Assessment of nocturnal versus daytime gas exchange in stable COPD

With emphasis on hypoventilation during spontaneous sleep and in sleep influenced by alcohol or zopiclone

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Scientific environment

The present work was performed from 2008 to 2015 at LHL-klinikkene Glittre in Hakadal, a pulmonary hospital owned by the Norwegian Association of Heart and Lung Patients (LHL). The study was carried out in cooperation with the Norwegian National Centre of Excellence in Home Mechanical Ventilation (NKHR), Haukeland University Hospital, Bergen and with the Department of Clinical Science, University of Bergen. Sleep was scored by Registered Polysomnographic Technologist (RPSGT) Paul Murphy, Gothenburg, Sweden, PhD RPSGT Brit Øverland, Lovisenberg Diakonale Sykehus, Oslo, associate professor PhD RPSG Janne Grønli, Department of Biological and Medical Psycology, University of Bergen and nurse Thomas Berge, Center of Sleep Medicine, Haukeland University Hospital, Bergen. The project has been financially supported by the Norwegian ExtraFoundation for Health and Rehabilitation through EXTRA funds, LHL's Research Fund, LHL-klinikkene Glittre, NKHR, Takeda Nycomed funneled via the Norwegian Lung Medicine Society, Major Eckbo's endowments and the University of Bergen.

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Despite being a small clinic of only 96 beds, LHL-klinikkene Glittre has contributed to the scientific base of knowledge by more than 30 original research papers, 5 PhD and 8 MSc degrees during the past decade. As several previous projects, this study also relied on the efforts, enthusiasm and the necessary accuracy in collecting scientific data of many of the employees at the hospital. Although I cannot mention all, I wish to express my gratitude to the former and the present directors of LHL-klinikkene Glittre, Dr Olav Kåre Refvem and Olav Ulleren who have shown great interest in my work and made it possible to finish the study despite several unforeseen obstacles. Also, I wish to express a special thank you to my former and present superiors Dr Anne Norlund and Dr PhD Aina Kjensli for their friendship, support and faith in my ability to finish what sometimes felt like "the never ending story". Special thanks to the nurses Jorun Helgesen, Inger Åshild Krog, Berit

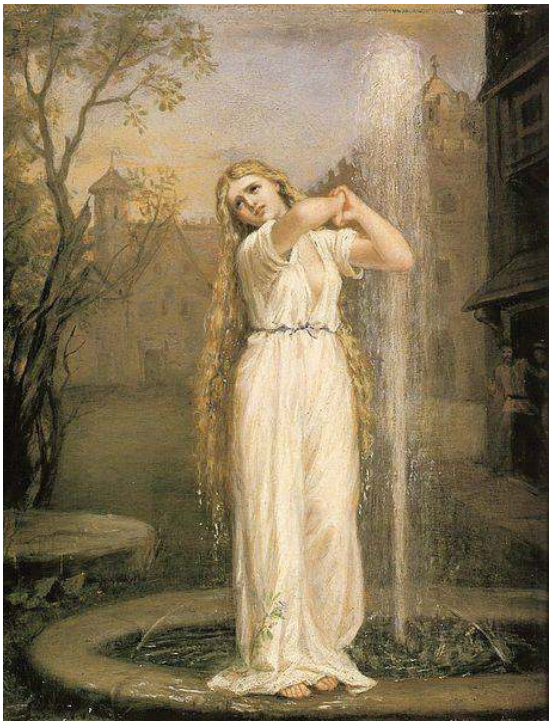
Grønvold and Berit Sylstad who spent literally hundreds of hours mounting sleep recording electrodes, belts, probes and wires on the patients, and to the laboratory personnel Grethe Dahle, Liv Karin Vesteng, Christine G. Karlsen, Jan Inge Krog, Turid Vestli and Mona Lisa Digernes for collecting lung function data and blood samples.

I am also grateful to all the participating study subjects, literally being patient in enduring the extra daytime tests and the sleep studies; fortunately only a couple of them ending up with a hangover after the double nightcap.

I wish to thank my colleagues and friends both at Glittre, at home and in Kenya for their enthusiastic support and help. Finally, this work had been impossible without my family. Special thanks to my parents Gerd and Jostein for encouraging my endless wondering of "why" from early childhood and for lending us their quiet place on the savannah in Kenya during the writing of the papers. Likewise, my dear wife Ragnhild and my daughters Solveig, Anna, Mari and Ingrid deserve my warmest gratitude for their unconditional love, patience and support and for reminding me of the wider perspective of life.

Hippopotamuses going to sleep with apneas of up to five minutes after a night of grazing on the banks of Mara River in Kenya (private photo)

Preface



Undine, painted 1872 by John William Waterhouse (photo from Wikipedia)

The water nymph Undine is a mythological figure of European tradition. According to one version of the myth, Undine, having been betrayed by her mortal husband, took from him all automatic functions, requiring him to remember to breathe. When he finally fell asleep, he died [1].

Abstract

Background/purpose: Chronic hypercapnic respiratory failure (CHRF) is associated with increased mortality in patients with chronic obstructive pulmonary disease (COPD), and sleep hypoventilation (SH) has been proposed as a possible predictor for CHRF in COPD. SH was previously found in COPD patients with CHRF using long term oxygen therapy (LTOT). However, SH in normocapnic, non-LTOT subjects have not been described. More than half of COPD patients have difficulties in initiating or maintaining sleep or are excessively sleepy at daytime. Hypnotics and alcohol are often used although both are known to depress the respiratory drive to breathe, and little is known regarding SH due to these agents. We have explored the associations between sleep architecture and nocturnal and daytime blood gases in stable COPD, both in spontaneous sleep and during sleep influenced by alcohol or the hypnotic zopiclone.

Material/methods: Paper I is an observational sleep study in a pulmonary rehabilitation hospital of 100 (39 male) stable COPD inpatients, mean FEV1 1.1 L (42% of predicted), mean age 64 years, using polysomnography with transcutaneous measurement of carbon dioxide pressure increase ($\Delta p_{tc}CO_2$). Paper II and paper III presents data from interventional sleep recordings from 26 (9 male) and 31 (10 male) of the same subjects described in paper I, influenced by 0.5 mg ethanol/kg bodyweight or a pill of 5 mg zopiclone, respectively.

Results: SH in spontaneous sleep was found in 15%, and although most had CHRF, six subjects were daytime normocapnic. Alcohol induced a mean (95% confidence interval) increase in the $\Delta p_{tc}CO_2$ during sleep of only 0.1 kPa (0.0-0.2, p=0.047) with no significant increase in the frequency of SH, whereas zopiclone increased the mean (SD) $\Delta p_{tc}CO_2$ with 0.23 (0.33) kPa, and the frequency of SH from 19% to 42% (p=0.020).

Conclusions/consequences: SH is found both in hypercapnic and normocapnic COPD subjects. Whether it is a real predictor of CHRF should be investigated by prospective case-control studies. A moderate dose of alcohol has only minor effects on breathing at sleep whereas zopiclone increases the frequency of SH in COPD.

List of publications

Holmedahl NH, Øverland B, Fondenes O, Ellingsen I, Hardie JA. *Sleep hypoventilation and daytime hypercapnia in stable Chronic Obstructive Pulmonary Disease.* International Journal of Chronic Obstructive Pulmonary Disease 92: 265 - 275 (2014) doi: 10.2147/COPD.S57576 | Pubmed: 24600219.

Holmedahl NH, Øverland B, Fondenes O, Ellingsen I, Hardie JA. *Alcohol at bedtime induces minor changes in sleep-stages and blood gases in stable chronic obstructive pulmonary disease.* Sleep and Breathing 19: 307-314 (2015) doi: 10.1007/s11325-014-1020-y | Pubmed: 24935686.

Holmedahl NH, Øverland B, Fondenes O, Ellingsen I, Hardie JA. *Zopiclone effects on breathing at sleep in stable chronic obstructive pulmonary disease.* Sleep and Breathing 19: 921-930 (2015). doi:10.1007/s11325-014-1084-8 | Pubmed:25501294.

Contents

1. Abbreviations

Diagnoses and therapy

COPD	Chronic Obstructive Pulmonary Disease
OSA	Obstructive Sleep Apnea
CPAP	Continuous Positive Airway Pressure
IPR	Inpatient Pulmonary Rehabilitation
LTOT	Long Term Oxygen Therapy
NIV	Non Invasive Ventilation

Function and classification

FEV1	Forced Expiratory Volume first second (by spirometry)
FVC	Forced Vital Capacity (by spirometry)
TLC	Total Lung Capacity
RV	Residual Volume of the lung
DLCO	Diffusing capacity of the Lung for Carbon monOxide
BMI	Body Mass Index (bodyweight/(height in meters) squared)
6MWD	Six Minute Walking Distance at pace decided by the patient
MMRC	Modified Medical Research Council questionnaire
BODE	Body mass index, airflow Obstruction, Dyspnea, Exercise (indicator of prognosis in COPD)
GOLD	Global initiative of chronic Obstructive Lung Disease

Gases and pressures

CO_2	carbon dioxide
O_2	Oxygen
pO_2	pressure of oxygen
pCO_2	pressure of carbon dioxide
p_aCO_2	arterial pressure of carbon dioxide
$p_{et}CO_2$	end tidal expiratory pressure of carbon dioxide
$p_{tc}CO_2$	transcutaneous pressure of carbon dioxide
$\Delta p_{tc}CO_2$	$p_{tc}CO_2$ *increase* from the pre sleep $p_{tc}CO_2$
S_aO_2	arterial oxygen saturation
S_pO_2	oxygen saturation measured by pulse oximeter
kPa	kilopascal (1 kPa = 7.50 mmHg)
mmHg	millimeters of mercury (1 mmHg = 0.133 kPa)

Sleep

AASM	American Academy of Sleep Medicine
AHI	Apnea Hypopnea Index (number of events per hour of sleep)
EEG	ElectroEncephaloGraphic trace (of brain activity)
EMG	ElectroMyoGraphic trace (of muscle activity)
EOG	ElectroOculoGraphic trace (of eye muscle activity)

REM	Rapid Eye Movement sleep
NREM	Non- Rapid Eye Movement sleep
N0	awake after initial sleep onset
N1	Subgroup of NREM, transition from wakefulness to sleep (EEG changing between alpha and theta waves)
N2	Subgroup of NREM, intermediate sleep (theta wave EEG including sleep spindles and K-complexes)
N3	Subgroup of NREM, deep sleep (≥ 20% delta (slow) wave activity in EEG)
PG	PolyGrapy (recording of airflow, respiratory movement in thorax and abdomen, position and oxygen saturation)
PSG	PolySomnoGraphy (recording of sleep, eye and leg movement, electric heart activity, airflow, respiratory movement in thorax and abdomen, position and oxygen saturation. In this study also including transcutaneous pressure of carbon dioxide)
TST	Total Sleep Time

Hypoventilation

CHRF	Chronic Hypercapnic Respiratory Failure (defined as awake daytime seated $p_aCO_2 \geq 6.3$ kPa in stable phase of COPD)
SH	Sleep Hypoventilation (defined by the AASM as an increase from pre sleep $p_aCO_2 \geq 1{,}3$ kPa to > 6,7 kPa for ≥ 10 minutes sleep *or* an increase in p_aCO_2 to > 7,3 kPa for ≥ 10 minutes sleep)

Statistics

CI	Confidence Interval (a range of good estimates of the true, unknown parameter)
IQR	InterQuartile Range (midspread measure of dispersion; IQR = $75\%_{Quartile} - 25\%_{Quartile}$)
SD	Standard Deviation (measure of dispersion; SD = the square root of the datasets' variance)
p	probability of finding the observed sample results, or "more extreme" results, when the null hypothesis is actually true (any value ≥ 1)

1 General introduction

1.1 Background

A great proportion of the inpatients at Glittreklinikken pulmonary hospital has COPD and many of them report low quality of sleep. The disease severity in these patients is quite diverse; the expiratory and static lung volumes differ considerably, some have respiratory failure with low arterial pressure of oxygen (p_aO_2) and/or increased pressure of carbon dioxide (p_aCO_2), some hypoventilate during sleep and some have frequent obstructive sleep apneas. Classification, treatment options and evaluation of prognosis in COPD is reasonably well established according to symptoms, spirometric parameters and daytime arterial blood gas pressures [2]. However, blood gas changes *during sleep* both in COPD patients and in normal individuals is sparsely investigated. As a physician at the hospital searching for diagnosis and treatment of sleep related breathing disturbances in my COPD patients, I encountered difficulties in interpreting the results from nocturnal pulse oximetry and transcutaneous measurements of carbon dioxide pressure ($p_{tc}CO_2$), realizing the need to determine whether the patient actually was asleep when these data were recorded. Furthermore, I was concerned about the possible risks of hypoventilation during sleep when these lung diseased patients were influenced by hypnotic medication, alcohol or supplementary oxygen; all agents commonly used by our patients and all known to somehow alter breathing [3-5]. Also, sudden death, probably by cardiac arrhythmias is common in COPD [6], and often occurs in the morning [7]. Thus, a study was initiated at Glittreklinikken, collecting arterial and venous blood samples, spirometry, static lung volume, Impulse Oscillometry and Negative Expiratory Pressure data, 24 hour electrocardiographic recordings and polysomnography (PSG) including $p_{tc}CO_2$-traces from stable COPD patients. This thesis presents the findings from spontaneous sleep as well as zopiclone (a hypnotic drug) and alcohol influenced sleep in relation to some of the data collected at daytime in these subjects.

1.2 Chronic Obstructive Pulmonary Disease (COPD)

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a common, treatable and preventable disease, characterized by persistent, usually progressive airflow limitations, with a chronic inflammatory response in the airways and lungs to noxious particles or gases [2]. Major symptoms are dyspnea, cough and sputum production. The airflow limitation is caused by a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person [2]. COPD is now considered the third leading cause of death worldwide [8], with a prevalence estimated to approximately 9-10 % in the adult population [9,10]. In Norway, one study reports a GOLD-defined COPD prevalence of 7 % [11].

Comorbidities are often present and have a significant impact on the prognosis, with respiratory failure being considered the major cause of death in advanced COPD [12,13]. Chronic hypercapnia has previously been shown to predict increased mortality in COPD-patients [14], and in a recent prospective cohort study of 2,249 patients with oxygen-dependent COPD, P_aCO_2 was an independent prognostic factor with a U-shaped association with mortality [15].

