause of the oxygen desaturations during sleep in these patients (161). At a later stage, Flenley coined the term “overlap syndrome”, which describes the group of patients who suffer from both OSA and COPD, in whom arterial oxygen saturation in particular may be more affected during sleep than when the two diseases occur independently of each other (162). The prevalence of the overlap syndrome is unclear, but approximately 11% of patients with OSA have been shown to have obstructive airway disease (163;164). However, it

should be noted that, in these studies, obstructive airway diseases were classified according to the outcome of the spirometry test and it is unclear whether all the patients also had symptoms of respiratory disease. Patients with overlap syndrome run the risk of developing respiratory insufficiency and cor pulmonale, as suggested by Chaouat et al. (164). Hyper reactivity tests on patients with snoring and OSA have not revealed any relationship between airway obstructivity and the severity of snoring or OSA (Lin & Lin, Lung, 1995). However, others have reported an association between chronic bronchitis and OSA (165;166).

Several studies have evaluated the significance of pulmonary measurements for the identification of OSA in patients with suspected OSA (167-171). Sanders et al. published data on a “saw tooth pattern” on the flow volume loop (172). Haponik et al. reported that 40% of patients with sleep-disordered breathing had abnormal flow-volume curves in that the curves display an abnormal pattern related to extra-thoracic factors rather than intrapulmonary obstructivity, as FEV₁/VC% was within the expected normal range in most patients (167). Riley and co-workers, however, failed to demonstrate this. The study population was small, however (15 patients with OSA and 10 controls) (168), and sensitivity has been shown to be low, also if the flow-volume manoeuvre is performed in the supine position (169-171). Subsequent studies have reported that flow-volume curves obtained from breathing through the nose may be more accurate in detecting patients with OSA (173).

Ventilatory response to CO₂

Investigations of the functionality of the respiratory centre in patients with OSA in comparison to healthy non-snoring individuals have been published previously. Most studies have focused on patients with OSA with and without daytime hypercapnia and on patients with the obesity-hypoventilation syndrome. Studies of patients with snoring and obstructive hypopneas, however, appear to be rare.

It was previously stated in this section that there is a considerable variation in the ventilatory response to CO₂ in healthy subjects and this is certainly also the case when it comes to patients with OSA. CO₂ sensitivity has been reported as being reduced (174-177), unchanged (178-180) or increased (181). An increase in ventilatory response to CO₂ has also been noted in patients with OSA who underwent tracheotomy treatment indicating an initial decreased response (182). However others have not been able to demonstrate this (176;183). The hypercapnic ventilatory response to CO₂ is generally lower than normal in hypercapnic OSA patients (184).

As in healthy subjects, several factors influence CO₂ sensitivity in patients with OSA. The effect of some confounders was evaluated in a study by Sin et al. (179). They studied the hypercapnic ventilatory response to CO₂ in a large number of subjects with (n=104) and without OSA (n=115). No correlation was found between apnoea-hypopnoea index (AHI) and ventilatory response to CO₂ in a multivariate analysis taking body mass index (BMI), gender, PCO₂ and age into account. However, a relationship between age, daytime PCO₂ and hypercapnic ventilatory response to CO₂ was reported. No differences regarding CO₂ sensitivity between OSA patients and healthy controls not matched for age or weight were reported by Bittencourt and co-workers (178) but a relationship between obesity and ventilatory drive was found. Nor were any differences in hypercapnic ventilatory response to CO₂ found in a recent study by Radwan et al (185). However, an increased response to CO₂ during hypoxia was seen in 35% of patients.

The significance of an increase in chemical drive in patients with OSA is very unclear. In fact, only one study has reported an increase in hypercapnic ventilatory response in patients with OSA (181). In that study, the ventilatory response was studied in age- and BMI-matched groups of patients with heavy snoring, normocapnic OSA, hypercapnic OSA and in patients with the overlap syndrome (patients with combined OSA and COPD). A group of patients who were investigated but found not to have OSA served as a control group. Normocapnic OSA patients were found to have a higher hypercapnic ventilatory response to CO₂ (2.41 ± 0.26 l/min/mmHg) in comparison to the control group (1.66 ± 0.16 l/min/mmHg; $p < 0.05$). An increased hypercapnic ventilatory response was also seen in the group of patients with overlap syndrome. No differences in ventilatory response were reported for the heavy snorers group; in fact the average ventilatory response to CO₂ had a tendency to be lower in this group (1.26 l/min/mmHg). The authors concluded that the increase in hypercapnic ventilatory response to CO₂ might contribute to obstructive breathing during sleep, as an augmentation ventilatory drive has been reported in subjects with profound periodic breathing (33). An increase in the adrenosympathetic response to stress could also lead to an increase in hypercapnic ventilatory response (186).

Lung volume and oxygen saturation during sleep in OSA

Oxygen desaturations are frequent findings during sleep in patients with OSA. Different factors such as apnea length (25;187), type of apnea (188) and the placement of the oxyhemoglobin dissociation curve (189) are of importance for the severity of desaturations and hypoxemia during sleep in patients with OSA. Another very important factor appears to be lung

volume. Bradley et al. have reported that PO_2 measured awake in the supine position, time spent in apnea and ERV were determinants of the mean $SaO_2\%$ in OSA patients (187). In addition, Sériès et al. studied pulmonary function in patients with OSA. The patients had normal forced expiratory flow in the sitting position, while the ERV was reduced in both the upright and supine position (190). An increase in closing volume measured in the supine position was also reported. It was concluded that the severity of nocturnal desaturation was substantially dependent upon the ERV and closing volume measured awake and most primarily in the supine position.

RATIONALE FOR THE PRESENT THESIS

When patients who seek medical care for snoring and suspected obstructive sleep apnea are investigated in terms of respiratory events during sleep, several different patterns of disordered breathing may be seen. Some patients are simply snorers, while others also display obstructive hypopneas, apneas and desaturations to varying degrees. As mentioned above, several factors such as age, gender and obesity contribute to these phenomena.

The instability of the upper airway and the arterial oxygen saturation level during sleep are affected by the overall function of the respiratory system. As a result, the question that naturally arose and formed the main hypothesis in the present work was whether dysfunctions in the respiratory system essentially contribute to the different respiratory patterns observed during sleep. To test this hypothesis, a series of studies was performed which made it possible to further analyse different aspects of a possible relationship between pulmonary function measured during wakefulness and respiration during sleep in patients with snoring and obstructive sleep apnea. The analysis was based on measuring respiratory centre function as well as pulmonary function in healthy non-snoring subjects and in a large number of patients with varying degrees of nocturnal apnea and desaturation. A new technique based on spiral computer tomography (CT) was also developed in order to investigate the regional aeration of the lungs during wakefulness and sleep in healthy subjects, as well as in patients with OSA.

The specific aims were

To evaluate differences in CO₂ sensitivity between healthy subjects and patients with varying occurrence of nocturnal apneas and desaturations and to examine factors influencing CO₂ sensitivity in these patients (*Paper I*)

To study the relationship between lung volume measured during wakefulness and nocturnal apnea and desaturation frequency (*Paper II*)

To study the distribution of air in the lungs during wakefulness and sleep in healthy subjects and in patients with OSA (*Papers III and IV*)

SUBJECTS & METHODS

Ethical aspects

All the studies were approved by the local ethic committee and informed consent was obtained from each participating subject/patient.

Study population

Papers I and II

A number of consecutive patients referred to the department for an investigation of snoring and suspected sleep apnea were included in the study. Based on the outcome of an ambulatory sleep apnea screening investigation performed in the home environment (see below), the subjects were divided into three different diagnostic groups representing different degrees of obstructive breathing during sleep. The following criteria were set for the groups: a history of snoring with an AI of < 5 and an ODI of < 5 = snoring alone (SA); snoring with an AI of < 5 and an ODI of > 5 = snoring with desaturations, “obstructive hypopnea” (OH); snoring in which both the AI and the ODI were ≥ 5 = obstructive apnea (OA). An additional number of patients were found to have mainly central apneas and/or hypoventilation in the nocturnal recording and were therefore not further analysed.

A total of 78 patients were studied in Paper I. The group consisted of 60 men (age 27-70 years) and 18 women (age 37-67 years). In Paper II, nine patients were excluded due to a history of respiratory symptoms. The remaining study population was 54 men (age 27–70 years) and 15 women (age 37–67).

The control group in Papers I and II consisted of healthy subjects randomly selected from the local population register. A total of 400 letters were sent out, and 364 answers were finally received (response rate = 86.5%). In this group, 84 subjects denied having problems with snoring and daytime sleepiness and were willing to participate in the study. Thirty-three

randomly-selected subjects from this group then underwent a nocturnal ambulatory sleep apnea recording. One subject was unable to perform satisfactory spirometry test and seven subjects (age 50 ± 14 years, BMI 30 ± 6 ,) had an ODI of more than 5 (ODI= 6.6 ± 2.1 ; SaO₂min= 81 ± 2 %) and were not included in the study. As a result, all the subjects included in the control group had an AI and an ODI of less than 5. The final control group thus consisted of 25 subjects for Paper I, 15 men (age 50 ± 13 years) and 10 women (46 ± 7). In Paper II, two of these subjects (one man and one woman) were excluded due to a history of respiratory symptoms.