Cigarette smoking is one of the most important causes; hence smoking cessation is the single most effective intervention to reduce the risk of developing COPD and to slow its progression [16]. Treatment of COPD includes bronchodilators, glucocorticoids, methylxanthines, phosphodiesterase-4 inhibitors, supplementary oxygen, vaccines, nutritional supplements, pulmonary rehabilitation, ventilator support and surgery [2].

1.3 Normal human sleep

Sleep is a natural, periodically recurring state of inactivity, characterized by the loss of consciousness and reduced responsiveness to external stimuli. In contrast, wakefulness is the absence of sleep and is marked by consciousness, awareness and

activity [17]. The purpose of sleep is uncertain but it appears to be an active process of complex activity in the brain.

1.3.1 Sleep stages and scoring

Electro-encephalo/oculo/myo-graphic traces (EEG, EOG and EMG, respectively) differentiate wakefulness from sleep, as well as the two states within sleep; rapid-eye-movement (REM) and non-rapid-eye-movement (NREM) sleep [18]. NREM sleep is subdivided in stages N1 (transition from wakefulness to sleep), N2 (intermediate sleep) and N3 (deep sleep) [19]. The individual is most easily awaken in stages N1 and N2 compared to N3, the latter being necessary for restorative sleep, whereas in REM sleep episodic bursts of rapid eye movements are observed, skeletal muscles are atonic and dreaming is frequent.

Historically, the stages of sleep according to EEG traces were first described by Loomis et al in 1937 [20], dividing sleep into 5 levels from wakefulness to deep sleep. In 1953 rapid eye movement (REM) sleep was discovered as distinct, thus sleep was reclassified by Dement and Kleitman into REM and 4 NREM stages [21]. Sleep scoring rules were standardized in 1968 by Rechtschaffen and Kyles in the "R&K sleep scoring manual" [18], whereas a major revision was published in 2007 by the AASM commissioned Visual Scoring Task Force [19]. The most significant difference between the initial R&K versus the revised AASM scoring manual was the merging of the NREM stages S3 and S4 described in the R&K manual into one N3 "slow wave sleep" stage in the AASM manual.

1.3.2 Arousals

An arousal is an abrupt change in the EEG-pattern typically as a shift from a deeper to a lighter NREM-stage, representing a short awakening without reaching consciousness. The role of arousals in normal sleep is a matter of debate, as it can be viewed both as a natural part of sleep homeostasis and as a defense mechanism, protecting from external or internal dangers [22]. Noise or sharp light can in this context be viewed as an external danger, whereas hypercapnia and hypoxia has been proposed as an internal danger.

1.3.3 Sleep architecture

In adults, a nightly sleep pattern typically starts with NREM in increasing depth of sleep before the first episode of REM occurs after 80-100 minutes. Thereafter, NREM sleep and REM sleep cycle with a period of approximately 90 minutes [23]; REM-sleep constituting approximately 20 % of the total sleep time (TST). With increasing age, TST and the TST-percentage of N3 and REM-sleep decreases, whereas N1 and N2 TST-percentage and time awake after sleep onset (N0) increases [24].

1.4 Breathing in normal human sleep

Breathing is primarily regulated by the p_aCO_2; an increase of only 0.13 kPa (1 mmHg) in p_aCO_2 will increase the ventilation with approximately 2.5 to 3 L/min [25]. In sleep, the respiratory system seems to be challenged by a significant reduction in minute ventilation and worsening of blood gases [26]. In support of the internal defense hypothesis regarding arousals, some studies have shown a p_aCO_2 arousal threshold increasing with depth of sleep, with lower threshold values of p_aCO_2 in hypoxic compared to hyperoxic conditions [27,28].

As major functions of respiration during NREM sleep differ from REM sleep, these two states are viewed separately, and when considering breathing during NREM sleep, the unsteady, light sleep (N1 and part of N2) is separated from the steady, deep sleep (stable breathing N2 and N3).

1.4.1 Drowsiness or unsteady NREM sleep

At sleep onset, the level of vigilance oscillates for 10 to 20 minutes between arousal, N1 and N2 sleep and breathing is unstable, with regular fluctuations of increase and decrease in the breathing amplitude [29,30]. This may in turn result in alternating hyperventilation and hypoventilation, including apneas of 10-40 seconds at the nadir of the oscillations [31,29]. As ventilation is regulated by negative feedback, primarily by the p_aCO_2, this breathing instability can be explained by a higher p_aCO_2 set point during sleep compared to wakefulness, and by a delay between blood gas changes

and chemoreceptor response. Thus, at sleep onset, ventilation is up-regulated or down-regulated according to the different set-points [29].

1.4.2 Stable NREM sleep

Stable sleep is established only when the ventilation and sleep stage fluctuations reach a stable state. Sleep will then typically progress through stable state N2 to deep sleep N3. During NREM sleep the ventilation decreases approximately 15% from wakefulness, resulting in a p_aO_2 decrease between 0.5 and 1.3 kPa [26], whereas the p_aCO_2 increases up to 0.9 kPa above supine awake values [32-34]. These changes occur despite a 10% to 20% reduced O_2 uptake and CO_2 production [29]. Rib cage muscular breathing activity is increased in NREM sleep compared to abdominal (diaphragm) muscle activity, the total airway resistance increases more than twofold and the geniohyoid muscle tone is significantly reduced, all factors contributing to the decrease in minute ventilation in stable NREM sleep [35-37].

1.4.3 REM sleep

Breathing during REM sleep is irregular both in frequency and tidal volume, quite different from the regular periodic breathing at sleep onset [30]. The breathing irregularities are linked to bursts of rapid eye movements, giving name to this particular sleep stage. In contrast to NREM sleep, rib cage muscle activity in REM sleep is depressed, leaving most of the breathing pump work to the diaphragm. Very few studies of REM sleep arterial blood gases in normal subjects have been performed. However, the average ventilation, tidal volume and respiratory frequency during REM sleep seem to differ little from NREM sleep, there is a lack of reliable information on P_aCO_2 whereas the hypoxemia seen in NREM is unchanged or slightly worse in REM sleep [29].

1.5 Breathing at sleep in COPD

Polysomnography from COPD subjects has shown poor sleep quality in terms of reduced total sleep time, disturbed sleep architecture, and highly frequent arousals [38-41]. Compared to normals, sleeping COPD subjects become significantly more

hypoxemic than when awake – even more hypoxemic than during exercise at daytime [42]. The pO_2 is progressively reduced with depth of sleep, with the lowest levels during REM sleep, at which oxygen saturation can be extremely low, especially in those with low daytime p_aO_2 [43,44]. This hypoxemia is clinically significant as it affects the hematologic and cardiovascular system [45-47], and may even contribute to nocturnal death [48]. Whether nocturnal hypoxemia affects the quality of sleep in terms of sleep fragmentation is unclear, as sleep hypoxia in one study did not increase the frequency of arousals [49].

1.5.1 Sleep hypoventilation in COPD

In normal sleep, changes in lung mechanics, muscle contractility and central respiratory control lead to hypoventilation, resulting in a moderate increase in p_aCO_2. The same mechanisms apply in COPD sleep. However, in these patients the hypoventilation seems to be more pronounced, especially in REM sleep, when the desaturation during bursts of rapid eye movement is accompanied by hypoventilation rather than by apneas [50]. This can partly be explained by the rapid, shallow REM-sleep breathing which reduces the alveolar ventilation; already compromised by an increased physiological dead space typically found in advanced COPD. Hypoventilation in COPD is also a consequence of chronic hyperinflation with a more or less flattened diaphragm. Thus, the respiratory pump is more dependent on the accessory respiratory muscles, in which central control is depressed during REM sleep. Finally, hypoventilation increases the brains' extracellular level of bicarbonate, blunting the central hypercapnic drive to breathe [51].

Sleep hypoventilation (SH) has previously been defined as an increase in $p_aCO_2 \geq 1.3$ kPa (10 mmHg) from the awake, supine value. O´Donoghue et al studied 54 stable COPD subjects with daytime chronic hypercapnic respiratory failure (CHRF) using LTOT, utilizing PSG with $p_{tc}CO_2$, and found that 43% of the patients spent ≥ 20% of sleep time with $p_{tc}CO_2 > 1.3$ kPa above waking baseline [52]. Tarrega et al measured p_aCO_2 at night (3 a.m.), in the morning (7 a.m.), and at daytime in 80 hypercapnic COPD subjects on LTOT , and found 21% of the night or morning samples of $P_aCO_2 \geq 1.3$ kPa above daytime P_aCO_2 [53]. Thus, SH seem to be highly prevalent in

subjects with severe COPD with CHRF on LTOT. However, it is unclear if SH is associated to daytime hypercapnia per se, as to our knowledge; no studies prior to ours are performed assessing SH in normocapnic or non-LTOT-using COPD subjects. Neither has the increase in $p_{tc}CO_2$ ($\Delta p_{tc}CO_2$) according to sleep stages previously been described in detail, hypothesizing greater between stage differences in subjects with versus without SH.

According to the recent revision of the PSG scoring rules from the American Academy of Sleep Medicine (AASM), SH is scored when the P_aCO_2 (or surrogate) > 55 mm Hg (7.3 kPa) for ≥ 10 minutes or if there is an increase in the p_aCO_2 (or surrogate) ≥ 10 mm Hg ([1.3 kPa] in comparison to an awake supine value) to a value exceeding 50 mm Hg (6.7 kPa) for ≥ 10 minutes [54].

1.5.2 Overlap syndrome (COPD and obstructive sleep apnea)

Obstructive sleep apnea (OSA) is diagnosed if the frequency of apneas/hypopneas per hour (AHI) ≥ 15, or AHI ≥ 5 with daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or choking [55]. Prevalence of OSA in subjects with COPD seems to be no greater than the prevalence of OSA alone [56]. However, patients with both COPD and OSA (Overlap syndrome) face an increased risk of death and hospitalization because of COPD exacerbation [57]. One retrospective study from a sleep center indicated that Overlap patients have more severe daytime hypercapnia compared to subjects with COPD or OSA alone [58], but to our knowledge, this has not been confirmed by prospective studies. Nor has comparisons been made of $\Delta p_{tc}CO_2$ during sleep in subjects with Overlap versus COPD only.

1.5.3 Treatment of chronic respiratory failure in COPD

Long term oxygen therapy (LTOT) in COPD patients with daytime hypoxemia increases survival and improves quality of life [59-61]. However, the efficacy of exclusively nocturnal oxygen supplementation in subjects with episodic sleep desaturations has to our knowledge not been evaluated in prospective studies [62]. LTOT implies continuous use of supplementary oxygen, including during sleep, a treatment which is known to increase the p_aCO_2 in some COPD patients. This

hypercapnia can be overcome by simultaneous treatment with nocturnal oxygen and non invasive ventilation (NIV) [63]. The beneficial effects of NIV on gas exchange in COPD patients was described as early as in 1951 [64], however the search for etiology, predictors and effective treatment of CHRF in these patients is still going on. The idea of resting the respiratory muscles fatigued by the chronic hyperinflation in severe COPD led to a series of studies, first with negative pressure, later with positive pressure ventilation. The negative pressures were poorly tolerated, and the study results were contradictory regarding improvement of respiratory muscle function or daytime p_aCO_2 [65]. Studies utilizing positive pressure ventilation were more promising, although three large, randomized trials in 2000, 2002 and 2014 failed to show improved survival in COPD patients using NIV and LTOT compared to LTOT alone [66,67], and in hypercapnic COPD-patients initially treated with NIV because of acute respiratory failure [68]. On the other hand, in 2009 McEvoy et al found NIV to improve sleep quality and p_aCO_2 and marginally improving survival [69], whereas Köhnlein et al recently found significantly improved survival after 12 months of NIV [70]. Thus, at present, whether NIV should be used in COPD with CHRF is a matter of controversy. However, in Overlap patients, continuous positive airway pressure (CPAP) treatment has been shown to improve survival and decrease hospitalizations [57].

1.6 Effect of alcohol in COPD and in normal subjects

Alcohol is known to be both a cause of lung disease and a therapeutic agent. Heavy consumption increases the risk of developing COPD [71,72], whereas mild intake is associated with higher forced expiratory volume first second (FEV1), less COPD symptoms and reduced mortality [73,74]. Since ancient Egypt, alcohol has been known to relive chest tightness [75], and intravenous ethanol has been shown to relieve bronchial obstruction in subjects with atopic asthma, with roughly 40% of the effect of salbutamol [76]. In insomniacs, a moderate dose of alcohol improves sleep maintenance [77]. In normal, awake individuals, an occasional, moderate dose of alcohol depresses the hypercapnic and hypoxic drive to breathe [78], and during

alcohol influenced sleep, the inspiratory airway resistance is increased and the hypercapnic respiratory drive tends to decrease [79,4]. Alcohol also alters the sleep architecture resulting in increased N3 and less REM sleep [80], and increased frequency of arousals, oxygen desaturations and apneas [81,82]. As many COPD patients are hypoxic and hypercapnic when awake, concern can thus be raised regarding the risk of further blood gas deterioration in alcohol influenced sleep. Indeed, a study of 20 COPD subjects (19 men), showed that alcohol increased the number and duration of sleep apneas as well as TST [83], and in another study of five individuals with severe COPD (four men), alcohol reduced the TST, REM % of TST and the mean oxygen saturation measured by pulse oximetry (S_pO_2) [84]. However, to our knowledge, no previous sleep-studies have been published on alcohol induced blood gas changes including $\Delta p_{tc}CO_2$ and their relation to sleep architecture and frequency of apneas/hypopneas. Nor have the association between such blood gas changes and daytime COPD characteristics been described.

1.7 Effect of hypnotics in COPD and in normal subjects

Difficulties in initiating or maintaining sleep, or excessive daytime sleepiness, is experienced by more than half of the COPD population [85]. Also, sleep related complaints are ranked third, after dyspnea and fatigue, in frequency of complaints in these patients [86]. Thus, hypnotics are frequently used despite guidelines recommending avoiding such drugs if possible [39,16]. In support of these recommendations, a recent, longitudinal, cohort study of 2249 patients with severe COPD using LTOT indicated that although the use of benzodiazepines was not associated with increased hospital admission rates, these drugs were associated with increased mortality with a dose – response trend [87]. True causal effects could not be stated however, as the study was not prospectively randomized.