Paper III

In order to study lung aeration during wakefulness and sleep in normal subjects, seven male subjects (age 23–46 years) and three women (age 23–29 years) were asked to participate in the study. One additional subject was also scheduled for the investigation but was unable to fall asleep and was therefore not included in the study. They were all non-smoking, healthy subjects without complaints of snoring or daytime sleepiness.

Paper IV

A total of 12 patients with OSA defined as an AHI of >15 registered in an ambulatory sleep apnea recording performed within six months prior to the study were investigated. All of them had clinical symptoms with a history of snoring, apneas and daytime sleepiness. Their ODI ranged from 11 to 62 and the lowest nocturnal SaO₂% ranged between 65–85%. All the patients were non-smokers at the time of the study.

Additional analysis

To enable a comparison of lung aeration during normal sleep and during regular anaesthesia, the data for 13 patients (seven women and six men), age 50 ± 17 years, from an earlier anaesthesia study (191) were re-evaluated. In brief, intravenous anaesthetics (fentanyl and propofol) were used for the induction and maintenance of general anaesthesia. During the induction of anaesthesia, subjects breathed 30% oxygen in nitrogen and, after orotracheal intubation, their lungs were ventilated with the same mixture of gas for the following thirty minutes. To test the effect of a change in gas mixture, the inspiratory concentration of oxygen was then switched to 100% in seven subjects. The same analytical procedures in the CT scans (see below) were used as in the subjects studied during sleep.

Ventilatory response to CO₂ and lung volumes was also analysed in a group of OSA patients participating in a weight reduction program. They were

studied before and one year after weight reduction. All patients were also on treatment with nCPAP. This group comprised eight patients with OSA, six men and two women (age 49 ± 7 years). They were all obese with a BMI >30 .

Methods

Subject characteristics

Height (cm, *shoes off*) and weight (kg, *regular clothes*) were measured and the body mass index was calculated ($\text{BMI} = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$) (192). In the subjects participating in Studies I and II, measurements also comprised external neck circumference (cm) measured at the superior border of the cricothyroid membrane with the patient in the upright position (87), and abdominal circumference (cm) (88).

Nocturnal recording of respiration and saturation

All the control subjects and patients in Papers I, II and IV underwent a nocturnal registration of apneas and desaturations. For the latter, validated unattended recording devices were used: MicroDigitrapper-S (M-S) and the analytical software Multigram SA; TM, Synectics Soft, Stockholm & Dallas (193) (Papers I, II and IV) and the Embletta, Flaga, Reykjavik, Iceland (five patients in Paper IV) was used (194). The registration was performed in the home environment and careful information was given to the patient both orally and in written and video instructions. The MicroDigitrapper-S has been shown to have high sensitivity and specificity when the automatic analysis performed by the computer software is examined visually and edited manually for the presence of respiratory events such as apneas and desaturations. In the case of the Digitrapper, both the sensitivity and specificity exceed 90% when cut-off values for AHI are set at > 10 , > 20 and > 40 .

This ambulatory method does not permit the scoring of accurate sleep time, as EEG, EMG, and EOG are not registered. In the validation study (193), indices were instead based on total time in bed (hours) and the same technique was used in the present study. This procedure may underestimate indices such as AI and ODI and the occurrence of OSA to some extent, as time in bed has been shown to produce lower indices compared with calculations of accurate sleep time (195).

The following registered parameters were analysed to detect nocturnal obstructive breathing and obstructive apneas: oro-nasal flow (thermistor), chest movement (mattress - with a polyvinylidenefluoride motion sensor) and

abdominal respiration movement (piezo-electric belt positioned at the level of the diaphragm). Arterial oxygen saturation was measured with a finger pulse oximeter. Each recording was examined visually and apneas and oxygen desaturations were rated manually. By definition, an apnea was scored when airflow ceased in the nose and mouth for at least 10 s (20) and a desaturation was defined as a drop in saturation level of 4% or more from the previous baseline (39). A desaturation that occurred without a preceding apnea was interpreted as being caused by a hypopnea rather than as being a false positive desaturation (*Papers I and II*). In Paper IV a hypopnea was defined as a 50% reduction in respiratory amplitude with a concomitant desaturation. The apnea index (AI = number of apneas/h), apnea/hypopnea index (AHI = number of apneas + hypopneas/h) and oxygen desaturation index (ODI = number of 4% desaturations/h) were calculated on the basis of total time in bed.

Polysomnography (Papers III and IV)

Registration of sleep during the CT studies was performed with digital recording equipment (Galileo, Esaote, Italy and EMBLA, Flaga HF, Iceland) and comprised measurements of electroencephalogram (EEG; leads C3/A2 and C4/A1), electro-oculograms (EOG) and submental electromyograms (EMG). In addition, airflow was registered from the nose and mouth by thermistor and/or a nasal pressure cannula. Due to the digital processing of the recorded signals, there is a delay of approximately 2 seconds before the signals actually appear on the computer screen. Respiratory movement was therefore also measured with a stretch-sensitive piezo-electric respiratory effort belt. This belt was directly connected to a XY writer in order to obtain more time-accurate visual guidance to respiration during CT scanning (see below). Sleep staging was performed according to standard criteria (11). Pulse oximetry was performed in order to record the arterial oxygen saturation level during sleep (EMBLA Oximeter, type M, Flaga HF, Iceland and Novametrix, 7100 CO2SMO, USA). A person not involved in the studies also analysed the sleep recordings.

Pulmonary function tests

Lung volumes

In Papers I and II, lung volumes were measured by body plethysmography (equipment: Sensor Medics 6200 Autobox D_L) in the sitting position. The vital capacity (VC) was measured, as well as the forced expiratory volume in one second (FEV₁). The FEV₁/VC quotient was calculated. Total lung capacity was determined by measuring the functional residual capacity (FRC) and different subdivisions were calculated, such as the expiratory

reserve volume (ERV), residual volume (RV) and the RV/TLC quotient. Four subjects failed to perform a satisfactory spirometry test.

For Studies III and IV, the FRC was measured after 15 minutes of rest in the supine position by multiple nitrogen washout and airway closure by single-breath nitrogen washout (196). Reference values from Hedenström (24) (*Papers I and II*) and from European Community of Coal and Steel (197) (*Papers III and IV*) were used.

CO₂ sensitivity

Sensitivity to CO₂ was tested using the rebreathing method described by Read (40). The test was performed with the subject in the sitting position, rebreathing into a bag-in-bottle system. The bag was initially filled with 100% O₂ for the hypercapnic ventilatory response to CO₂ and, after a 15-minute rest period, with room air for testing hypercapnic ventilatory response to CO₂ under hypoxia. The ventilation per minute (VE, l/min) was measured by the use of a pneumotach, and the end expired concentration of CO₂ was analysed using a mass spectrometer (Airspec MGA 2000). During both tests, the VE was plotted breath by breath against the end tidal concentration of CO₂ (F_{et}%CO₂). The slope of the linear increase in V_E against the increase in F_{et}%CO₂ was calculated as VE/F_{et}%CO₂ (l/min/%). The difference between CO₂ sensitivity during hyperoxic and hypoxic conditions was also calculated. In 15% of the cases the test result could not be interpreted either due to technical problems or because the subject interrupted the test before a linear increase in ventilation had occurred.

Arterial blood gases

Arterial blood was drawn after at least 10 minutes of rest from arteria radialis, with the subject in the supine position. The blood sample was analysed for PCO₂, PO₂, SaO₂% (BGE Instrumental Laboratories). In 14 subjects (14%), no blood gas data could be obtained.

Computed tomography during wakefulness and sleep

Computed tomography (CT) of the lungs was used to study lung density (198) (Somatom Plus, Siemens, Erlangen, Germany and Light Speed Plus, GE Medical, Milwaukee, USA). This method has been widely used to evaluate lung morphology and to detect and evaluate atelectasis during anaesthesia (191;199;200) and permits the analysis of lung density (198;201) and calculation of the amount of gas in relation to lung tissue (202;203). Due to artefacts on the left lung in the CT scans, mainly from the heart, the analysis of lung aeration was carried out on the right lung. Even if lung density has been seen to show a tendency to be more pronounced in the right lung (198), the significance of this has been uncertain and subsequent studies

(199) have reported no differences in lung densities between the right and left lung. A ventro-dorsal difference in density is, however, to be expected. Due to the effect of gravity, this difference is caused by a vertical change in intra-pleural pressure, increasing both ventilation and perfusion down the vertical axis (204;205). During spontaneous breathing, no significant difference in density between apex and base has been reported (198).

All the subjects were studied in the supine position. A minimum of 15 minutes of rest preceded the awake CT scans. In two subjects, awake CT scanning was performed after sleep.