All currently available hypnotics acts at different moieties of the gamma-aminobutyretic $acid_A$ benzodiazepine receptor complex, and have various degree of anxiolytic, muscle relaxant, anticonvulsant, amnesic, as well as sleep promoting

properties [88]. The drugs are typically grouped as benzodiazepines and non-benzodiazepines according to their molecular structure; however, binding to the same receptor complex they induce sleep by basically the same mechanisms. In healthy subjects, benzodiazepines improve sleep quality by reducing the latency to sleep onset and increasing the TST [89], whereas sleep architecture is changed by an increased N2 percentage of TST and decreased N1, N3 and REM percentage of TST [90]. The longer acting benzodiazepines (e.g. flurazepam) seem to have mild respiratory depressant properties in healthy subjects [3]. In COPD patients, the intermediate acting benzodiazepine temazepam (half-life of between 8 to 15 hours) did not change the patients' mean or highest $p_{tc}CO_2$ during sleep in one of the first studies measuring nocturnal $p_{tc}CO_2$ to assess the effects of benzodiazepines [91]. The short acting, non-benzodiazepine zopiclone appears to have no significant effect on desaturations during sleep, or on daytime blood gases [92]. However, the latter study from 1990 included only six patients and did not report nocturnal recordings of pCO_2. Thus, it is of interest to study whether this frequently used hypnotic induces sleep hypoventilation in stable COPD patients.

Eszopiclone, an isomer of zopiclone, has been shown to *reduce* the number of apneas/hypopneas in subjects with OSA [93], whereas a non-significant trend towards an *increased* AHI was found in the small group of COPD patients on long term administration of zopiclone mentioned above [92]. The impact of a single dose of zopiclone on the frequency of sleep apneas/hypopneas in stable COPD patients is to our knowledge not previously described.

2 Study aims

The purpose of this thesis was to assess the sleep induced changes in blood gases in stable COPD-subjects, specifically the phenomenon of sleep hypoventilation in association to sleep architecture, apneas/hypopneas and daytime COPD-characteristics, both in spontaneous sleep and in sleep influenced by alcohol or the hypnotic zopiclone. The research questions were:

Paper I:

1. Is sleep hypoventilation (SH) associated with daytime hypercapnia?
2. Is the $p_{tc}CO_2$ increase from pre sleep value ($\Delta p_{tc}CO_2$) between sleep stages different in subjects with versus without SH?
3. Do subjects with Overlap (COPD and OSA) differ from those with COPD only, in $\Delta p_{tc}CO_2$ or in daytime p_aCO_2?

Paper II:

1. How is the sleep architecture, blood gases and frequency of apneas/hypopneas changed by a moderate dose of alcohol (0.5 mg per kg bodyweight) prior to sleep?
2. Is the alcohol induced changes in blood oxygen saturation or carbon dioxide pressure during sleep associated to daytime COPD characteristics?

Paper III:

1. To what extent does 5 mg zopiclone induce sleep hypoventilation in stable COPD?
2. What impact does 5 mg zopiclone have on the frequency of sleep apneas/hypopneas in stable COPD?

3 Material selection and methodological considerations

3.1 Study setting

This thesis is based on data collected from inpatients at Glittreklinikken pulmonary hospital in Hakadal, Norway. Every year, between 600 and 700 patients with chronic obstructive pulmonary disease (COPD) are admitted to the hospital from all parts of Norway for four weeks of inpatient pulmonary rehabilitation (IPR). Disease severity in these patients varies greatly; some are working fulltime whereas others are on the waiting list for lung transplantation. At present, 13 doctors specialized in pulmonary and internal medicine, as well as occupational diseases and general practice work at Glittreklinikken.

3.2 Study population and sampling

Inclusion of patients to the study started in April 2009, with only two nights of PSG per patient (no "first night" for acquaintance, see 3.4.4 Polysomnograpy below). During the first month it became evident that the protocol needed revision regarding this point, inclusion was stopped and the data from the first two patients were excluded. Then, from January 2010 through June 2011, with revised protocol and study logistics, the study leader (author) screened the arrival journal including spirometry and laboratory reports of all new patients to decide who were eligible for the study. Inclusion criteria were a COPD diagnosis according to the GOLD guidelines [2] and being able to complete the routine diagnostic procedures at the clinic. Exclusion criteria were a prior diagnosis of OSA, COPD exacerbation within 3 weeks prior, other serious lung comorbidity (ie, cancer, sarcoidosis, restrictive lung disease) or diseases affecting thoracic or abdominal movement, unstable angina pectoris, uncontrolled hypertension or diabetes mellitus, myocardial infarction within last 3 months, cerebral infarction and addiction to drugs, alcohol, or narcotics.

At the end of each week, the list of eligible patients with $P_aCO_2 < 6.3$kPa (normocapnic) were numbered in randomized order. To stratify for gender, a "male" or "female" tag was blindly selected from a box; the selected gender with the highest number on the list was the first one to be asked to participate. Then the tag was put back and a new, blind, gender selection was done, and so on. If a patient declined to participate I moved to the next one on the list with the same gender. The same procedure was applied if information about alcohol problems or drug abuse not given in the arrival journal became evident during the inclusion interview. However, one specific case was excluded, recorded as missing due to information about regular benzodiazephine use which came up *after* the person had been included and the first PGS had been recorded.

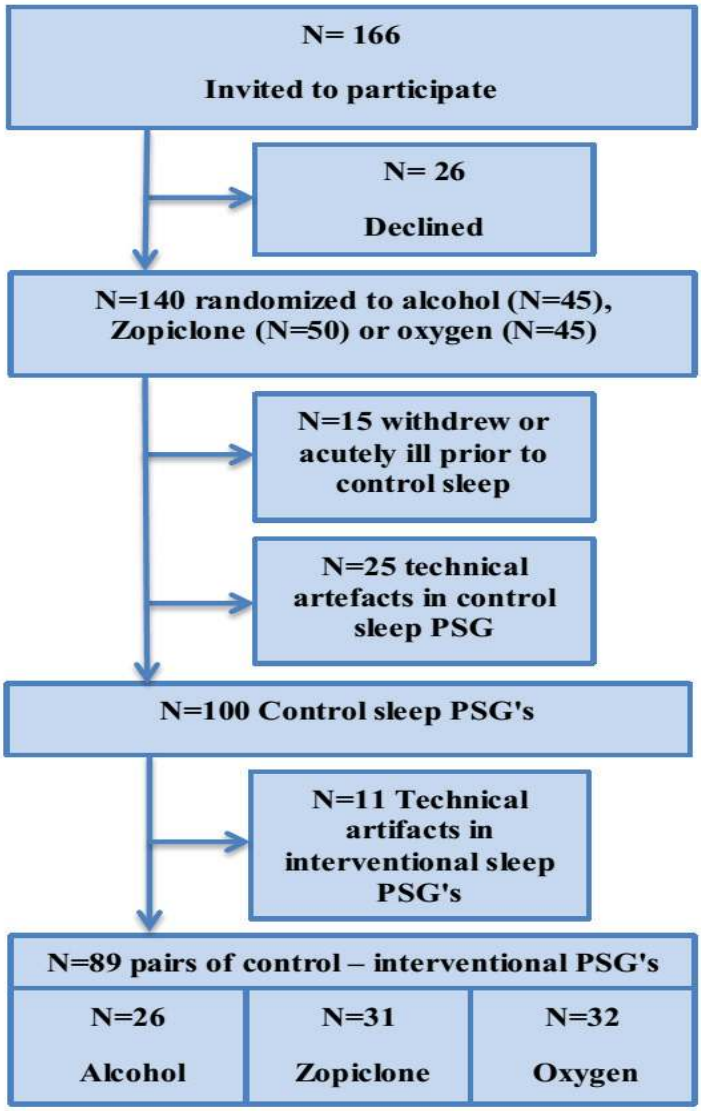
According to the calculations of sample size in the study protocol (see 3.5.4 Statistics), we intended to include 60 normocapnic subjects and 60 subjects with $P_aCO_2 \geq 6.3$kPa (CHRF). However, after the initial study start in April 2009 it became evident that the hypercapnic subjects were indeed few. Thus, to include as many CHRF patients as possible, these were oversampled by asking *all* who were eligible to participate in the study, not stratifying this group for gender, and in priority of the normocapnic subjects. Despite this, I was not able to include the intended number of CHRF subjects in the time available for inclusion.

After informed and written consent to participate, the subjects were randomized to receive alcohol, zopiclone or supplementary oxygen prior to one of the nights of PSG by selecting a tag with an "A", "Z" or "O" respectively from another box. The box contained 10 tags of each letter, when empty; all 30 tags were put back. The order of interventional or spontaneous sleep was finally randomized by blind selection of "I" or "S" tags from yet another box.

We had the equipment and personnel capacity to include a maximum of three patients per week. As shown in figure 1, 166 patients were eligible and invited during the study period of 18 months. Among the 26 declining to participate, three patients did not want to stop taking zopiclone for the time required and another two did not want

to take pills or alcohol (supplementary material to Paper I has a detailed description of the other reasons for not participating). 66 PSG's were lost prior to analysis of control (spontaneous) sleep, and another 11 PSG's were excluded prior to analysis of interventional sleep compared to control sleep.

Figure 1 Study inclusion



3.3 Study design

Table 1 Design and methods for the three included papers

Paper	Design	Method	N	Comparison
I	Observational	Independent samples of PSG with $p_{tc}CO_2$	100	CHRF yes/no SH yes/no
II	Randomized, not blinded cross-over	Paired samples of PSG with $p_{tc}CO_2$	26/26	Each subject its own control
III	Randomized, not blinded cross-over	Paired samples of PSG with $p_{tc}CO_2$	31/31	Each subject its own control

In paper I, the degree of daytime hypercapnia and sleep hypoventilation were analyzed in 100 stable COPD-patients. Arterial blood gases were sampled at daytime prior to the PSG, and according to their p_aCO_2-value the patients were divided in two groups; with or without CHRF. Following PSG and $p_{tc}CO_2$ analysis the patients were then re-divided in another two groups; with or without SH. The distribution of demographics, lung function and other clinical and laboratory data collected at daytime, as well as sleep parameters including TST, awakenings, sleep stage distribution, apneas/hypopneas, arousals, increase in $p_{tc}CO_2$ and minimum S_pO_2 were then compared according to whether or not the patient had CHRF or SH.

In paper II, twenty-six of the patients described in paper I served as their own control in evaluating the effect of 0.5 mg alcohol per kg bodyweight on sleep architecture and nocturnal ventilation. Alcohol as 96% ethanol was diluted in approximately 200 ml of orange juice and ingested as fast as possible after the patient had gone to bed. To ensure alcohol was taken, breath analysis by alcometer was performed immediately before the nurse turned off the light.

The same design was applied in paper III, analyzing the effect of 5 mg zopiclone taken orally as a pill approximately 30 minutes prior to sleep by another 31 of the 100 patients in paper I.

No patient received more than one intervention.

3.4 Measurements

3.4.1 Lung function testing

All pulmonary function tests were performed by experienced laboratory personnel according to standardized criteria [94-96]. Reference values were based on data from the European Community for Steel and Coal [97]. Testing of post bronchodilator spirometry (FVC, FEV1), static lung volumes (TLC, RV) and diffusion capacity of the lungs (DLCO) were performed on MasterScreen Pneumo, Jaeger-Toennies, Hoechberg, Germany. At Glittreklinikken, volume calibration using a 3 liters syringe is performed daily, as well as ambient pressure adjustments, gas calibrations and body box (pletysmography) volume settings. Biologic quality controls are run weekly.

3.4.2 Measurement of dyspnea, prognostic considerations

The five point Modified Medical Research Council questionnaire (MMRC) [98] originates from England but is widely used in clinical as well as scientific settings [98]. To our knowledge, a validated Norwegian version was not available. Hence, prior to study start a translated draft in Norwegian was translated back to English by teacher, author and translator Richard Peel, a native Englishman with university education from Oxford, Bristol, Oslo and Bergen and with more than 30 years occupational experience in Norway. Mr. Peel did not initially know the original English version. After the back-translation he participated in a discussion with a group of physicians at Glittreklinikken (specialists in pulmonary, occupational and general medicine) regarding a few words of discrepancy between the original and his

back-translated English text, and a consensus was agreed on the final Norwegian version. As the translation was not tested by cognitive debriefing or other methods of patient interviews it can be argued that it is not fully validated. However, by using a questionnaire with the original English text above the Norwegian translation of the five paragraphs I consider the scoring to be sufficiently accurate for our purpose (see appendix 7.1).

The BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index is a prognostic indicator in COPD [99]. BMI was calculated from the patients' weight and height, airflow obstruction as FEV1 measured by spirometry, dyspnea graded by the MMRC and the exercise capacity indicated by the 6 minute walking distance (6MWD). MMRC score and BODE index is reported in all three papers [100].

3.4.3 Arterial blood gases

Arterial blood gas samples reported in all three papers were obtained at approximately 2 pm prior to the PSG nights. After at least 5 minutes of seated rest, about 3 ml of blood was drawn by single puncture of the patients' radial artery. Pre-heparinized syringes were used[1], air bubbles immediately removed and the samples analyzed on ABL 720Flex[2] within 10 minutes. No complications were observed during or after this procedure. The blood gas analyzer was calibrated and quality controlled several times daily according to the manufacturers' recommendations, precision and accuracy was additionally controlled by an external laboratory quality system[3]. All blood gas analyses were performed by experienced personnel.