Technical and methodological aspects

To enable the assessment of regional dynamics and the identification of inspiratory and expiratory phases awake and during sleep, a novel approach to CT scanning was required. At end expiration, the position of the diaphragm was located from a frontal scout view covering the chest. A spiral scan (exposure time: 4 sec), covering the basal 4 cm of the lung, was then performed during normal breathing (exposure started at or close to end expiration, as guided by the spirogram from the respiratory belt device). The recording (X-ray attenuation values against time) thus reflected the breathing of the subject and enabled the detection of end-inspiratory and end-expiratory CT data (Figure 1). Measurements were made both during wakefulness and during sleep. Slice thickness was 10 mm, table movement 10 mm/sec and exposures were made at 165 mA and 120 kV. With a matrix of 512 x 512, the resulting picture element (pixel) was approximately 0.6 x 0.6 mm.

In two of the subjects in Paper III and in three patients in Paper IV and in one additional volunteer, a spiral CT of the basal 4 cm of the lung was obtained during breath-holding at FRC. This was done in order to check whether there was any change in the density of the lung over the distance studied. Analysis of the variation in lung density over this lung segment, however, revealed no significant change regarding density or gas/tissue ratio over the 4 cm horizontal lung segment.

Analysis of CT scans & calculation of lung aeration

Each spiral scan was reconstructed into 11 images, each 10 mm thick and with a 3 mm increment. Regional aeration was then analysed in each image by calculating lung aeration (see below) in four circular regions of interest (ROI) (199). The ROIs were 2 cm in diameter and distributed along the border of the lung, from the ventral (non-dependent) to the dorsal (dependent) lung region (Figure 1).

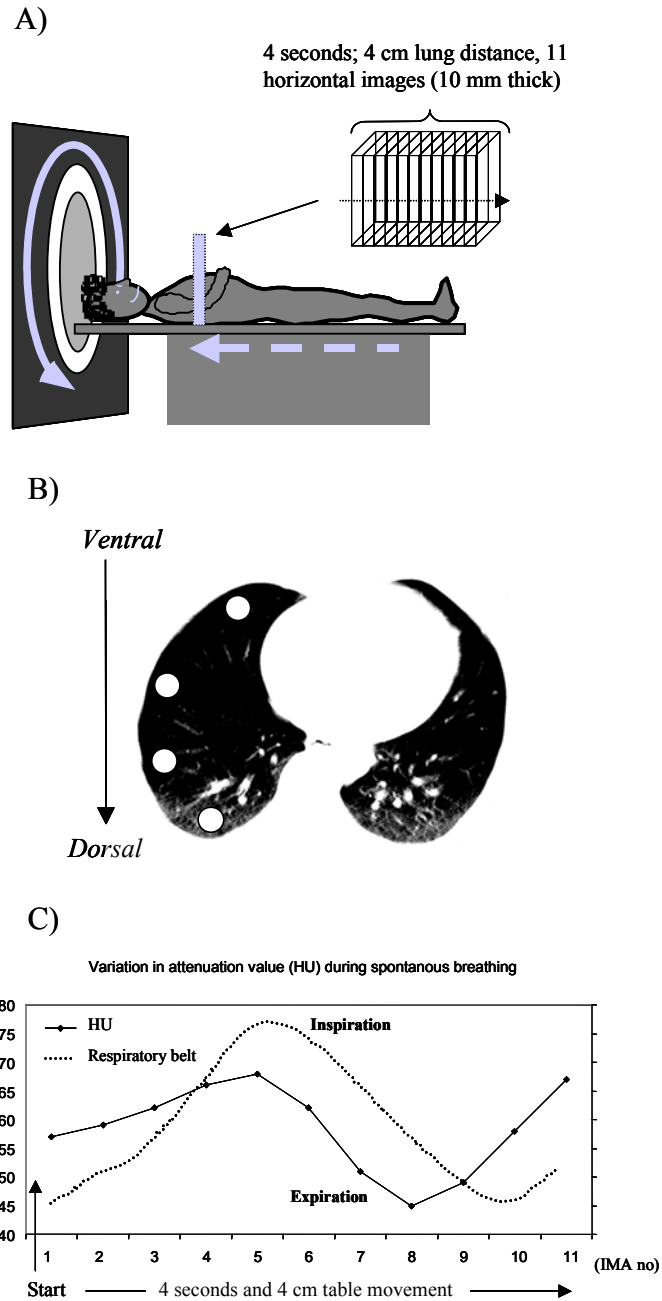


Figure 1. **A)** The subject move through the CT, covering a lung distance of 4 cm, from the diaphragm and cephalad. **B)** Positioning of the four ROIs. **C)** Illustration of the start of the CT scanning as guided by the respiratory belt (here manually drawn to simulate a breath, dotted line). The solid line displays the variation in attenuation value over the breath allowing the identification of expiration and inspiration.

The density of each ROI was calculated from the X-ray attenuation, expressed in Hounsfield units (HU), and included numbers between -1000 and -100 HU. The HU scale ranges from -1000 HU (air), via 0 HU (water) to +1000 HU or more (bone). The density of the lung in a particular pixel with an attenuation of x HU is:

$$\text{Lung density (g/ml)} = (x + 1000)/1000$$

So, if the attenuation is -800 HU in a pixel, a common value in a well-aerated lung region, the density is 0.2 g/ml. This value is the weighted mean of the lung tissue, blood and gas in that particular pixel. The inverse of the lung density is the "specific lung volume" (1/lung density), equalling 5 (ml/g) in this example. The density of the lung tissue is usually taken as 1.065 g/ml and its inverse value (0.939 ml/g) is the "specific lung tissue volume" (1/lung tissue density) (198). The aeration of the lung in each pixel per unit tissue can then be calculated as:

$$\text{Volume gas (ml)/weight of tissue (g)} = \text{Specific lung volume} - \text{specific lung tissue volume}$$

In the example above with a pixel of -800 HU, the lung density is 0.2 g/ml and the specific lung volume is 5 ml/g. In the same way, the specific lung tissue volume is 0.939 ml/g. The pixel thus contains 4.061 ml gas/g lung tissue.

Calculation of lung aeration has been done by others in a similar manner and provides a reasonable estimation of lung inflation (202).

Comparison of lung aeration during wakefulness and sleep

The dynamic change in lung aeration over time, as assessed from the 11 reconstructed images in the four different specific regions (ROIs) was related to respiration as recorded by the respiratory belt, allowing the identification of expiratory and inspiratory phases (Figure 1). The lowest aeration value seen in the series of images (i.e. at FRC) was identified for each ROI and a comparison of lung aeration was made for each subject between wakefulness and sleep. In addition, in eight subjects an analysis was made also of regional ventilation, both awake and during sleep. Ventilation was calculated both as the tidal variation in "ml gas/g lung tissue", in similar with the calculation of regional aeration (see above), and as aeration in a particular ROI (% air: $-x\text{HU}/10$).

Statistical methods

Throughout the study, descriptive statistics were calculated for the mean, standard error of mean (SE) and standard deviation (SD). Comparisons of data between more than two groups were made by a one-way analysis of variance (ANOVA). Adjustment for multiple comparisons were made using Tukey's test. Differences between independent groups were tested with the Mann-Whitney U-test. Group comparisons were also made for paired observations using a paired t-test and Wilcoxon's rank sum test. The association between respiratory variables and nocturnal respiratory events was found using correlation analysis (Pearson's and Spearman's rank correlations). In addition, both simple and multiple regression analyses were used. Skewed data were transformed whenever necessary. A p-value less than 0.05 was considered statistically significant.

Data were analysed using the Statistical Package of Social Sciences (SPSS) ver. 6.1–11.0, Matematica ver. 3, and Origin ver. 7.0.

For detailed information on the statistical analysis, please see the method section in each separate paper.

RESULTS AND DISCUSSION

In all, 35 healthy subjects and 90 patients with varying degrees of snoring and OSA were studied in terms of their ventilatory and pulmonary function awake and during sleep. The main finding in the present investigation is that, as the measurements of various lung-function and ventilation variables indicate, several aspects of respiratory function are affected in patients with snoring and OSA in comparison to healthy non-snoring subjects. In addition, the results indicate that the amount of obstructive breathing during sleep is related in part to respiratory function. For further details about subjects, see the individual Papers I-IV.

Sensitivity to CO₂ and ability to ventilate

Of the 78 patients that were studied, 25 were classified as snorers (SA), 19 as snorers with hypopneas and significant desaturations (OH) and 32 as snorers with obstructive apneas (OA). Contrary to the specific hypothesis of the study, the main result was, that the hypercapnic ventilatory response to CO₂ ($VE/F_{et}CO_{2hy}$) was higher in OA patients than in healthy subjects and in patients with snoring (*Paper I*) (Figure 2). The sensitivity to CO₂ was also higher for the OH and OA groups in comparison to healthy subjects in hypoxic conditions ($VE/F_{et}CO_{2ho}$) (Figure 2). The difference between $VE/F_{et}CO_{2hy}$ and $VE/F_{et}CO_{2ho}$, was most pronounced in patients in the OH group and significantly larger in comparison to subjects in the control group.

This result was not expected, as several previous authors have reported otherwise (174-177;184). The tone in the upper airway muscles appears to depend on the satisfactory function of the respiratory centre, as well as respiratory timing. A hypercapnic stimulus increases respiratory nerve activity and thereby also muscle activity (133;134). Insufficient sensitivity to CO₂ might therefore be expected to induce upper airway collapse during sleep. Lopata and Önal studied the ventilatory response to CO₂ in healthy subjects, obese subjects, patients with OSA and patients with obesity-hypoventilation syndrome (177). They found that obese subjects, as well as patients with OSA had a lower sensitivity to CO₂ than healthy non-obese subjects.

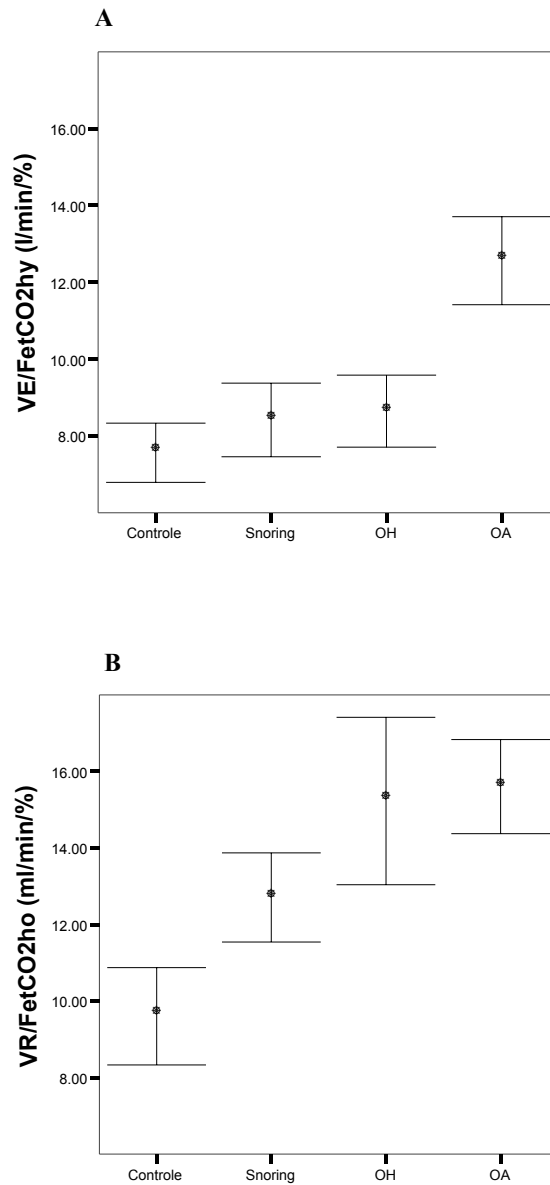


Figure 2. **A)** Ventilatory response to CO₂ tested in hypercapnic conditions. Patients in the OA group had higher response in comparison to healthy subjects and snorers ($p < 0.01$). **B)** Ventilatory response to CO₂ tested in hypoxic conditions. Patients in the OH and OA group had higher response than control subjects ($p < 0.01$). Note also the marked increase in response to CO₂ seen during hypoxic conditions for the SA and OH groups, while patients in the OA group lack this response. Bars represent the mean and standard error (SE).

In addition, OSA patients displayed a decrease in occlusion pressure (P0.1: the pressure generated by respiratory muscles during inspiration against an occluded airway), indicating a true diminished ventilatory drive. Similar findings were also reported by Sullivan et al. (174) and Garay et al. (184), where it was shown that both normocapnic and hypercapnic patients with OSA had a lower ventilatory response to CO₂ than a control group. Gislason and Tammivara drew similar conclusions but also reported that the ventilatory response might be reduced due to airway obstructivity, as has also been suggested by others (182;206). It therefore appears to be indisputable that, when hypercapnia is present, the ventilatory response is reduced in heavily obese subjects as well as in patients with OSA. In the present study, 13 subjects had hypercapnia (defined as a PCO₂ of > 6.0 kPa) and, as expected, they displayed a lower ventilatory response to CO₂ in comparison to subjects with normal PCO₂ when analysed separately. It is not likely that this could have influenced the results of group comparisons, as these subjects came from all four diagnostic groups and there were no significant differences in terms of arterial blood gases between the groups (*Paper I*). In addition, a sub-analysis from which these 13 subjects were removed did not change the results in a significant way.

However, when the present investigation was conducted, one author had previously reported increased ventilatory response to CO₂ (181). In the report by Verbruechen et al. patients with snoring and OSA were studied with regard to CO₂ sensitivity and pulmonary function. When it came to the OSA patients, one group with hypercapnia and one with normocapnia were investigated. It was reported that normocapnic patients with OSA had a higher ventilatory response to CO₂ than control subjects, but no differences were found in comparison to snorers, as reported in the present study. No significant change in CO₂ sensitivity was noted when the patients received nCPAP treatment over a period of four nights. However, a follow-up study conducted by the same authors indicated a decrease in ventilatory response to CO₂ after one year of nCPAP treatment (207). The authors referred to a couple of mechanisms that might have contributed to the increase in sensitivity. Firstly, it was suggested that periodic breathing during sleep might be seen in subjects with increased CO₂ sensitivity, as described by Chapman et al. (33), see below. It was also suggested that, according to Engel and Ritchie (186), the increased sensitivity could be secondary due to adrenosympathetic stress. A review of some of the data reported previously on ventilatory drive in OSA patients also indicates that these patients actually do present an increased need to breathe, most probably due to an increased drive. Benlloch et al. (180) did not find any significant differences regarding CO₂ sensitivity in terms of ventilatory response, but they did

report an increase in respiratory drive with a higher P0.1 and higher minute ventilation in patients with OSA in comparison to a BMI-matched control group.

An increased response to CO₂ in hypereroxic and hypoxic conditions has been shown in subjects with periodic breathing (33). Chapman and co-workers studied the breathing pattern of healthy subjects and found that the hypercapnic ventilatory response was almost twice as high in subjects with periodic breathing (artificially provoked) during sleep compared with subjects without. It was also seen in this study that periodic breathers experienced an increase of more than 30% in their ventilatory response to CO₂ when tested awake in hypoxic conditions, while the increase was more modest in the non-periodic breathing group (15%). In the present investigation (*Paper I*) a 26% increase in ventilatory response to CO₂ was noted among healthy subjects when tested in hypoxic condition. This is to be expected as hypoxia attenuates the response to CO₂ (56;208). A marked increase was seen in the patients with snoring (SA group; 51% increase) and in patients with mainly obstructive hypopneas and desaturations (OH group; 77%). Surprisingly, the patients with OSA (OA group) did not display any further aggravation in their response to hypercapnia in hypoxic conditions, as the increase here resembled that observed in healthy subjects (26% increase). To the knowledge of the author of the present thesis, this has not been demonstrated previously and could indicate a successive change in chemo-sensitivity among patients with varying degrees of obstructive breathing during sleep.

Increased ventilatory drive can be seen in patients with asthma. Kelsen and colleagues demonstrated this in 15 normocapnic patients with asthma (209). Airway obstructivity was obvious with an FEV₁/VC of 55% and an increase in RAW, FRC and RV. In comparison to healthy control subjects, the patients displayed an increase in occlusion pressure response to CO₂, while no significant difference was reported in terms of the ventilatory response to CO₂. This indicates an increase in ventilatory drive, this is not revealed by the ventilatory response test, as the patients might be more or less unable to increase ventilation as a response to hypercapnic stimulus due to airway obstructivity. Most of the patients studied in the present investigation had normal lung function in terms of FEV₁/VC% as well as FEV₁ (*Papers I and II*). Even if a small difference was noted for FEV₁/VC% in some analyses (*Paper II*), the differences were within the range of normality. In addition, even if there was a trend towards signs of airway obstructivity between the diagnostic groups, the RV/TLC% and FEV₁/VC% values displayed a trend towards increase and decrease between the four groups (*see Paper I for a detailed description*), no significant differences were found in terms of main lung function variables which are normally used to detect airway

obstructivity. The patients studied in the present investigation were therefore able to increase ventilation when stimulated by increasing CO₂ levels. In addition, arterial blood gases were within the normal range, even if a similar trend was also seen for PCO₂ and PO₂ (expressed as percentage of the normal value, *Paper I*). However, the lower ERV seen in patients with nocturnal apneas and desaturations (*Papers I and II*) might very well reflect diffuse airway obstructivity, as suggested by Bradley and co-workers (206) (see discussion section, Lung volume, below).