[1]PICO 50, Radiometer, Copenhagen, Denmark

[2] Radiometer, Copenhagen, Denmark

[3] Labquality Oy, Helsinki, Finland

3.4.4 Polysomnography

To record electrical activity in the brain, EEG electrodes with contact gel were placed on the scalp at positions A1, A2, C3, C4, O1, O2 and GND (described in detail on page 23 in the AASM Manual for the Scoring of Sleep and Associated Events [19]). Also according to the AASM recommendations, ocular muscle activity was recorded by one EOG electrode lateral to each eye, and muscle activity by EMG electrodes one on each side of the chin and one on each leg. Heart muscle activity was recorded by two ECG-electrodes, one on each of the clavicles. All electrodes were kept in place by tape and a head net bundled the thin wires, emerging at the vertex (figure 7, section 5.1.3 Polysomnography). Nasal flow was detected by a pressure sensor through a plastic cannula placed in the patients' nostrils. Thoracic and abdominal movements were recorded by stretch sensitive belts, and patient position by a sensor fixed to the thoracic belt as shown in figure 7. A probe for pulse oximetry[4] (section 3.4.6) was taped to one finger tip, and the TOSCA 500[5] probe (section 3.4.5) for recording the $p_{tc}CO_2$ and another pulse oximetry signal was fixed to the forehead. All electrodes, probes, sensor and belts were fixed between 5 and 7 pm and connected through the EMBLA A10[6] system to an online recording computer with Somnologica Studio Version 3.3 software[7]. A bedside trolley carried the computer and its screen, the EMBLA A10 system, the TOSCA 500, and an extension power cable long enough for the patient to reach the toilet. Sufficient signal quality was checked in the computer program, and then the patient was disconnected from all devices, carrying the cables in a small bag at the waist. Although one patient reported scaring a moose on a walking trail outside the clinic with his odd headgear, most of the study subjects stayed at their room until re-connecting to the computer at bedtime. After helping the patient to bed and connecting the cables and the TOSCA 500 sensor, the night nurse

[4] Nonin Medical Inc., USA

[5] Radiometer, Basel, Switzerland

[6] Medcare Flaga, Reykjavik, Iceland

[7] Medcare, Flaga

gave alcohol, zopiclone or oxygen when appropriate, and started the recording. After approximately 30 minutes she returned to the patients' room, controlled the quality of the PSG recording on the screen, checked whether alcohol was actually taken using an alcometer[8], noted the estimated blood alcohol content, the $p_{tc}CO_2$ reading on the TOSCA 500 and finally the time as she turned off the lights. If the patient was in need of going to the toilet during the night, the trolley was brought along; alternatively a bedside commode was used. The night nurse silently looked in to the patient's room several times during the PSG recording and was instructed to wake the patient if the $p_{tc}CO_2$ had increased more than 3 kPa from the value at lights off.

When the patient woke in the morning, the nurse was called. She noted the time and any events during the night (trouble with falling asleep, periods awake, toilet visits, technical problems etc), stopped the recording and removed electrodes, belts sensor and probes. The recording was quality assessed before it was sent it to the polysomnographist for sleep scoring.

3.4.5 Transcutaneous pressure of carbon dioxide ($p_{tc}CO_2$)

The method implied fixing a probe in a drop of contact gel to the skin on the patients' forehead as shown in figure 7, section 5.1.3. The skin was heated to 42 degrees Celsius by the probe in order to maximize the arterial flow in the capillary bed below the sensor. According to the manufacturer this temperature is tolerated for up to 12 hours without causing tissue damage [100]. The carbon dioxide pressure (pCO_2) sensor of the TOSCA 500 consists of a Stow-Severinghaus type electrode in which the pCO_2 is measured by determining the pH of an electrolyte solution; a change in pH being proportional to the logarithm of the pCO_2 change. Generally, there is a high correlation between p_aCO_2 and $p_{tc}CO_2$. However, when the skin is heated the $p_{tc}CO_2$ is elevated approximately 4.5% per degrees Celsius and the living epidermal cells produce their own CO_2, contributing to the capillary pCO_2 with approximately 0.65

[8] Lion Alcometer 500, Lion Laboratories Ltd., Vale of Glamorgan, UK.

kPa [101]. The signal from the sensor is calibrated within the TOSCA 500, output value adjusted to compensate for these effects.

In addition to this calibration there were several other aspects to be considered regarding the use of $p_{tc}CO_2$ in this study; the following briefly described pilot studies are not previously published.

First, to investigate whether $p_{tc}CO_2$ changes could substitute for p_aCO_2 changes, clinical data were obtained from 18 (14 male) stable COPD subjects prior to the main study (supplementary material, Paper I). All had an indwelling arterial catheter and the TOSCA probe fixed to an earlobe according to the manufacturers' recommendations. Arterial samples were drawn from the catheter every 20th minute, simultaneously recording the $p_{tc}CO_2$ displayed on the TOSCA. The arterial samples were analyzed within five minutes; 9 to 18 pairs of p_aCO_2 $p_{tc}CO_2$ data being obtained from each patient. The mean of the SD's for each patients' set of data pairs was 0.19 kPa (ranging from 0.13 kPa to 0.30 kPa). As we intended to record the pCO_2 *changes* in sleeping COPD patients, this *variance* of the $p_{tc}CO_2$ - p_aCO_2 difference for each individual was the matter of interest, more than the difference itself. Thus, with near 95% probability the $p_{tc}CO_2$ value recorded would be 0.38 kPa below or 0.38 kPa above the p_aCO_2 + ($p_{tc}CO_2$ - p_aCO_2); a total variance range of 0.76 kPa. We found this variance acceptable to regard $p_{tc}CO_2$ changes as a surrogate for changes in p_aCO_2 during sleep in this patient group.

Second, as we used two capnographs during the study we wanted to investigate whether the TOSCA 500 appliances display identical values when measuring $p_{tc}CO_2$ simultaneously on the same subject. Clinical data was obtained from another 8 COPD patients in two different situations. The two $p_{tc}CO_2$ probes were fixed one on each side of the sagittal line at the forehead, center of probes 32 mm apart. After stabilization of approximately 30 minutes the $p_{tc}CO_2$ differences were recorded once every 30th second for 10 minutes (21 readings). Then, to reveal any significant, skin thickness, or local vascular differences, the probes switched place and new stable readings were obtained as described above. Data showed TOSCA #2 displaying

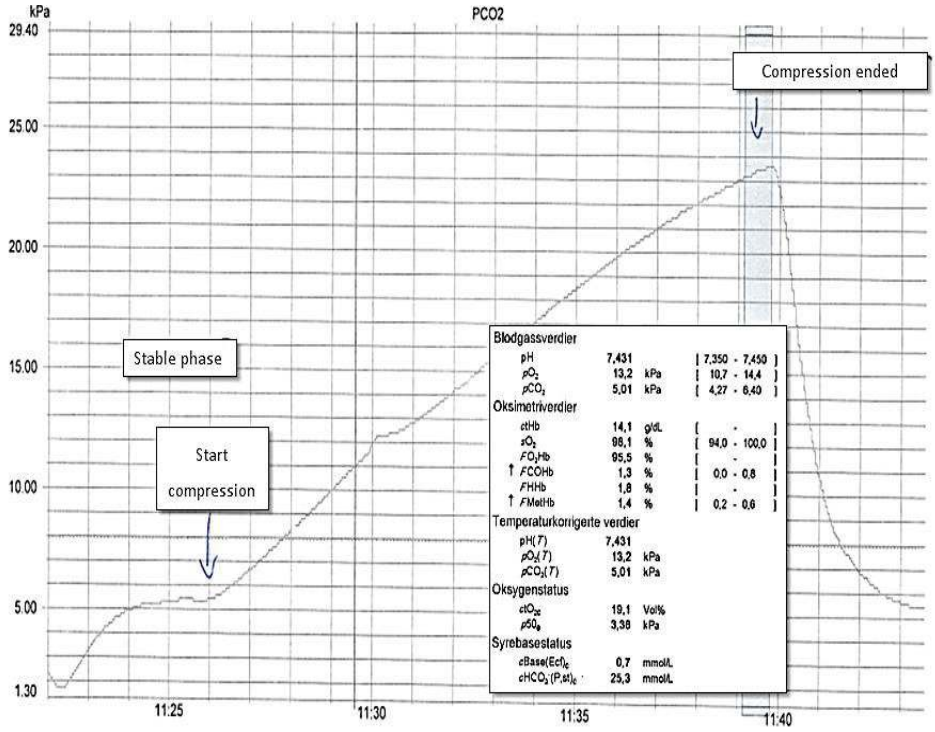
significantly higher $p_{tc}CO_2$ values compared to TOSCA #1 regardless of its probe being fixed to the left versus right side of the forehead, the mean (SD) difference between the readings being 0.30 (0.24) kPa and 0.24 (0.21) kPa respectively ($p<0.05$ in both situations). We concluded that differences observed between p_aCO_2 and $p_{tc}CO_2$ partly may depend on the transcutaneous appliance used, and with the importance of using the same capnograph for all recordings on the same patient.

Third, a delay time from an alveolar change in pCO_2 until the first response in $p_{tc}CO_2$ is expected. As described in the supplementary material to Paper 1 (and in poster, Appendix 7.2), nine COPD patients (six male) were studied. The supine study subject was breathing through a tight fitting mask with an inlet valve selecting either room air or a gas mixture of 4% CO_2 in air from a bag. Data were collected during three phases, each lasting 200 sec: 1) stable phase breathing room air, 2) increasing phase breathing 4% CO_2 in air, and 3) decreasing phase after switching back to breathing room air. $p_{tc}CO_2$ was recorded every 5^{th} second for two minutes, then every 10^{th} second in each phase. Arterial samples were drawn from an indwelling arterial catheter three times during phase 1), every 5^{th} second the first 30 sec of phase 2) and 3), then every 30^{th} sec for a total of 150 sec. We defined first response time (FRT) as the time from an alveolar pCO_2 change (start of phase 2) until $p_{tc}CO_2$ had changed more than two SD's from the mean value of phase 1). Results showed a mean (SD) FRT in increasing phase of 54 (18) sec, and in decreasing phase 57 (15) sec. For p_aCO_2 the FRT was 13 (6) sec and 12 (3) sec respectively. Thus, the $p_{tc}CO_2$ data recorded in the PSG were left shifted two sleep epochs (60 sec) prior to data analysis.

Finally, in some of the first recordings we found $p_{tc}CO_2$ sharply increasing < 20 kPa with simultaneously slightly *increased* S_pO_2-values. This was suspected to be an artifact resulting from the $p_{tc}CO_2$ probe being compressed between the ear and the pillow. Thus, due to this observation we fixed the probe to the forehead instead of the earlobe for the rest of the study. Nevertheless, a few recordings with the probe on the

forehead had to be excluded as well, due to a similar artifact when the probe was compressed between the patients' forehead and arm (figure 2).

Figure 2 Compression of TOSCA[9] probe between arm and forehead



Notes to figure 2: Transcutaneous pressure of carbon dioxide ($p_{tc}CO_2$ [kPa]) measured by TOSCA on the y-axis, time in minutes on the x-axis. The TOSCA probe was applied to author' forehead in supine position. After a stabilizing period of approximately 2 minutes (11:24 – 11:26), the probe was compressed by the dorsal side of left underarm for about 14 minutes (11:26 – 11:40). An arterial blood gas sample was obtained from the right a.radialis before compression was terminated at 11:40; measured values inserted in text box. As shown, p_aCO_2 was 5.0 kPa whereas $p_{tc}CO_2$ was measured to 23.6 kPa.

[9] Radiometer, Basel, Switzerland

3.4.6 Pulse oximetry (S_pO_2)

Pulse oximetry is commonly used in clinical and scientific settings [102,103]. The arterial oxygen saturation is computed by comparing the transmission of two wavelengths of red light (absorbed by deoxyhemoglobin) and infrared light (absorbed by oxyhemoglobin) either through e.g. a finger tip or as a reflection from a white surface. Two light emitting diodes are switched on and off several hundred times per second; thus light absorption by oxyhemoglobin and deoxyhemoglobin is recorded during pulsatile and nonpulsatile flow. Microprocessors compute the arterial oxygen saturation, updating the average of the last 3-6 seconds every 0.5-1 second [104]. It is not possible to calibrate a pulse oximeter, but they have an accuracy of approximately 1-2 % compared to the "gold standard" S_aO_2 [105]. In this study two different S_pO_2 probes were simultaneously used; one taped to a finger tip, the other integrated in the TOSCA 500 sensor fixed to an earlobe or at the forehead. The latter recorded a signal reflected from the white plastic fixing clip at the ear lobe or the white skull bone on the forehead. The S_pO_2 signal from the finger tip was processed in the EMBLA A10, trace recorded in the PSG whereas the computed S_pO_2 signal from the TOSCA 500 was recorded as a separate trace in the same PSG.

3.5 Analyses

3.5.1 Sleep scoring

Sleep was scored according to the 2007 AASM manual based on traces of EEG, EOG and EMG, thoracic and abdominal respiratory movements, nasal airflow and arterial oxygen saturation, commencing at lights-off-time in the evening (intention to sleep) and ending at rise time in the morning. Each epoch of 30 seconds was scored as stage N1, N2, N3, REM-sleep or N0 (awake after initial sleep onset). According to the AASM recommendations (criterion A), a hypopnea was scored when nasal pressure dropped ≥ 30% for ≥10 seconds with ≥ 4% desaturation drop from baseline, with ≥ 90 % of the event's duration meeting the amplitude reduction criteria for hypopnea [54]. Overlap (COPD + OSA) was diagnosed if the frequency of apneas/hypopneas

per hour of sleep (AHI) ≥ 15 as we did not have systematically recorded data on daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or choking [55]. Also as defined by the AASM, SH was scored when a sum of ≥ 20 epochs (10 minutes) of the total sleep time showed an increase in the mean $p_{tc}CO_2 \geq 1.33$ kPa above the pre-sleep $p_{tc}CO_2$ and to a level > 6,7 kPa [19]. Results according to the other definition of SH given by the AASM, as a $p_{tc}CO_2 > 7.3$ kPa for ≥ 10 minutes of sleep, was reported only in Paper III. Like S_pO_2, the $p_{tc}CO_2$ was recorded as a continuous trace in the PSG, however, as apneas or hypopneas resulting in alveolar changes in pCO_2 will be apparent as changes in $p_{tc}CO_2$ after approximately 1 minute (section 3.4.5 above), the $p_{tc}CO_2$ recording was time corrected accordingly prior to calculations of whether SH was present or not.

Sleep scoring was done by two independent, experienced polysomnographists, a random selection of 10 PSG's were scored by yet another two experienced sleep scorers and the results from the initial scorer with the best match to the two latter were chosen for analysis.

3.5.2 $p_{tc}CO_2$ analyses

The TOSCA 500 recorded the $p_{tc}CO_2$ value 10 times per second; these data were exported from the Somnologica to the Statistical Package for the Social Sciences (SPSS) software for further calculations. Pre-sleep $p_{tc}CO_2$ was defined and calculated as the mean value of the first 3 minutes of the last 6 minutes prior to sleep onset. As sleep is scored in epochs of 30 seconds, the mean $p_{tc}CO_2$ of each epoch was calculated and the maximum value was recorded. These values were time corrected two sleep epochs backwards to synchronize with the other PSG events of that particular epoch (as described in section 3.4.5). This enabled calculation of the mean $p_{tc}CO_2$ of each *sleep stage* as the mean of all epoch's mean $p_{tc}CO_2$ of that particular sleep stage, and calculation of the mean *increase* of the $p_{tc}CO_2$ (mean$\Delta p_{tc}CO_2$) as this sleep stage's mean $p_{tc}CO_2$ minus pre-sleep $p_{tc}CO_2$. The *NREM mean* $\Delta p_{tc}CO_2$ was calculated as the mean of all NREM epoch's mean $p_{tc}CO_2$ minus pre-sleep $p_{tc}CO_2$, whereas the *total sleep mean* $\Delta p_{tc}CO_2$ was calculated as follows: (NREM mean$\Delta p_{tc}CO_2$ *NREM sleep time/total sleep time) + (REM mean$\Delta p_{tc}CO_2$ *REM

sleep time/total sleep time). Also, the maximum $p_{tc}CO_2$ increase (*Max Δ $p_{tc}CO_2$*) was reported for each sleep stage, for NREM sleep and for total sleep.

3.5.3 S_pO_2 analyses

The data from the two separate, continuous S_pO_2 traces in Somnologica were exported to the SPSS and the average S_pO_2 from the TOSCA 500 and the EMBLA A10 was calculated for each epoch and each sleep stage, for NREM sleep and for total sleep. Likewise, the minimum S_pO_2 was recorded for each epoch, each sleep stage, etc. As we experienced several technical flaws with the finger tip sensor (loosening from finger and breakage in the electronic circuitry), the S_pO_2 signal from the TOSCA 500 was chosen for the mean and minimum S_pO_2 calculations reported in all three papers. However, as the finger tip sensor provides the default signal in the EMBLA A10, this trace was routinely used for sleep scoring provided it was of acceptable quality.

3.5.4 Statistics

The main working hypothesis prior to this study was that patients with CHRF had greater $\Delta p_{tc}CO_2$ increases during sleep than normocapnic subjects. Thus, to calculate sample size prior to patient inclusion, we analyzed nocturnal $p_{tc}CO_2$ data from 20 COPD-patients (seven with CHRF) at Glittreklinikken (clinical data, not published). Measurements were done by TINA[10], reporting $p_{tc}CO_2$ every 5th minute. As PSG was not recorded, printed reports from TINA were manually screened to find a stable $p_{tc}CO_2$-value 15-30 minutes prior to expected time of sleep onset (pre sleep $p_{tc}CO_2$), and the maximal $p_{tc}CO_2$-value during the night. The maximal $p_{tc}CO_2$ increase ($max\Delta P_{tc}CO_2$) was calculated for each patient by subtracting the pre sleep $p_{tc}CO_2$ from the maximal $p_{tc}CO_2$. For the whole group the standard deviation (SD) of these $max\Delta p_{tc}CO_2$-values was 0.95 kPa. A clinically significant difference in the mean values of $max\Delta p_{tc}CO_2$ between the groups with CHRF versus the normocapnic subjects was considered to be at least 0.5 kPa. Thus, standardized difference was

[10] Radiometer, Copenhagen, Denmark

calculated to 0.53 (0.5 kPa/0.97 kPa), and with power of 85% and a 2-sided significance level of 0.05, necessary sample size was calculated to 120 subjects in total (i.e. 60 normocapnic and 60 with CHRF) [106].

To get an impression of the statistical power prior to analysis of data from the interventional studies (alcohol and zopiclone), results from spontaneous sleep were used to calculate sample size. The SD of the mean increase in $p_{tc}CO_2$ during spontaneous sleep was 0.32 kPa; we assumed this to be unchanged during alcohol and zopiclone sleep. A minimal detectable difference of 0.25 kPa was considered clinically significant for the interventional studies. Thus, with 80% power and a two-sided significance level of 0.05, calculations showed that N=28 subjects were needed for each study.

Concordance between the sleep scorers were measured by Cohen's kappa. Prior to statistical analysis, all data were assessed for normality and homogeneity of variance, the normally distributed data presented as mean (SD) or median (interquartile range) whereas data with skewed distribution being presented as median (interquartile range). Differences in continuous variables *between* groups were analyzed with Student's one sample t, Mann-Whitney U or Kruskal-Wallis tests as appropriate, differences in categorical variables by Pearson chi-square or Fisher's exact test. Differences in continuous variables *within* groups (paired data) were analyzed by Student's two samples t-test (parametric data) or Wilcoxon signed rank test (non-parametric data). Paired proportions were assessed by McNemar chi square test (p-values without Yates' correction). Correlations between variables were assessed by Pearson's r.

In Paper I and II, hierarchial multiple regressions were performed. In Paper I to assess whether the maximal CO_2 increase during sleep independently predicts daytime arterial pCO_2 when controlling for COPD severity and use of supplementary oxygen, and in paper II to determine whether the decrease in oxygen saturation in alcohol

influenced sleep can be explained by daytime COPD characteristics. Calculations were performed using IBM SPSS Statistics version 19 and 20[11].

3.6 Ethics

3.6.1 General aspects

Results from most of the standard procedures and tests for all inpatients at Glittreklinikken (eg spirometry, body pletysmography, venous and arterial blood sampling, ECG etc) were utilized in the study. In addition the study patients were asked to fill in questionnaires (MMRC, CAT, etc), we drew two extra arterial samples for blood gas analysis and they went through three nights of PSG with $p_{tc}CO_2$. The included patients had to refrain from hypnotics, other respiratory depressing drugs and alcohol other than study medication or study alcohol from 48 hours prior to first PSG and until they had finished all study tests. In addition, we estimated expiratory flow limitation by negative expiratory pressure and by impulse oscillometry and we recorded 24 hour ECG (results published elsewhere but not reported in this thesis).

Puncture of the radial artery can lead to infection or inflammation; in worst case destruction of the artery with compromised circulation of the hand. Likewise, venous puncture can result in infection or inflammation. However, when following standard hospital procedures the risk of such complications is minimal. A transient pain due to subcutaneous bleeding from the artery is not unusual but is considered negligible by most patients.

For the recording of PSG, electrodes are mounted at the scalp, laterally to the eyes, on the cheeks, chest and legs; belts are fixed around the abdomen and thorax, an air flow sensor under the nose, a S_pO_2-probe taped to one finger and finally a probe for $p_{tc}CO_2$ and another S_pO_2 measurement at the forehead. This mounting procedure takes up to

[11] IBM Corporation, Armonk, NY, USA

an hour; the patient can not shower with the equipment and have to bring the trolley with computer and instruments along to the toilet if necessary. This can obviously result in some discomfort and reduced sleep quality. However, we followed standard procedures for PSG recording according to the AASM to minimize the discomfort, and as previous studies have shown only the first night to differ from the next ones regarding sleep architecture [107,108] we did not consider this distortion to be a significant problem for the participants.

Patients were anonymized by giving each a unique number and all study results were identified by this number. The list connecting the patients' name to this number was kept in a password secured file not open to anyone but the study leader.

3.6.2 About giving alcohol

Giving alcohol to a person with a former dependency of alcohol can lead to relapse of the problems, and some are teetotalers of other reasons. To avoid inclusion of such patients, I read the arrival journal looking for a history of alcohol problems or substance abuse prior to invitation to participate in the study. Also, the patient was specifically asked about drinking habits and use of potentially addictive drugs during the inclusion interview. The amount of alcohol given was calculated to give an alcohol concentration of approximately 0.7 parts per thousand 90 minutes after drinking, equivalent to a moderate intoxication without being considered overly drunk. The same amount of alcohol per kg body weight has previously been used in studies of COPD patients [84,109]. As a precaution for CO_2 narcosis due to retention in alcohol sleep, the $p_{tc}CO_2$ values were checked every other hour by the night nurse, with instruction to wake the patient if the $p_{tc}CO_2$ increase exceeded 3 kPa. If they were not able to wake the patient the doctor would be called.

3.6.3 About giving zopiclone

Patients using zopiclone or other hypnotics were asked to refrain from such medication 48 hours prior to first PSG and throughout the study, and they were free to withdraw from the study at any time during the week of tests. In fact, three patients

rejected to participate of this reason, and another patient was excluded after initial inclusion due to use of a benzodiazepine. Zopiclone is known to reduce the hypercapnic ventilatory response in awake, healthy individuals [110], and as COPD patients often have worse ventilation/perfusion matching in their lungs compared to normal subjects, hypoventilation during sleep was expected. However, as this drug is regularly used by thousands of COPD patients, and with the precaution to wake the patient if the $p_{tc}CO_2$ increased more than 3 kPa, we regarded the risk of harmful CO_2 retention to be low.

With the precautions taken and considerations as described above, we felt it safe to ask the patients to participate in the study, and the protocol was approved by the Ethical Committee of Eastern Norway, the Ministry of Health and Social Affairs and the Data Protection Authority of Norway.

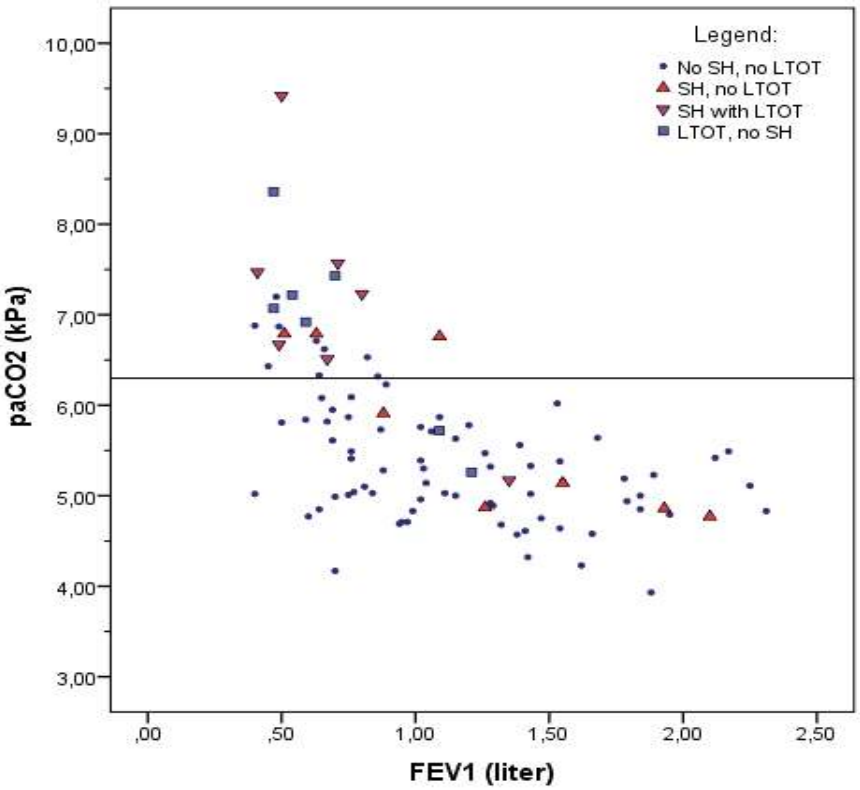
4 Main results

Our findings with reference to the numbered *research questions* in section 2 Study aims are presented below.

4.1 Sleep hypoventilation

1. *Is sleep hypoventilation (SH) associated with daytime hypercapnia?*
   Patients with daytime hypercapnia (CHRF) as a group had a greater maximal CO_2 increase from pre sleep value (sleep max $\Delta p_{tc}CO_2$) and SH was more frequently found compared to the normocapnic patients (median (IQR) 1.2 (0.8) kPa versus 0.8 (0.4) kPa (P=0.003), and 9 subjects versus 6 subjects (P=0.001), respectively). However, only one of the 6 normocapnic SH subjects used LTOT, and as a group these six subjects had significantly better FEV1 compared to the group of 9 hypercapnic SH subjects (median (IQR) 1.5 (0.8) L versus 0.6 (0.3) L respectively). As sleep hypoventilation by various definitions previously has been a frequent finding in severe COPD with CHRF and LTOT [52,53], we wanted to investigate whether the sleep max $\Delta p_{tc}CO_2$ can independently predict daytime p_aCO_2 when controlling for COPD severity (FEV1) and use of supplementary oxygen (LTOT). A hierarchical multiple regression model was performed; after entering FEV1 (liters) and LTOT (yes/no) at Step 1, 52% of the variance in daytime p_aCO_2 was explained. After entry of sleep max $\Delta p_{tc}CO_2$ (kPa) at Step 2 the total variance explained by the model was 56%. Thus, sleep max $\Delta P_{tc}CO_2$ explained an additional 4% of the variance in daytime P_aCO_2 after controlling for LTOT and FEV1. Figure 3 illustrates the association between FEV1, P_aCO_2, use of LTOT and SH.

Figure 3 Forced expiratory volume first second (FEV1) versus daytime arterial pressure of carbon dioxide (P_aCO_2), markers on sleep hypoventilation (SH) and long term oxygen therapy (LTOT), horizontal line indicating hypercapnia (6,3 kPa)

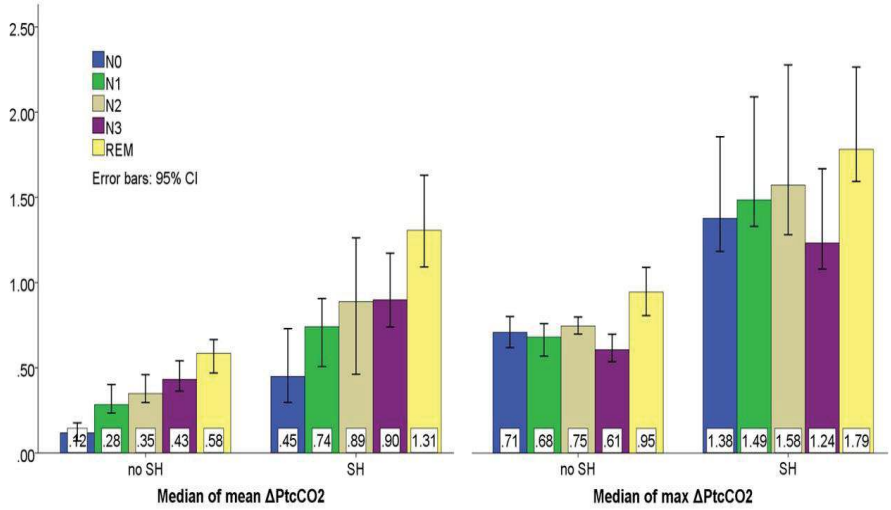


2. *Is the $p_{tc}CO_2$ increase from pre sleep value ($\Delta p_{tc}CO_2$) between sleep stages different in subjects with versus without SH?*

   In subjects without SH, we found a pattern of gradual increase in the mean $\Delta p_{tc}CO_2$ according to sleep stages, as indicated in figure 4 below. In the SH patients, this pattern was not so evident, as the mean $\Delta p_{tc}CO_2$ was the same in stages N2 and N3. Nevertheless, the difference between NREM and REM sleep was twice as high in the SH-group compared to the No-SH group. A different pattern is evident when looking at the median of the *maximal* $\Delta p_{tc}CO_2$ (cluster 3 and 4 in figure 4), as *lower* values are recorded during N3 sleep, both in the No-SH and in the SH group. This is in accordance with the

more stable breathing pattern typically found in N3 as compared to N1, N2 and REM sleep (see section 1.4.2).