So what is the reason for the increased ventilatory response to CO₂ found here? It must be stated here that the design of the present study does not fully answer this question. It could be suspected that the sleep fragmentation from which the OSA patients suffer may change and influence the CO₂ responsiveness. However, sleep fragmentation does not appear to have any impact on the awake ventilatory response to CO₂, and it might in fact be reduced rather than increased (210). As stated previously, several factors influence the sensitivity to CO₂. In the present study (*Paper I*), correlation analysis revealed that a number of variables influenced the ventilatory response to CO₂ when tested in both hyperoxic and hypoxic conditions. A correlation was found between AI and VE/F_{et}CO_{2hy} ($r=0.40$; $p<0.001$) and VE/F_{et}CO_{2ho} ($r=0.33$; $p<0.01$). A significant correlation was also found between ODI and VE/F_{et}CO_{2hy} ($r=0.24$; $p<0.05$) and VE/F_{et}CO_{2ho} ($r=0.31$; $p<0.01$). Variables representative of obesity displayed a clear association with both VE/F_{et}CO_{2hy} and VE/F_{et}CO_{2ho} and the strongest association was seen for neck circumference ($r=0.50$; $p<0.001$). Furthermore, ERV was found to influence the ventilatory response in hypoxic conditions but not in hyperoxic conditions. This supports the above hypothesis that obesity-induced changes in pulmonary function might aggravate CO₂ sensitivity. However, apnea and desaturation frequency per se might also make a small contribution to increased sensitivity.

In the multiple regression analysis, AI, PCO₂ and sex (male gender) were found to be significant independent predictors of the variation in VE/F_{et}CO_{2hy}. Neck circumference was included in the analysis as the obesity variable due to the strongest single correlation and was found to improve the model R² but was not an independent predictor. The model R² was slightly smaller when the ODI was entered into the model instead of the AI. The ODI, however, was not independently correlated to VE/F_{et}CO_{2hy}. When it came to VE/F_{et}CO_{2ho}, gender and ERV remained as sole predictors.

Obesity may therefore influence the ventilatory response to CO₂, possibly due to changes in the lung volume and the ability to ventilate. If gross obesity and hypercapnia are present, the sensitivity to CO₂ is probably reduced in OSA patients. However, this is not likely in normocapnic OSA patients where the ventilatory drive appears to increase and the results of the

present investigation also indicate that CO₂ sensitivity might be increased if the ability to ventilate is intact. The present study further indicates that changes in over-all respiratory function due to obesity and the frequency of apneas and desaturations during sleep might be responsible for this increase in respiratory centre sensitivity, even if the cause and the effect remain unclear. The fact that respiratory centre activity is increased and is more sensitive to a hypercapnic stimulus when stressed under hypoxic conditions even in patients with snoring and obstructive apneas (thereby milder degree of obstructive breathing during sleep), is a new finding.

Lung volume

The association between lung volume and apnea and desaturation frequency (*Paper II*) was studied in the majority of the subjects presented in Paper I. The main finding was that patients with snoring and OSA were more obese and a pronounced difference was seen for the lung variable ERV. The ERV was reduced by approximately 40% in the patients with snoring and OSA in comparison to healthy subjects ($p < 0.001$) (Figure 3). In addition, the ERV was found to be an independent determinant of the variation in nocturnal apnea and desaturation frequency (*Paper II*).

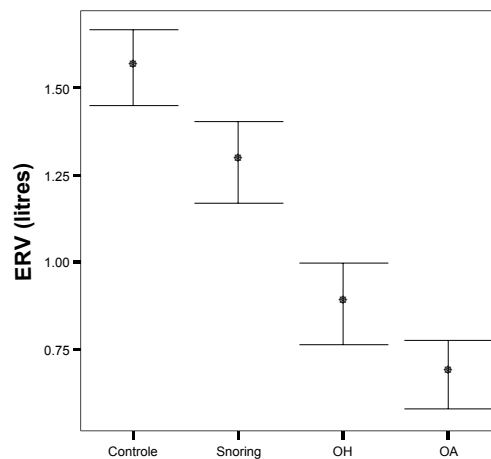


Figure 3. Illustration of measured ERV in healthy subjects and snorers and patients with hypopneas (OH) and obstructive apneas (OA). In order to illustrate the gradual decrease in ERV among patients with different degrees of nocturnal apnea and desaturation, the figure uses a similar group division as that used in Paper I. Bars represent the mean and standard error (SE).

As mentioned previously, a low ERV was observed in patients with abnormal breathing patterns during sleep many years ago (16;17;150;151). The significance of these observations was, however, not clear. The observation of a low ERV in OSA patients in the present study thus supports these observations but also suggests that the effect of reduced lung volume on nocturnal apnea and desaturation frequency, is similar to the effect of obesity. Önal et al. (152) studied the relationship between different respiratory parameters and AHI in a group of patients (n=34) with suspected OSA. In this unselected group of patients, 12 were found to have obstructive airway disease and 18 had a restrictive pattern with reduced FRC. Correlation analysis revealed a significant association between FRC ($r=-0.57$; $p<0.01$), inspiratory airway conductance (GAW) ($r=-0.47$; $p<0.05$) and AHI in the group without obstructive airway disease. The ERV was also lower than expected for the whole group of patients studied (0.71 ± 0.09 l) but no correlation to AHI was reported. According to the authors, the reduction in FRC causes more negative inspiratory pressure, thereby increasing the possibility of upper airway closure during sleep to explain their findings. Zerah-Lancner et al. have also reported on a correlation between airway obstructivity and OSA (153;154). In one of the studies, pulmonary function tests were performed on 170 patients who had no symptoms of asthma or COPD. A correlation between forced expiratory volumes, airway conductance and AHI was reported. According to the authors, this suggests a combination of both upper and lower airway obstructivity. In the same study it is also shown that the ERV was reduced in the patients, but that the ERV was almost equal among in the different OSA severity groups that were studied. The same was true of the FRC, which was within the normal range (153). From the same group, it was later reported that it was possible to distinguish patients with OSA among obese subjects using a logistic regression model (154).

The significance of reduced lung volume in the pathogenesis of snoring and obstructive apnea was evaluated in an important study conducted by Hoffstein and co-workers (155). In nine overweight patients with OSA and 10 age- and weight-matched controls, the relationship between lung volume and pharyngeal cross-sectional area was analysed using an acoustic reflection technique. The area of the upper airway was measured during expiration from TLC down to RV. The main finding was that the cross-sectional area was significantly smaller in OSA patients at all lung volume levels. It was also seen that the area decreased with expiration in both groups, but that the difference was greatest in OSA patients. It was shown that obese patients with OSA had a significantly lower FRC than healthy controls (68% of predicted vs. 94% of predicted; $p<0.001$). Similar results were subsequently also reported among women with OSA (156). In the present study, the FRC correlated to the AI ($r=-0.23$; $p<0.05$), ODI ($r=-0.35$;

$p < 0.01$) and the lowest nocturnal saturation value ($r = 0.39$; $p < 0.001$) but did not remain as an independent predictor in the multiple regression analysis. This is in line with the observation made by Sériès et al. (190), who reported that the fall in $\text{SaO}_2\%$ in subjects with OSA is highly correlated to lung volume. Bradley et al. have also reported a strong correlation between ERV and mean nocturnal $\text{SaO}_2\%$ (187). The physiological mechanism was not clarified, but an increase in the closure of peripheral airways, especially in the dependent regions of the lung, was suggested. The latter phenomenon during sleep was also studied in the present thesis (see below).

The extent to which obesity induced changes in lung volume actually contribute to the severity of snoring and OSA is not at all clear. In the present study correlation analysis revealed an equally strong association between weight, BMI and ERV and AI and ODI. In addition, multiple regression analysis also indicates that the ERV has an impact on apnea and desaturation severity that is equal to that of obesity (*Paper II*).

The fact that the ERV and not the FRC was independently correlated to AI/ODI may reflect the presence of diffuse airway obstructivity, as suggested by Bradley et al. (187). Obstructive pulmonary disease, such as asthma and COPD, may reduce the ERV. The ERV is then reduced due to an increase in residual volume, which is a result of chronic air-trapping. In this case, the FRC is increased. In the restrictive disease total lung capacity is decreased thereby decreasing both the ERV and FRC. In the present study, patients with snoring and OSA had a low ERV but a normal FRC and it was only the ERV that was found to have an independent impact on nocturnal apnea and desaturation frequency. As the patients in the present study were healthy when it came to their respiratory function awake, it might be anticipated that obesity reduced their ERV but that they were suffering at the same time from airway closure, which tends to increase their residual volume. The net effect is therefore that the FRC is not reduced as might be expected in the case of pure obesity. This means that the independent correlation between the ERV and AI/ODI indicate that patients with OSA already suffer from the closure of peripheral airways in the upright position. When measuring closing volume in OSA patients in the supine position, airway closure was obvious (*Paper IV*). The fact that lung volume and closing volume are of importance in the variation in the degree of nocturnal hypoxemia in OSA patients is in line with and confirms previously reported data (187;190).