Figure 4 $\Delta p_{tc}CO_2$ according to sleep stages



Notes to figure 4: Each bar represents the sleep stage median value of the mean, and alternatively the maximal $\Delta p_{tc}CO_2$ in kPa. The first and third clusters represent the 85 patients without sleep hypoventilation (no SH), second and fourth clusters represent the 15 patients with sleep hypoventilation (SH).

3. *Do subjects with Overlap (COPD and OSA) differ from those with COPD only, in $\Delta p_{tc}CO_2$ or in daytime p_aCO_2?*

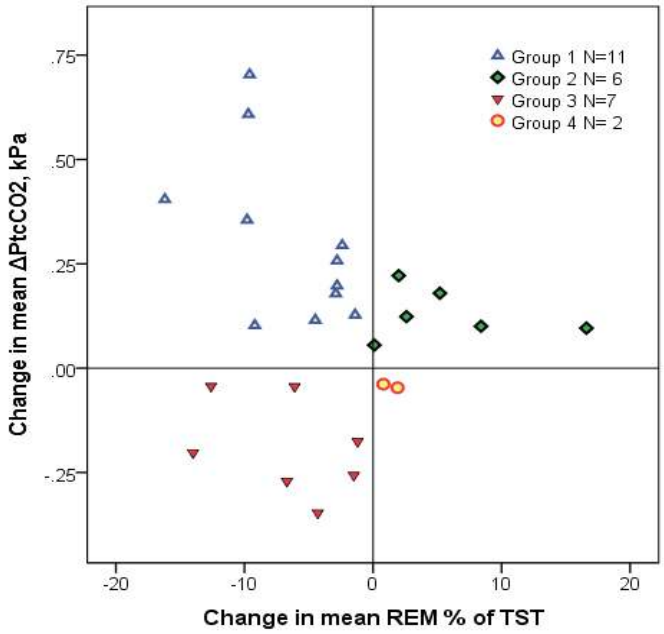
   Despite exclusion prior to the study of patients with previously diagnosed OSA, only 25 of the 100 subjects had less than 5 apneas/hypopneas per hour (AHI). As the study was not designed for diagnosing OSA, no record of daytime sleepiness or other OSA-symptoms was available; hence AHI $\geq$ 15 was chosen to define Overlap, whereas subjects with AHI < 5 were defined as COPD only. During sleep, the group of 27 Overlap patients had lower minimum REM sleep S_pO_2 compared to the group of 25 patients with COPD only (median (IQR) 78 (19) % versus 87 (8) % respectively). However, no differences were found in the mean or maximal $\Delta p_{tc}CO_2$ or in the frequency of SH between the groups, nor did they differ in daytime p_aCO_2.

4.2 Alcohol intervention

1. *How is the sleep architecture, blood gases and frequency of apneas/hypopneas changed by a moderate dose of alcohol prior to sleep?*

   Alcohol sleep was compared to control sleep in 26 subjects (nine males). As a group, they spent less time in REM sleep as percentage of TST when influenced by alcohol; they also had less awakenings and slightly increased mean $\Delta p_{tc}CO_2$ (mean differences (SD) 3 (7) %, 8 (13) awakenings and 0.10 (0.25) kPa, respectively). The groups mean S_pO_2 (SD) was 0.9 (2.1) % lower in NREM alcohol sleep, whereas no significant S_pO_2 changes were found in REM sleep or N0 (awake after initial sleep). Neither did alcohol change the groups mean frequency of oxygen desaturations per hour (ODI) or the AHI. However, as indicated in figure 5, several subgroups showed opposite characteristics; as approximately one third of the patients *increased* their REM % of TST, and about one third had *lower* values of $\Delta p_{tc}CO_2$ during alcohol influenced sleep. Also, in the subgroup of 6 patients with Overlap, we found *lower* AHI and ODI during alcohol sleep, whereas the mean $\Delta p_{tc}CO_2$ increased and the REM % of TST decreased in this group (see table 3 in paper II).

Figure 5 Alcohol induced changes in mean $\Delta p_{tc}CO_2$ versus changes in REM percentage of TST



Notes to figure 5: Each subject (N=26) is represented by a colored figure according to group (legend in panel). Mean $P_{tc}CO_2$ in group 1 (median (IQR) 0.26 (0.28) kPa) differed significantly from group 3 (-0.20 (0.23) kPa, P<0.0005), but not from group 2 (0.11(0.10) kPa, P=0.027). The change in REM percentage of TST was significantly different between the groups 1 and 2 (median (IQR) = -4.5 (6.9) % versus 3.9 (8.9) %, P=0.001). Abbreviations: Change in mean $\Delta P_{tc}CO_2$=difference in the mean increase in transcutaneous carbon dioxide pressure between alcohol and control sleep. Change in mean REM % of TST=difference in the mean rapid-eye-movement-sleep-percent of total sleep time between alcohol and control sleep.

2. *Is the alcohol induced changes in blood oxygen saturation or carbon dioxide pressure during sleep associated to daytime COPD characteristics?*

   In the group of 26 patients, three LTOT-users were outliers in the data distribution of the mean S_pO_2 change. When controlling for LTOT, the changes in the mean S_pO_2 induced by alcohol was correlated to daytime p_aO_2 and inversely correlated to p_aCO_2 (Pearson's r=0.5 (P=0.009) and r=-0.6 (P=0.002), respectively). However, this was not the case regarding the alcohol-sleep changes in the mean $\Delta P_{tc}CO_2$, nor did changes in the mean S_pO_2 or mean $\Delta P_{tc}CO_2$ during alcohol-sleep correlate to spirometry or demographic data. A hierarchical multiple regression model with LTOT, daytime p_aCO_2 and p_aO_2 explained 49% of the variance in the alcohol induced S_pO_2 change.

4.3 Zopiclone intervention

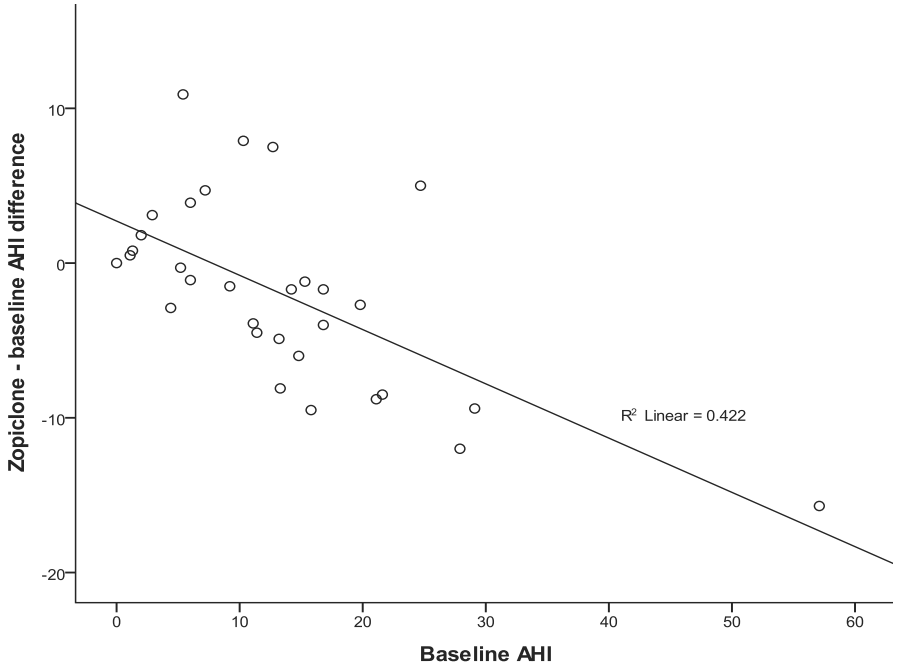
1. *To what extent does 5 mg zopiclone induce sleep hypoventilation in stable COPD?*

   Without significantly changing the mean REM-sleep percentage of TST in the 31 subjects as a group, zopiclone increased the mean $\Delta P_{tc}CO_2$ from baseline; both in REM sleep, NREM sleep and even in stage N0 (awake after sleep onset) with a mean (SD) of 0.25 (0.40) kPa, 0.22 (0.32) kPa and 0.14 (0.27) kPa, respectively. The number of patients with SH increased from 6 subjects (19%) to 13 subjects (42%). REM sleep minimum oxygen saturation did not change significantly from baseline to zopiclone sleep.

2. *What impact does 5 mg zopiclone have on the frequency of sleep apneas/hypopneas in stable COPD?*

   No significant difference was found in the median AHI between baseline and zopiclone sleep considering the whole group. However, in the subgroup of 11 subjects with Overlap (AHI≥15), zopiclone reduced the AHI with a median difference (IQR) of -8.5 (7.8), and an inverse correlation was found between the baseline AHI and zopiclone-baseline AHI-difference, as shown in figure 6.

Figure 6 Baseline apnea/hypopnea index (AHI) correlates inversely with Zopiclone – baseline AHI difference



Notes to figure 6: Each subject (N=31) is represented by a dot. Pearsson correlation r= -0.65 (P<0.0005)

5 General discussion

The results from the study are discussed in detail in the papers I-III. In this general discussion, the study limitations and some of the methodological considerations are highlighted, as well as the SH phenomenon in relation to CHRF, as observed in spontaneous sleep and during sleep influenced by alcohol and zopiclone. Finally, some aspects of SH and apneas/hypopneas during alcohol and zopiclone influenced sleep in subjects with Overlap versus COPD only are discussed.

5.1 Material and methods

5.1.1 The study material and design

To our knowledge, no studies of spontaneous sleep with PSG including $p_{tc}CO_2$ of as many as 100 normocapnic and hypercapnic COPD subjects have previously been published, nor are we aware of interventions with alcohol or zopiclone in groups of comparable numbers. As such, this study significantly contributes to the literature regarding nocturnal gas exchange in stable COPD. However, although effort was made in order to randomize the selection of the participants from the general COPD population and in designing the study, several aspects must be considered when interpreting the findings, and caution taken in generalizing the results.

First, a possible selection bias prior to referral and admission must be addressed. Patients are referred to Glittreklinikken by pulmonary specialists and general practitioners from all parts of Norway and all applications are examined by pulmonary specialists at the clinic; patients with no previous history of attending IPR-clinics are prioritized whereas admission may be refused to patients with diseases or conditions incompatible with IPR. Also, patients with very severe COPD and frequent exacerbations may be not being referred at all as their doctor might judge them unfit for lung rehabilitation. Likewise, there is a possibility of patients with primarily sleep related breathing problems not being referred of the same reason.

Second, as the waiting list for admission is long, failure of motivation is a drop-out cause as well as no-show due to acute illness or other reasons. Having CHRF implies an increased risk of COPD exacerbations and even death, thus reducing both the number of referred hypercapnic patients and the number of such inpatients eligible for participating in the study. In fact, we were not able to include the intended 60 subjects in the CHRF group during the study period of 18 months, thus reducing the statistical power of the data.

Third, due to lack of CHRF patients, these were not stratified for gender like the normocapnic subjects. Hence, only four of the 24 CHRF subjects were male. However, as the CHRF groups' median (interquartile range) age was as high as 68 (15) years, the low percentage of males can be due to this genders' lower mean living age. In 2013 the expected living age in Norway was 83,6 years in females, 79,9 years in men, with COPD increasing mortality rates [111].

To sum up the considerations above, we believe our results regarding spontaneous sleep can be considered as representative for the cohort of stable COPD patients in Norway being motivated for pulmonary rehabilitation. However, we have missed the group having very frequent exacerbations that undoubtedly have more serious sleep respiratory disturbances than those described in this study. Also, having relatively few patients with CHRF makes the results regarding this subgroup vulnerable to type II statistical errors, as low statistical power reduces the probability of correctly rejecting a false null hypothesis.

The open label study design (having no placebo group) in the alcohol and zopiclone interventions certainly can be a confounder. However, the knowledge of drinking alcohol or taking a sleeping pill will probably result in faster sleep onset and/or deeper sleep, and as shown in Paper I, the $p_{tc}CO_2$ increases with depth of sleep. Thus, as discussed in detail in paper II and III, we believe that *not blinding* patient or study personnel probably implied a *more accentuated result* regarding sleep hypoventilation. Importantly though, the sleep scorers were blinded to information

regarding control or interventional sleep, as such knowledge could interfere with their scoring.

Finally, more detailed information on OSA-symptoms or alcohol consumption as discussed in the three papers and below (sections 5.1.3 and 5.2.3) would have increased the statistical power concerning the differences between COPD only and Overlap patients. As mentioned above, type II statistical errors must be considered with the low number of subjects in these subgroups. More participants in each group may have explained to more detail the differences regarding sleep architecture and hypoventilation in alcohol sleep.

5.1.2 Blood gas measurements during sleep

The gold standard for blood gas measurement is analyses of samples from arterial puncture. However, obtaining such material during sleep is difficult, as arterial sampling can disturb sleep and the number of samples is limited, with the risk of missing important gas pressure changes due to unstable respiration. Thus, surrogates are frequently used, as transcutaneous or end-tidal expiratory gas analysis of pCO_2 ($p_{tc}CO_2$ or $p_{et}CO_2$, respectively), and oxygen saturation measurements by pulse oximetry (S_pO_2). In patients with COPD, $p_{et}CO_2$ is considered too inaccurate to substitute for arterial pressure of carbon dioxide (p_aCO_2) [112], whereas $p_{tc}CO_2$ has a lag-time compared to p_aCO_2, and technical artifacts due to compression or loosening of the $p_{tc}CO_2$-measuring skin probe can occur. Likewise, reduced peripheral circulation or loosening of the S_pO_2-probe (e.g. from the finger tip) can result in too low values as compared to arterial oxygen saturation (S_aO_2).

To overcome some of these challenges, a number of investigations were performed and precautions taken prior to data analysis (Supplementary material to Paper I, Appendix 7.2 and section 3.3.5).

A small pilot study concluded with equivalence between *changes* in $p_{tc}CO_2$ and p_aCO_2, whereas another clinical study showed a possible $p_{tc}CO_2$ *measurement error* between two TOSCA 500 devices of approximately 0.3 kPa. Thus, an individual pre-sleep $p_{tc}CO_2$ value was calculated and the same device was utilized on both sleep

recordings from each patient. A third pilot study showed that a change in alveolar pCO_2 (e.g. following an apnea or hypopnea) will result in arterial and transcutaneous pCO_2 changes after approximately 10 seconds and one minute, respectively. Hence, to synchronize respiratory events recorded in the traces of nasal flow and thoracic and abdominal belt movements with the $p_{tc}CO_2$ trace, the latter was left-shifted 1 minute.

To avoid compression from the pillow when the patient slept on the side, the $p_{tc}CO_2$-probe was fixed to the patients' forehead rather than to the ear flip (figure 7 below and section 3.4.5).

Finally, as the signal from the finger-probe was of poorer quality in some recordings, the S_pO_2-signal from the $p_{tc}CO_2$-probe fixed to the forehead was chosen for the S_pO_2-calculations (section 3.5.3).

5.1.3 Polysomnography

For a full polysomnograpy, several sensors, electrodes, wires and belts are connected to the body, and this can obviously disturb sleep. Previous studies of consecutive PSG recordings has shown the first night's sleep to differ from the second night, however, the second and forthcoming nights can be expected to show similar results [107,108]. Thus, all patients slept an initial night for adaptation before recording of spontaneous or interventional sleep commenced in randomized order the second and third night. The synchronized measurements of $p_{tc}CO_2$ and S_pO_2 with the other PSG traces enabled a detailed assessment of the blood gases in the different stages of sleep during free breathing, apneas or hypopneas.

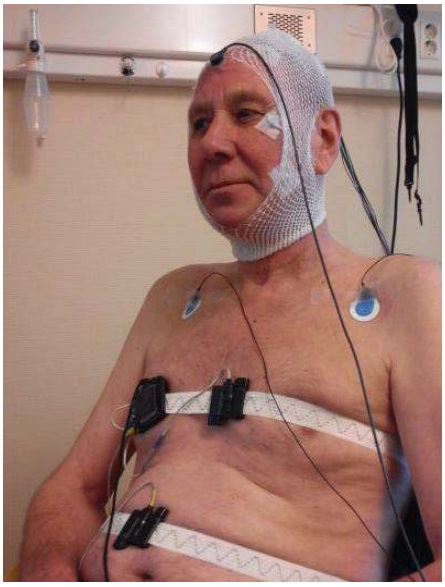


Figure 7 Study patient with electrodes, belts and $p_{tc}CO_2$ probe on forehead. Private photo with permission

As discussed in the papers I-III, the high frequency of apneas/hypopneas was unexpected (27% having an AHI ≥15). As previous studies indicate a prevalence of OSA in COPD of only about 5% [113], our study was not designed for diagnosing OSA by collecting data on daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or choking. Such data would have enabled a diagnosis of OSA with an AHI ≥5, thus increased the number of patients in the Overlap and COPD only groups as described in the three papers. However, using AHI ≥15 regardless of symptoms is a conservative and not uncommonly used definition of OSA both in science and clinical practice. Due to a somewhat surprisingly high AHI's scored by the first polysomnographist, we decided to have all the recordings re-scored by a second polysomnographist. Both scorers were well experienced, working independent of each other and blinded to patient information except their gender, age, height and weight. As the results from these two scorers differed substantially both in sleep stage distribution and frequency of apneas/hypopneas, another two polysomnographists scored a random selection of 10 PSG's, and the initial scorer having the best match to the latter two were finally selected for analyses. Concordance between the two controllers and the chosen initial polysomnographist was good (Paper I), so we believe the high prevalence of Overlap in this study is true, although it may not reflect the prevalence in the whole COPD population in Norway.

5.2 Sleep hypoventilation and chronic hypercapnic respiratory failure

5.2.1 Definition and prevalence of sleep hypoventilation

In their papers from 2003 and 2011, respectively, O'Donoghue et al and Tarrega et al presented findings of sleep hypoventilation by slightly different definitions (section 1.5.1), and they also defined daytime hypercapnia by different p_aCO_2 cutoff values [52,53]. Thus, comparing results and judging prevalence is difficult. Not making this easier, the more recent AASM scoring rules defines sleep hypoventilation in two quite different ways [54]. Defining SH merely as having a $pCO_2 > 7.3$ kPa for at least

10 minutes of sleep ($AASM_1$) will include almost all patients with daytime CHRF, regardless of the degree of CO_2 retention during sleep. The second definition ($AASM_2$) is in our opinion a better one, as it is specific to phenomena occurring during sleep – by defining SH as a pCO_2 *increase* of at least 1.3 kPa for ≥ 10 minutes to a value exceeding 6.7 kPa. Thus, the $AASM_2$ definition was chosen in the analysis of data for paper I and II. However, at the request from a reviewer of paper III, the $AASM_1$ definition was briefly mentioned, and values according to both definitions were stated in table 2 of paper III. As shown in this table, the number of patients with SH increased significantly in zopiclone sleep by both definitions, however, the SH scored *individuals* by the two definitions were not the same. Nevertheless, using the $AASM_1$ definition would not have changed the fact that SH is highly prevalent in this population, nor the conclusion of SH being more frequent in zopiclone sleep compared to spontaneous sleep (paper III).

In the analysis of spontaneous sleep in paper I (using the $AASM_2$ definition), we found a SH prevalence of 15% in the whole study population. As indicated in figure 3, only eleven of the 100 subjects in our study had CHRF and used LTOT, whereas SH was scored in six of these eleven patients (55%). Taken different SH and CHRF definitions into account, this prevalence is likely comparable to the results in previous studies, as O'Donoghue et al found sleep hypoventilation in 43% of their 56 stable COPD patients with CHRF using LTOT, whereas Tarrega et al reported a prevalence of 21% in 80 comparable subjects.

5.2.2 SH as a predictor of CHRF?

As shown in paper I, the regression model with the variables FEV1, use of LTOT and the maximal increase in $\Delta p_{tc}CO_2$, explains about half of the variation in daytime p_aCO_2. Independently, the $\Delta p_{tc}CO_2$ increase explained only an additional 4%, after controlling for LTOT and FEV1. Thus, although the effect is weak, this finding supports the hypothesis of SH being a possible predictor of CHRF. We found the *degree* of hypoventilation to depend on the sleep stage; the highest $\Delta p_{tc}CO_2$ values being found in REM sleep. Also, as shown in figure 4, the SH-group had greater between-stage differences, indicating that these individuals are unable to increase

their ventilation and/or have less stringent CO_2 homeostasis during sleep. For more than a decade, SH in COPD has been proposed to predict imminent CHRF as a consequence of impaired respiratory muscles, elevated resistive load and blunting of central chemoreceptors [114]. However, the fact that one third of our SH individuals were daytime normocapnic with only moderate COPD (figure 3), raises the question whether the SH phenomenon to some extent is *independent* of the failing respiratory pump in COPD. Subjects with congenital central hypoventilation syndrome (CCHS, also known as "Undines Curse", see preface) lack the central chemoreceptor control of breathing and seriously hypoventilate during NREM sleep, requiring ventilatory support to survive. Nevertheless, when awake, these individuals can breathe adequately by non-chemoreceptor inputs to the brain stem respiratory complex [115]. Sleep studies of normal individuals with arterial blood gases are few and small, and to our knowledge, the prevalence of SH according to the AASM definition is unknown. Thus, possibly, a reduced chemoreceptor function leading to SH - but not as serious as the rare condition of CCHS - can be found in individuals without COPD as well.

To our knowledge, all previous studies of NIV in stable COPD were performed in subjects with established CHRF *regardless* of the degree of hypoventilation during sleep. The results of this treatment has been conflicting, however, a recent study has shown that adding NIV to standard treatment improves survival of patients with hypercapnic, stable COPD when NIV is targeted to greatly reduce daytime hypercapnia [70]. If SH really is predicting imminent hypercapnic respiratory failure, we suggest it should be considered as an indication for NIV by itself, independent of daytime p_aCO_2. In fact, some clinical centers have implemented this view. The German guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure regard nocturnal hypercapnia as an independent indicator for the initiation of NIV in COPD patients [116]. Although these guidelines are based on consensus in expert conferences and relevant literature search, we have not found any studies reporting effects of this somewhat prophylactic treatment of CHRF, nor are we aware of planned studies of SH as an independent

indicator for NIV, with the aim to stop or delay the development of CHRF in stable COPD.

5.2.3 SH due to alcohol and zopiclone

As described in paper II, one of the consequences of giving a moderate dose of alcohol prior to sleep to a group of stable COPD-subjects is a very modest increase in the mean (SD) sleep $\Delta p_{tc}CO_2$ of 0.10 (0.25) kPa, and a decrease in the mean S_pO_2 of less than 1 %, whereas no blood gas changes are observed in the awake periods during the night. This alcohol induced, additional hypoventilation (coming on top of the "baseline" hypoventilation of each patient) occurs despite 3 % *less* REM sleep as percentage of TST – the sleep stage in which we have found the $\Delta p_{tc}CO_2$ to be greatest (paper I). From a clinical point of view, this sum up to that alcohol makes very small changes in blood gases and sleep architecture. However, although the study subjects were few, results from several subgroups diverged from the mean of the whole group, indicating that alcohol can have several effects on sleep architecture and the sleep respiratory drive to breathe, and also that COPD has several phenotypes. Approximately 1/3 of the subjects apparently had a beneficial effect of alcohol as the mean $\Delta p_{tc}CO_2$ *decreased*, maybe as a result of alcohols' bronco-dilating properties [117]. Another quarter benefited of more REM sleep (often regarded as a sign of better sleep quality) with only a slight increase in the mean $\Delta p_{tc}CO_2$ (group 2 in figure 5). In paper II the possible explanation of this subgroups' increased REM sleep as alcohol abstinence is discussed, and we find it unlikely that one quarter of the study group had an undisclosed alcohol problem. However, the aspect of alcohol *experience* can be an issue, both in regard to less hypoventilation and increased REM sleep, as inexperienced drinkers tend to be sedated (more REM sleep) while experienced drinkers are stimulated (less REM sleep) following consumption of the same amount of alcohol [118]. Also, moderate doses of alcohol are known to improve sleep maintenance [77]. Regrettably, no record was made of sleep complaints or alcohol experience in our study subjects, however, teetotalers are not unusual in Norway, and insomnia is highly prevalent in COPD [85]. The number of patients with SH increased from 2 to 5 patients in baseline versus alcohol sleep, but this increase was clearly not statistically significant as one of the patients had SH

only during spontaneous sleep, not in alcohol sleep. However, type II statistical errors must be considered with such small numbers of study subjects, and as the mean $\Delta p_{tc}CO_2$ showed a slight increase, it is possible that alcohol in fact does increase the risk of SH.

The subjects receiving 5 mg of the hypnotic zopiclone prior to sleep have an increase in the mean (SD) sleep $\Delta p_{tc}CO_2$ of approximately 0.22 (0.33) kPa; although not much from a clinical standpoint, this is about twice the increase of the alcohol-group. Importantly however, these two groups were not matched for age and blood gases, so differences between them must be viewed in this context; alcohol subjects versus zopiclone subjects having mean values of age 65.5 years versus 64.0 years, p_aO_2 9.7 kPa versus 9.1 kPa, and p_aCO_2 5.1 kPa versus 5.5 kPa, respectively. As the mean sleep $\Delta p_{tc}CO_2$ in the zopiclone group increased in all sleep stages and – unlike the alcohol group - also during N0, zopiclone seems to be an agent of mild hypoventilation both in awake and sleeping individuals, unlike alcohol, at the doses used. This is also reflected in the number of subjects with SH increasing significantly in zopiclone sleep. However, no subgroup with *lower* mean $\Delta p_{tc}CO_2$ was found in zopiclone sleep; the reason can be that this drug does not have any impact on the bronchial muscle tonus (like that of alcohol).

5.3 AHI changes due to alcohol and zopiclone in Overlap subjects

Subgroups with Overlap showed somewhat different characteristics from the COPD only groups, both in alcohol and in zopiclone sleep. Importantly though; the study was not primarily designed or powered to study the difference in AHI between Overlap and COPD, so caution should be applied in interpreting these results.

Paper III describes a significant drop in AHI when a subgroup of 11 Overlap patients was given 5 mg of the hypnotic zopiclone, a result in support of Eckert et al's findings in a group of OSA subjects [93]. A similar finding, although not as pronounced, is

shown in paper II; despite the average AHI not being changed by alcohol in the whole group of 26 subjects, a subgroup of six with Overlap (4 male) had lower mean values of AHI and ODI during alcohol sleep compared to control sleep. This result is in contrast to previous findings in asymptomatic and in snoring males, in mild to moderate OSA-males and in male, but not in female COPD patients [82,79,119,83,120]. However, we are not aware of studies of AHI change due to alcohol in Overlap subjects.

The respiratory frequency increased during zopiclone N0 and NREM sleep, a result in line with Ranløv et al and Beaupre et al in their studies of normal subjects and of COPD patients [110,121]. Thus, although the respiratory frequency was not analyzed in alcohol sleep, a possible explanation for the reduced AHI both in zopiclone and alcohol sleep can be an increased respiratory frequency and correspondingly low tidal volumes, as well as altered arousal threshold. In alcohol sleep, bronco-dilatation and less mucus possibly can reduce the number of hypopneas as well. A recent meta-analysis by Zhang et al including 448 patients with OSA found that non-benzodiazepine hypnotics (including eszopiclone) improve sleep without worsening AHI and S_pO_2, suggesting OSA patients with insomnia indeed may benefit from such hypnotics [122].