The independent effect of the ERV on AI was significant yet small and may not be of clinical importance other than when it is combined with other risk factors such as obesity and smoking (Figure 4). The effect on the ODI, on the other hand, is more pronounced, reaching a considerable effect in combination with obesity and smoking (Figure 5).

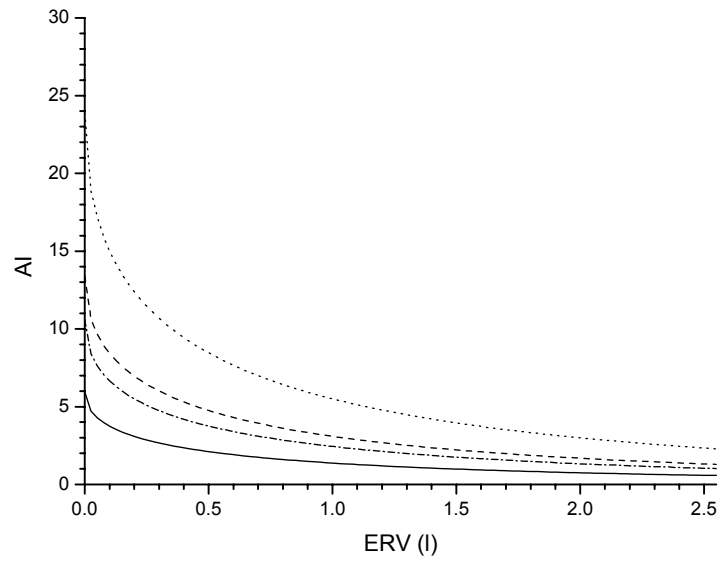


Figure 4. The diagram illustrates the influence of expiratory reserve volume (ERV, l) on the apnea index (AI) in a normal weight and non-smoking subject (continuous line), a normal weighted, smoking subject (dotted-dashed line), an non-smoking, obese subject (dashed line) and an obese, smoking subject (dotted line).

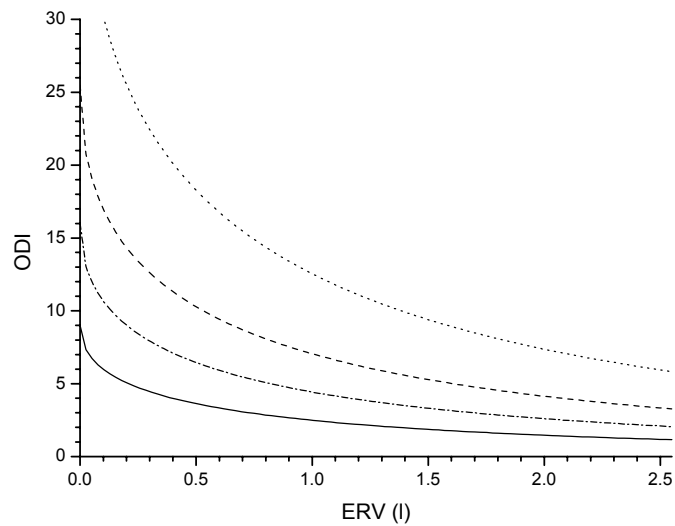


Figure 5. The diagram illustrates the influence of expiratory reserve volume (ERV, l) on the desaturation index (ODI) in a normal weight and non-smoking subject (continuous line), a normal weighted, smoking subject (dotted-dashed line), an non-smoking, obese subject (dashed line) and an obese, smoking subject (dotted line).

Ventilation and lung volume in OSA patients after weight reduction

Ventilatory response to CO₂ and lung volume was measured in eight patients before and after weight reduction. On average the patients reduced their weight from 107 to 100 kg ($p < 0.05$) and their BMI from 35 to 33 ($p < 0.05$) during a period of 12 months. A positive effect was noticed on both AI and ODI, which was reduced from 25 to 10 and from 46 to 23 respectively ($p < 0.05$ for both AI and ODI). The ventilatory response tended to be lower

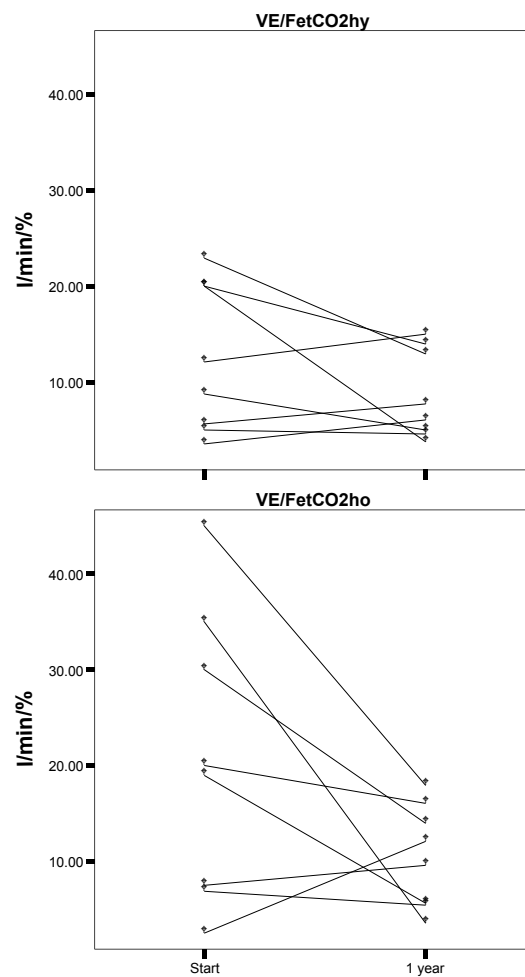


Figure 6. Ventilatory response to CO₂ in hyperoxic (upper panel) and hypoxic conditions (lower panel) in eight OSA patients before and after weight reduction.

after weight reduction when tested both in hyperoxic (12.7 ± 7.7 vs. 7.9 ± 3.9 ; $p=0.093$) and in hypoxic conditions (20.8 ± 15.0 ; $p=0.093$) (Figure 6). An improvement regarding the lung volume ERV was also noticed (from 0.5 to 0.9 l; $p=0.058$) (Figure 7).

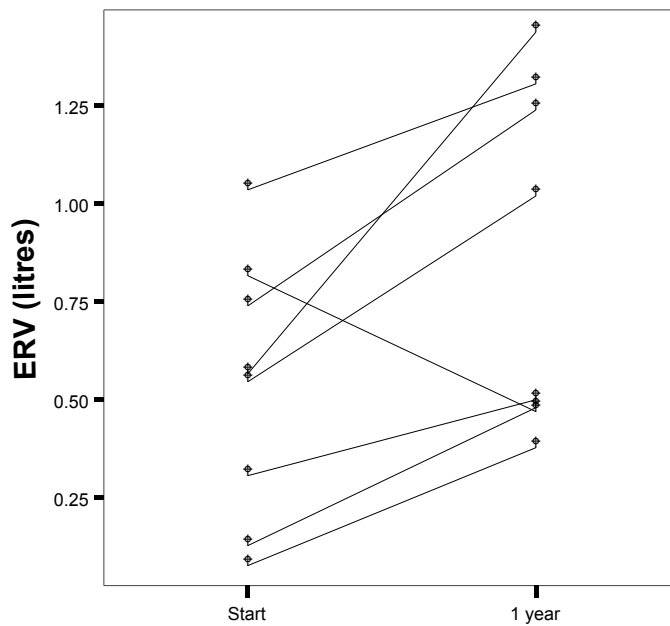


Figure 7. Individual change in ERV before and after weight reduction. In seven of the eight patients a higher ERV was observed after weight reduction.

Regional lung aeration and ventilation during sleep

The investigations performed on lung aeration during sleep present new data on regional lung aeration and ventilation during sleep in both healthy subjects and in patients with OSA. The significance of the observations and any clinical implications therefore need to be further verified and examined in future studies. Nevertheless, the new data that have been obtained provide a new and interesting insight into phenomena occurring within the lung during regular and obstructive breathing in the state of sleep.

Regional lung aeration at FRC

The main finding was, that during normal sleep, the dorsal lung region was denser than it was when the subjects were awake and it was found that lung aeration in the dorsal, most dependent, lung region was reduced by approximately 9% (*Paper III*). The average change was -10 ml gas/g lung tissue ($p<0.05$) when comparisons were made between wakefulness and sleep at or close to the FRC level (Figure 8). It was also found that, in the ventral lung region, lung aeration tended to increase (mean difference=20 ml gas/g lung tissue, 6% change; $p<0.01$). The healthy subjects studied here had normal lung function when awake but displayed a tendency towards increased airway closure, as evidenced by the closing volume measurements performed after rest in the supine position (*Paper III*).

In healthy subjects, a reduction in minute ventilation is seen during sleep (34) and lung volume (FRC) is reduced by approximately 7% during NREM sleep and by 10% during REM sleep (36). The present observation of a reduction in lung aeration in dependent lung regions and a slightly smaller increase in the ventral region is in accordance with this, where the net effect would be a reduction in the overall FRC.

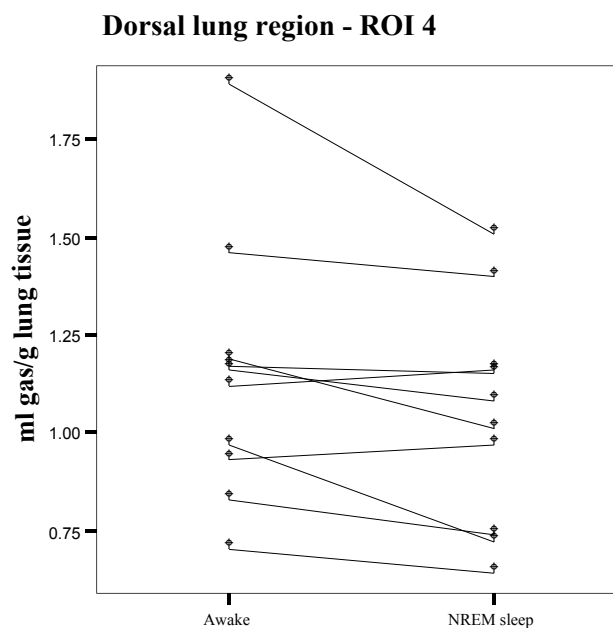


Figure 8. Individual change in lung aeration at FRC in the dorsal (dependent) lung region in healthy subjects studied during wakefulness and sleep.

Lung density

In experimental conditions (anaesthetised dogs), the difference in air content measured by means of computed tomography has been estimated at approximately 40% between ventral and dorsal lung regions and has been found to decrease by around 3% air per cm vertical lung distance (supine position) (201). Previous data from investigations in human, have estimated that the ventral-dorsal difference is around 11%. However this value was obtained during spontaneous breathing and in situations in which the whole lung was analysed (198).

In the present study, the average difference in air content between the ventral (ROI₁) and dorsal (ROI₄) lung region averaged $26 \pm 7\%$ air awake and $29 \pm 6\%$ air during NREM sleep ($p < 0.05$). Indirectly, this indicates a lung volume reduction during sleep (decreased FRC), as differences in lung density between non-dependent and dependent lung regions are larger at low lung volumes in comparison to when the lungs are more inflated (211).

Gas/tissue ratio

In a study by Pelosi et al., the gas/tissue ratio was estimated at FRC in awake healthy subjects during breath-holding at FRC (202). The dorsal lung region was then found to contain approximately 34% of the amount of air per volume tissue in comparison to the ventral lung region. The data obtained in the present study are well in line with this, estimating the gas/tissue ratio in the dorsal lung region during wakefulness at 32% of that in the ventral region. During NREM sleep, this figure was slightly less, averaging 28% ($p < 0.01$).

Lung aeration during anaesthesia

The change in lung aeration observed here during sleep is qualitatively similar to but quantitatively smaller than changes observed during anaesthesia. In this study, a new analysis of CT scans from a previously published study (191) of patients whose anaesthesia was induced and maintained during ventilation with 30% O₂ also revealed a decrease in dependent lung aeration (-26%) (thereby at the level of ROI₄) (Figure 9). During ongoing anaesthesia, when the inspiratory fraction of O₂% was switched from 0.3 to 1.0, aeration in the most dependent ROI was further reduced (-39%) and atelectasis in the most dependent regions below ROI₄ could be seen, in accordance with previous reports (212;213).

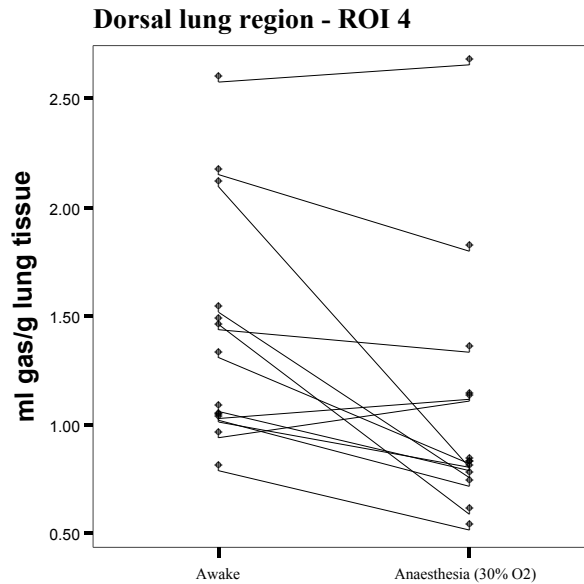


Figure 9. Plot of the individual fall in lung aeration in the dorsal lung region from wakefulness to anaesthesia. The analysis and calculation of regional lung aeration was performed on 13 patients undergoing anaesthesia. A significant loss of air was seen in the dorsal lung region (ROI₄, 26% fall; $p < 0.01$).

Regional aeration in a case of REM sleep

As a reduction in muscle tone and ventilation and lung volume is most pronounced during this sleep stage it could be hypothesised that a further decrease in lung aeration will occur in the dorsal lung region and that this might in fact reach a level at which ventilation-perfusion mismatch eventually affects arterial saturation. The first period of REM sleep is normally seen after 90 minutes of sleep. It was difficult for the subjects to maintain sleep long enough to reach that sleep stage. However, in one healthy subject, a period of REM sleep occurred with the presence of periodic breathing. Lung aeration was then more affected in this subject than when studied during NREM sleep (Figure 10). However, further studies are required to confirm whether this is actually the case.

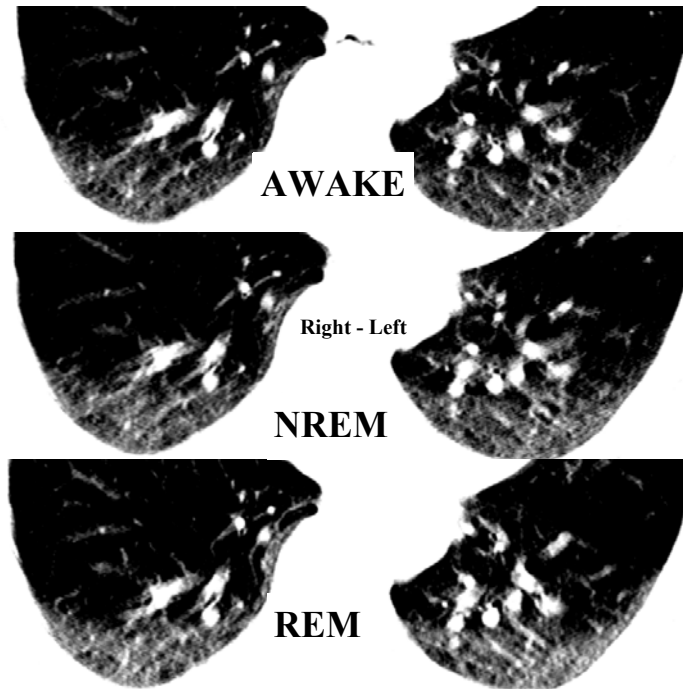


Figure 10. CT scans from one healthy subject obtained during wakefulness, NREM sleep and REM sleep. The scans focus on the mid and dorsal lung regions. In this case, aeration in the lowermost lung region (at the level of ROI₄) during wakefulness measured 0.84 ml gas/g tissue, 0.76 ml gas/g tissue during NREM sleep (-10%) and 0.65 ml gas/g tissue during REM sleep (-23%). Window 400 HU, Center -400 HU.

Regional lung aeration at FRC in OSA patients

When it came to lung volume measured in the supine position and during wakefulness, the patients displayed a marked reduction in ERV (0.16 ± 0.15 l) and increased closing volume (*Paper IV*). Like the healthy subjects, patients with OSA display reduced aeration in the dorsal lung region. Even if the decrease that was observed (when expressed as a percentage) tended to be greater than that during sleep in healthy subjects, comparisons between the OSA patients and the healthy subjects in the present study reveal that the decrease in the amount of gas observed among OSA patients was of equal magnitude (10 ml gas/g lung tissue) (*Paper IV*). The tendency towards more air in the ventral lung region seen during sleep in healthy subjects was not noted in the same way in OSA patients.

Interestingly, in patients with OSA, the reduction in lung aeration occurs at a lower level. It was found that they have lower aeration in the dorsal lung region both when awake ($p < 0.05$) and during sleep ($p < 0.05$) in comparison

to healthy subjects. It should also be noted that the decrease seen in healthy subjects contains data obtained during delta sleep, while the data for OSA patients in the present study were obtained during light sleep, stages I and II. This could conceal a larger reduction in aeration during delta sleep in OSA patients, even though previously reported data indicate that lung volume changes remain relatively constant during NREM sleep (37).