6 Conclusions and perspectives

6.1 Paper I

In this observational study of 100 (39 male) stable COPD patients with a mean FEV1 1.1 L (42% of predicted), 15 on LTOT, 24 having CHRF (daytime $p_aCO_2 \geq 6.3$ kPa) we found that:

- SH as defined by the AASM was more frequently found in subjects with CHRF compared to those with daytime normocapnia (38 % versus 8 % respectively), and a multiple regression model with the variables FEV1, LTOT and the maximal $p_{tc}CO_2$ increase during sleep explained 56 % of the variance in daytime p_aCO_2

- In subject *without* SH a pattern of gradual $p_{tc}CO_2$ increase from a pre sleep value ($\Delta p_{tc}CO_2$) according to sleep stages was evident, with a mean (SD) increase from NREM to REM sleep of 0.20 (0.16) kPa, whereas this increase was 0.46 (0.28 kPa) in the SH subjects

- No differences were discovered between the group of 27 subjects with Overlap (AHI $\geq$ 15) and the group of 25 subjects with COPD only (AHI < 5) in the daytime p_aCO_2, sleep mean or max $\Delta p_{tc}CO_2$ or in the SH frequency, although the Overlap group had a lower minimum REM sleep SpO2 compared to the group of COPD only (median (IQR) 78 (19) % versus 87 (8) % respectively)

6.2 Paper II

In this randomized, un-blinded, crossover study of 26 (9 male) stable COPD subjects from the same cohort as paper I, 3 on LTOT and 4 having CHRF, we found that a moderate dose of alcohol (0.5 g ethanol/kg bodyweight) taken immediately prior to intended sleep results in:

- A decrease in the REM sleep percentage of TST, less awakenings and a minor increase in the mean ΔptcCO2, with mean differences (SD) 3 (7) %, 8 (13) awakenings and 0.10 (0.25) kPa, respectively

- A minor drop in the mean (SD) S_pO_2 of 0.9 (2.1) % during NREM sleep, with no significant changes in REM sleep or during epochs awake after initial sleep onset (N0), nor in the frequency of oxygen desaturations (ODI)

- No significant changes in AHI overall, however, subjects with Overlap tend to have *fewer* apneas/hypopneas in alcohol sleep

- Alcohol induces changes in S_pO_2, but not in $\Delta\ p_{tc}CO_2$, correlate with daytime p_aO_2 and inversely with p_aCO_2 (r = 0.5 and -0.6 respectively); thus patients with the greatest S_pO_2 changes in during sleep tend to have better daytime blood gas values compared to those with less desaturations

6.3 Paper III

In this randomized, un-blinded, crossover study of 31 (10 male) stable COPD subjects from the same cohort described in paper I, 7 on LTOT and 8 having CHRF, we have found that a pill of 5 mg zopiclone taken 30 min prior to intended sleep results in:

- Nocturnal hypoventilation as a mean (SD) increase in the $\Delta\ p_{tc}CO_2$ during N0, NREM and REM sleep of 0.14 (0.27) kPa, 0.22 (0.32) kPa and 0.25 (0.40) kPa respectively, and a doubled frequency of subjects with SH, however no significant changes in S_pO_2.

- No significant changes in AHI considering the whole group, however, Overlap subjects tend to have fewer apneas/hypopneas in zopiclone sleep compared to those with COPD only

6.4 Clinical aspects and further research

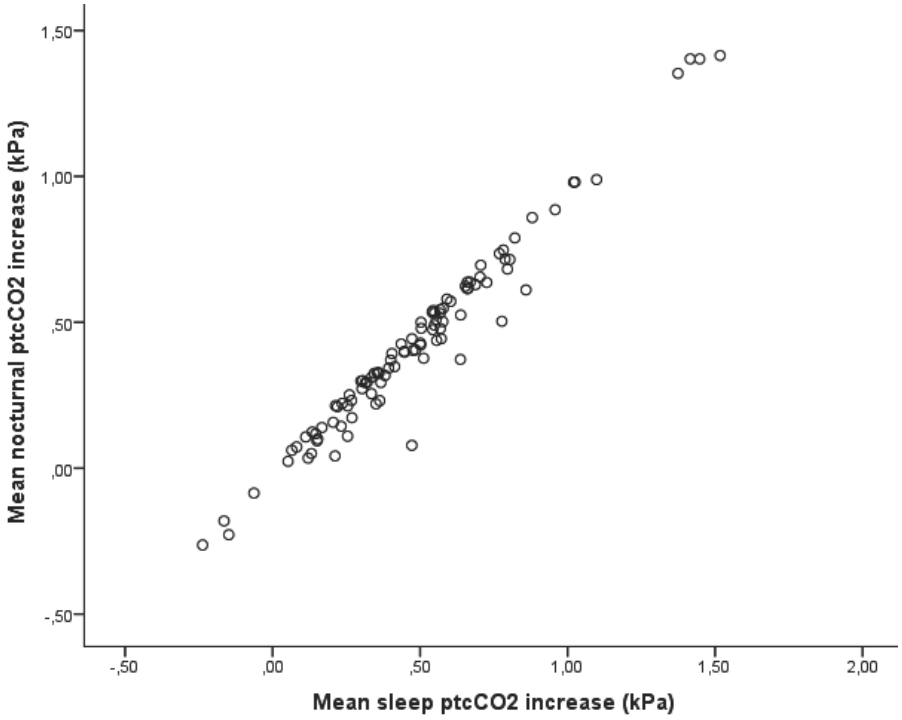
We have shown that an occasional, moderate dose of alcohol (e.g. two to three glasses of wine) does not gravely increase the risk of sleep hypoventilation in subjects with COPD, whereas a 5 mg pill of the hypnotic zopiclone improves sleep quality, however at the cost of an increase in the nocturnal $p_{tc}CO_2$ and an increased risk of SH. In subjects with Overlap however, both alcohol and zopiclone seem to *reduce* the number of apneas/hypopneas. Thus, from a clinical perspective it seems to be safe to give zopiclone to Overlap patients who - in the process of adaption to the CPAP mask - find it hard to sleep.

The questions of whether SH really predicts imminent hypercapnic respiratory failure, to what extent the SH phenomenon is independent of the daytime homeostasis of pCO_2, and ultimately, whether SH predicts death in COPD still remains to be answered. These answers are important in the selection of COPD patients to receive NIV; hence, sufficiently powered, randomized, prospective and longitudinal cohort studies of COPD patients with SH should be conducted. In addition to a diagnosis of CHRF, mortality should be an end point, due to the fact that CHRF is associated with increased mortality [14,15].

Figure 8 indicates that the mean value of nocturnal $p_{tc}CO_2$ (including the N0 periods) only slightly underestimates the true sleep mean $p_{tc}CO_2$, as only 3% of study subjects had a mean sleep $p_{tc}CO_2$ – nocturnal sleep $p_{tc}CO_2$ difference > 0.25 kPa. Hence, as PSG is costly and time consuming, I suggest polygraphy (PG) with a trace for $p_{tc}CO_2$ can be used as a SH screening tool for clinical purposes. In fact, a paper was quite

recently published describing this method in a study of SH in children with sleep disordered breathing [123].

Figure 8 Mean sleep versus mean nocturnal value of the transcutaneous carbon dioxide pressure increase (kPa)



Note to figure 8: N=100 subjects, each represented by a dot. Nocturnal $p_{tc}CO_2$ includes periods awake after initial sleep onset (N0).

7 Appendix

7.1 BODE index and MMRC

The MMRC translation was presented at the annual meeting of the Norwegian Lung Medicine Society in the fall of 2010, and is now included in the National professional guidelines for prevention, diagnosis and follow-up of COPD provided by the Norwegian Directory of Health [124]. The MMRC version as presented in figure 9, and the BODE index derived from this score, are now routinely reported in the COPD patients' journal at Glittreklinikken.

Figure 9 Modified Medical Research Council Dyspnea Questionnaire, Norwegian version

Norsk versjon MMRC og beregning av BODE-index

Side : 1 av 1

GKN3Kje.1.4.4.9 Norsk versjon MMRC og beregning av BODE-index

MMRC brukes som klassifikasjon av dyspnoe ved KOLS. Score på MMRC brukes også til å beregne BODE-index. Dette er vist å være en god prognostisk indikator ved KOLS. Legene skal registrere MMRC i innkomstjournal på samtlige pasienter, ikke bare ved KOLS. Hos de som har KOLS skal MMRC også registreres ved utreise, og BODE-index beregnes av legen på grunnlag av spirometri (beste FEV1), 6 min. gangtest ved utreise, MMRC-score ved utreise og BMI. Bode-index dikteres i epikrise under supplerende undersøkelser.

ID: **Dato:**

MMRC Norsk versjon (mai 2010, Glittreklinikken)

Sett kun ett kryss ved beskrivelsen som passer best for deg

☐ *0* *Breathless only with strenuous exercise*
Jeg blir tungpustet bare når jeg trener hardt

☐ *1* *Short of breath when hurrying on the level or up a slight hill*
Jeg får åndenød når jeg skynder meg på flat mark eller i slakk motbakke

☐ *2* *Slower than most people of the same age on a level surface, or have to stop when walking at my own pace on the level*
Jeg er tregere enn den fleste på min alder på flat mark, eller jeg må stoppe på grunn av tungpust når jeg går i mitt eget tempo på flat mark

☐ *3* *Stop for breath walking 100 meters, or after walking a few minutes at my own pace on the level*
Jeg må stoppe for å få igjen pusten etter 100 meters gange, eller etter noen få minutter i mitt eget tempo på flat mark

☐ *4* *Too breathless to leave the house, or breathless when dressing or undressing*
Jeg er så tungpustet at jeg ikke kommer meg ut av huset, eller blir tungpust ved på- og avkledning

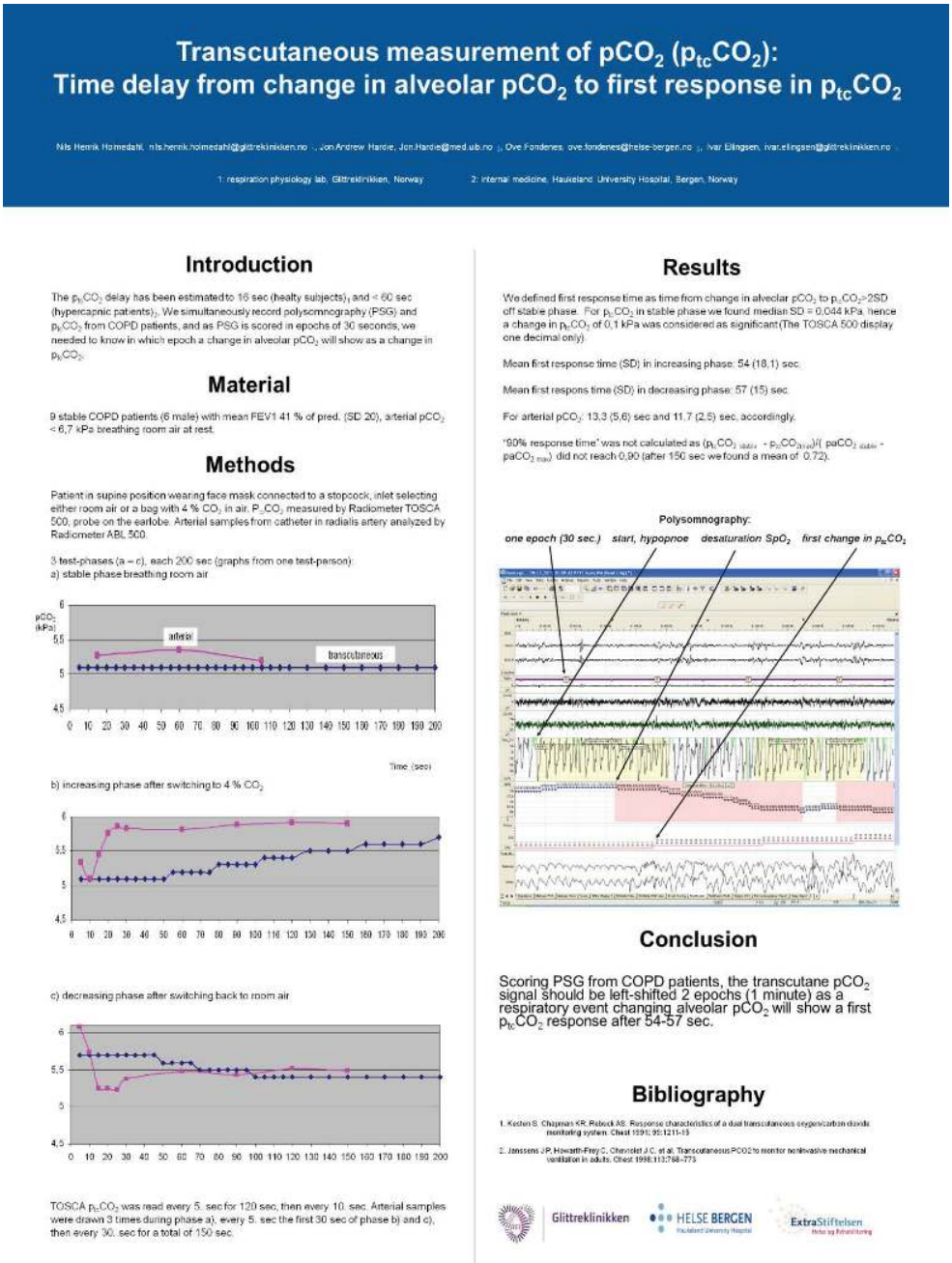
Beregning av BODE-index: max score 10

BODE poeng	**0**	**1**	**2**	**3**	**Pasientscore:**
FEV1 (% av pred.)	≥65	50-64	36-49	≤35	
6 min. gangtest (m)	≥350	250-349	150-249	≤149	
MMRC score	0-1	2	3	4	
BMI	>21	≤21			
SUM					

Ref: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004 Mar 4;350(10):1005-12

7.2 $P_{tc}CO_2$ time delay

Figure 10 Poster presented at the Amsterdam European Respiratory Society Congress 2011



8 Erratum

The following errors were found after publishing of the papers; however, they did not influence the main results or the conclusions.

1. Paper I, Supplementary material, **Table S1**, SES % for age group 60-69 years:
   The mean and SD results (reference values) is given as *86 (9.1) and 86 (7.9)*.
   Correct values are *86 (86) and 9.1 (7.9)*, respectively.

2. Paper I, Supplementary material, section **$P_{tc}CO_2$ delay time**, last two sentences:
   The results showed a first response time (frt) meaning time from change in alveolar PCO_2 to $P_{tc}CO_2$>2SD off stable phase as follows: Mean frt(SD) in increasing phase: 54*(5,6)* sec; Mean frt(SD) in decreasing phase: 57(15) sec. For arterial PCO2: *13,5(5,6)* sec and *11,7(2,5)* sec, accordingly.
   Correct:
   The results showed a first response time (frt) meaning time from change in alveolar PCO_2 to $P_{tc}CO_2$>2SD off stable phase as follows: Mean frt(SD) in increasing phase: 54*(18.1)* sec; Mean frt(SD) in decreasing phase: 57(15) sec. For arterial PCO2: *13.5(5.6)* sec and *11.7(2.5)* sec, accordingly.

3. Paper III, Discussion, 2.nd paragraph, 3.rd sentence:
   In *2007*, Brander et al. studied nine males with advanced COPD…
   Correct:
   In *1992*, Brander et al. studied nine males with advanced COPD…

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