The lower aeration noted during wakefulness in the patients could be attributed to obesity. The change in aeration from wakefulness to sleep, however, correlated to the ERV ($r=0.47$; $p<0.05$), while no association was seen with BMI ($p=0.331$) or FRC ($p=0.138$) (*Paper IV*). When correlation analysis was performed on each group of subjects separately, no significant correlation was found between BMI and lung aeration at ROI₄ either awake or during sleep. However, correlation analysis of a pooled data set containing the OSA patients and the healthy subjects ($n=22$) revealed some interesting associations. The analysis identified a correlation between BMI and lung aeration at ROI₄ both awake ($r=-0.42$; $p=0.054$) and more markedly during sleep ($r=0.52$; $p<0.05$). The lower lung aeration seen in patients with OSA is therefore partly due to obesity and the observed change in aeration in dependent lung regions depends on the awake ERV.

An interesting question arises from the observations made here. It is an accepted fact that nCPAP acts as a pneumatic splint that prevents the upper airway from collapsing during sleep. However, nCPAP has also been shown to have an effect on lung volume with an increase in FRC. It could therefore be hypothesised that nCPAP also prevents airway closure during sleep in OSA and thereby counteracts the observed decrease in lung aeration in dorsal lung regions. It remains to be seen whether this is the case, however.

Lung aeration during ongoing obstructive apnea

In two of the OSA patients, CT scans could be performed during ongoing obstructive apnea (*Paper IV*). Surprisingly, it was noted that lung aeration increased rather than decreased in both ventral and dorsal lung regions. Obstructive apnea causes considerable pressure swings (123) and can be compared to a Müller manoeuvre in which a subject breathes against a voluntarily occluded upper airway. It therefore seems likely that either the redistribution of air took place during the obstructive breathing event or that the apnea took place before end inspiration or expiration, thereby trapping air within the lung. Even if there are too few observations to calculate any statistics, this observation is important as it is generally stated that the lung volume at which the apnea occurs determines the degree of desaturation and affects mean arterial saturation, as discussed above. However, if the apnea occurs in the mid-inspiratory phase or if redistribution occurs within the

lung, this might protect and prevent airway closure and ventilation-perfusion mismatch, thereby mitigating the concomitant desaturation.

Possible mechanisms changing regional lung aeration

Normal physiology

Several mechanisms, such as a reduction in respiratory muscle tone, changes in respiratory timing, the central pooling of blood, reduced lung compliance and reductions in tonic inspiratory muscle activity, have been suggested as being potentially associated with the sleep-induced reduction in FRC (36-38). Respiratory muscle tone is reduced during NREM sleep (214) and REM sleep (215;216). The more pronounced decrease in the FRC reported during REM sleep is most probably due to the loss of muscle tone, which may promote airway closure and ventilation-perfusion mismatch in the dependent lung region and thereby contribute to the small yet significant desaturations seen in the healthy sleeping subject (35). The finding of a loss of air in the dorsal region and increased aeration in the ventral part may match the hypothesis of reduced muscle tone. The loss of tone allows the elastic forces of the lung tissue to pull in the rib cage and the diaphragm until the outward forces exerted by the chest wall and the inward forces from the lung establish a new balance. Loss of diaphragm tone facilitates the transmission of the higher abdominal pressure into the thoracic cavity and this causes a larger difference in pleural pressure surrounding ventral and dorsal lung tissue. When obesity is present, this phenomenon is likely to be more pronounced, which could explain why patients with OSA had lower lung aeration during wakefulness and sleep. It was found that FRC, measured awake in the supine position, correlated to the fall in lung aeration in the dorsal lung region from wakefulness to sleep ($r=-0.78$; $p<0.01$). Thus the smaller the FRC was awake the greater was the loss of air in the dependent lung region during sleep. This finding suggests that conditions that cause a low FRC will have greater consequences for the aeration of the lung during sleep.

However, it could be argued that dependent lung regions become denser over time when lying immobile on the CT table, in some cases for more than two hours. However, the observed change in lung aeration during sleep appears to occur more or less instantly and no correlation between the degree of change and time in the supine position or to sleep time was found. Moreover, the two subjects who were studied while awake after a preceding period of sleep displayed the same pattern of decrease in aeration during sleep as the subjects who had been studied awake first, before sleep. Finally, healthy, awake subjects that were resting supine for more than an hour displayed no decrease in aeration in dependent lung regions (212). These observations are consistent with the data reported by Ballard et al., showing

no relationship between study or sleep time and changes in FRC during sleep (37). They reported that the change in FRC occurred within 30 minutes of sleep and then remained relatively constant during NREM sleep, while a further decrease was seen during REM sleep.

Obstructive sleep apnea

Correlation analysis revealed that the ERV correlated to the change in lung aeration between wakefulness and sleep ($r=-0.69$; $p<0.05$) (*Paper IV*). However, no significant correlation was found between BMI or FRC and differences in lung aeration. This observation is directly in line with the results obtained when studying the relationship between lung volume and apneas and desaturations during sleep in OSA patients (*Paper II*). These observations therefore confirm the results of that study and strengthen the discussion relating to the occurrence of airway closure in OSA patients and its impact on lung aeration during sleep. A correlation was also found between sleep time and the fall in lung aeration in the dorsal lung region ($r=0.66$; $p<0.05$). Time in CT, however, did not correlate to the fall in lung aeration.

Regional ventilation – variation in lung inflation over a breath

When it comes to ventilation, large individual variations were noted, when it came to both healthy subjects and OSA patients, even if there was no significant difference between wakefulness and sleep for either the ventral or the dorsal lung region (*Paper III and IV*). During wakefulness in healthy subjects, the variation in lung density was most pronounced in the dorsal, dependent, lung region (*Paper III*). This is to be expected as, in just the same way as in regional aeration, there is a vertical gradient from non-dependent to dependent lung region in terms of ventilation while breathing awake, in spite of position (201;211). This is also the case when it comes to lung perfusion (217). In the present study, the average variation in lung density for the lower, dependent, lung region was 49 ± 29 HU awake and the variation in the upper, non-dependent, region was 38 ± 12 HU ($p=0.166$). The corresponding figures during sleep were, 55 ± 26 HU and 45 ± 44 ($p<0.092$).

However, when the amount of gas in relation to lung tissue weight was calculated, it was noted that the actual variation in gas in relation to lung tissue weight was the opposite. Lung inflation was therefore significantly higher in the ventral lung region in comparison to the dorsal region both awake and during sleep. Bearing in mind that there is a large documentation on the preferential distribution of ventilation to lower lung regions in resting conditions (218), this initially appears controversial. However, the gas/tissue quotient reflects regional inflation in relation to the amount of tissue and has in fact been shown to decrease from ventral to dorsal lung regions during

wakefulness in healthy subjects (202). Interestingly, it has been shown that, when breathing at low lung volumes, within less than 20% of the vital capacity (VC) (i.e. within ERV), the phenomenon of the distribution of ventilation is more uniform and may even be reversed, so that the uppermost lung regions become more ventilated than the dependent ones (29;219). This is also seen in obese subjects with a low ERV. Holley and co-workers have shown that, when an obese subject takes a full inspiration in the upright position from FRC, the lower zones are better ventilated than the upper ones. However, when breathing quietly, the opposite occurs in obese subjects with reduced ERV (30). In the present study in which the subjects were studied after rest in the supine position, airway closure was obviously present, both in healthy subjects and even more markedly in patients with OSA (*Papers III and IV*). This is reflected by an increase in CV and also by a low ERV in some of the healthy subjects. In fact, in five of the healthy subjects, the ERV was reduced to approximately 0.5–0.6 litres in the supine position, which may have already induced breathing at low lung volume during CT scanning in the awake state (*Paper III*).

CONCLUSIONS

Ventilatory response to CO₂

Patients with OSA display increased sensitivity to CO₂ in comparison to healthy subjects and snorers. An increased ventilatory response to hypercapnia is also noted in snorers and most markedly in patients with mainly obstructive hypopneas and desaturations. Nocturnal apnea frequency, obesity and reduced lung volume may have contributed to these results.

Lung volume

Patients with obstructive apneas and hypopneas have a lower ERV and higher closing volume than healthy controls. The ERV is found to correlate to nocturnal apnea and desaturation frequency to the same extent as obesity. The correlation is most pronounced when it comes to desaturations.

Lung aeration and ventilation during sleep

Reduced aeration is observed in the dorsal, most dependent, lung region during NREM sleep. In contrast, the ventral lung region displays an increased aeration. When it comes to regional ventilation, expressed as amount of gas in relation to amount of tissue weight, higher ventilation is noted in the ventral region in comparison to the dorsal lung region, probably because of airway closure when breathing at low lung volume. A negative correlation between awake FRC and loss of air in the dorsal lung region during sleep is found. Reduced respiratory muscle tone and airway closure are possible causative factors.

Lung aeration during sleep in patients with OSA

In comparison to healthy subjects, patients with OSA are found to have a lower aeration in dorsal lung regions awake and during sleep, most probably due to airway closure induced by obesity. A similar reduction in dorsal lung aeration is noted during sleep while the ventral region appears unaffected. Reduced ERV and sleep time correlates to the loss of air in the dorsal lung region during sleep.

During sleep with obstructive apneas it is noted that lung aeration is increased rather than decreased. However, this finding should be interpreted with care due to the small number of observations.

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