Tampere University

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Transcutaneous Carbon Dioxide in Sleep-disordered Breathing

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ACADEMIC DISSERTATION
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Evil is whatever distracts

- Franz Kafka

ABSTRACT

Obstructive sleep apnea (OSA) is a major public health problem. Severe OSA classified in terms of apnea-hypopnea index (AHI) is associated with increased morbidity and mortality. Milder forms of OSA and prolonged partial upper airway obstruction are not equally high-risk conditions, although affected individuals can be as symptomatic as those with severe OSA. Treatment regime for these patients vary from country to country.

While measurement of the arterial oxyhemoglobin saturation (SaO_2, SpO_2 with pulse oximetry) is mandatory in the evaluation of sleep-disordered breathing (SDB = all breathing abnormalities from normal breathing to apnea), CO_2 is rarely measured. CO_2 measurements have been mainly done in populations where hypercapnia (High arterial CO_2, ($PaCO_2$)) is suspected. There has not been a great need for CO_2 measurement in sleep research as the effects of severe SDB are readily seen with SpO_2. SpO_2 measurement is robust and the signal is simple to interpret and feasible for automatic analyses. At the moment, obtaining a good quality CO_2 signal requires more effort. The signals are affected by several factors and are prone to artifacts. On the other hand, the importance of CO_2 in the control of breathing and the wealth of information the CO_2 signal may contain, could improve the SDB diagnostics.

The aim of this study was to determine the patterns of transcutaneous CO_2 ($PtcCO_2$) during different forms of SDB, also including prolonged partial upper airway obstruction.

$PtcCO_2$ dynamics were studied retrospectively from cardiorespiratory polygraphic recordings performed at the Tampere University Hospital sleep clinic. These patients were referred to hospital due to a suspicion of SDB. A set of scoring rules was developed to characterize progressive flow limitation events. These events were then screened from 425 patient recordings performed between March 2004 and April 2007. Apneas, hypopneas and steady flow limitation were screened as sequences from 555 patient recordings from between June 2005 and May 2007. Physiology and anatomy change during pregnancy and sleep problems including SDB are commonly reported. In a prospective study, standard polysomnography

(PSG) with $PtcCO_2$ were performed in 18 healthy women during their third trimester and in 12 healthy non-pregnant controls for a more exact characterization of SDB.

Progressive flow-limitation was systematically associated with increasing $PtcCO_2$, whether or not, the episode was associated with increased respiratory effort. Respiratory efforts started to increase when $PtcCO_2$ exceeded the $PtcCO_2$ plateau level. $PtcCO_2$ plateau was the highest level of $PtcCO_2$ which was associated with stable breathing. Progressive flow limitation was associated with small SpO_2 drop, but not systematically.

Different sleep apnea types associated with different $PtcCO_2$ levels. $PtcCO_2$ during central and mixed sleep apnea did not differ from $PtcCO_2$ in wakefulness. $PtcCO_2$ during obstructive sleep apnea and hypopnea did not differ from $PtcCO_2$ levels observed during normal stable breathing in sleep ($PtcCO_2$ plateau). Steady flow-limitation sequences associated with $PtcCO_2$ levels that were higher than those observed during the $PtcCO_2$ plateau. There was no difference in SpO_2 between flow-limitation and stable breathing.

Pregnant women did not differ from controls in terms of SDB; flow-limitation, snoring, AHI and oxyhemoglobin desaturation index of 3% (ODI3) were similarly low in both groups. However, pregnant women more frequently presented $PtcCO_2$ "peaks", which were scarce in non-pregnant controls (n = 78 vs. 5). These peaks associated with flow-limitation and altered ventilatory control. $PtcCO_2$ levels were not different during wakefulness or sleep, but the variance of $PtcCO_2$ during non-rapid eye movement (NREM) sleep in pregnant women was smaller than in non-pregnant controls.

In conclusion, $PtcCO_2$ measurement is sensitive to ventilatory changes during sleep. Sleep-related increase in $PaCO_2$ can be identified with $PtcCO_2$. Progressive flow limitation associates with $PtcCO_2$ increase and $PtcCO_2$ levels associate to sleep depth as well as sleep apnea types. Ventilatory changes in pregnancy may lead to $PtcCO_2$ "peaks", which have not been described before.

TIIVISTELMÄ

Obstruktiivinen uniapnea on huomattava kansanterveydellinen ongelma. Erityisesti vaikeaan uniapneaan liittyy lisääntynyttä sairastuvuutta ja kuolleisuutta. Obstruktiivisen uniapnean lievempiin muotoihin tai osittaiseen ylähengitystieahtaumaan ei liity vastaavaa riskiä, mutta näistä tautimuodoista kärsivät eivät oireiden perusteella välttämättä eroa vaikeasta uniapneasta. Viimeksimainittujen hoitokäytännöt eroavat alueittain ja maittain.

Valtimoveren happikyllästeisyyden (SaO_2, SpO_2 jos pulssioksimetri) mittaaminen on pakollista unenaikaisten hengityshäiriöiden (kaikki normaalista hengityksestä apneaan) arvioinnissa. Hiilidioksidia (CO_2) sen sijaan mitataan harvemmin. CO_2-mittauksia on tehty pääosin potilasryhmissä, joissa hypercapnia (korkea valtimoveren hiilidioksidipitoisuus) on todennäköistä. CO_2:n mittaamiselle unen aikana ei ole ollut suurta tarvetta, koska vaikeiden unenaikaisten hengityshäiriöiden seuraukset ovat nähtävissä SpO_2-mittauksella. SpO_2-mittaus on vakaa ja signaali on helppo tulkita, joten automaattiset analyysit ovat yleisesti käytössä. Tällä hetkellä hyvälaatuisen CO_2-signaalin saaminen on hankalampaa, koska mittaus on alttiimpi virheille. Toisaalta, CO_2 on tärkeä hengityksen säätelijä ja CO_2-signaalin sisältämä informaatio voi parantaa unenaikaisten hengityshäiriöiden diagnostiikkaa.

Tämän tutkimuksen tarkoituksena oli määrittää transkutaanisen eli iholta mitattavan hiilidioksidin ($PtcCO_2$) toimintaa unenaikaisten hengityshäiriöiden aikana, sisältäen myös osittaisen ylähengitystieahtauman.

$PtcCO_2$:n dynamiikkaa tutkittiin takautuvasti Tampereen yliopistollisen sairaalan unilaboratoriossa tehdyistä yöpolygrafioista. Nämä tutkimukset on tehty mahdollisen uniapneaepäilyn vuoksi. Progressiiviselle virtausrajoitukselle kehitettiin kriteeristö ja kyseisiä hengitysjaksoja seulottiin 425 potilaan aineistosta, joka oli kerätty aikavälillä 3/2004 – 4/2007. Apneaa, hypopneaa ja tasaista virtausrajoitusta puolestaan tutkittiin jaksoina 555 potilaan aineistosta, joka oli kerätty välillä 6/2005 – 5/2007. Raskauden aikana fysiologia ja anatomia muuttuvat ja uniongelmat sekä unenaikaiset hengitykseen liittyvät ongelmat ovat tavallisia. Etenevässä tutkimuksessa tehtiin 18 terveelle, viimeisellä raskauskolmanneksella olevalle ja 12 terveelle verrokille unipolygrafia ja $PtcCO_2$-mittaus. Tutkimuksen tarkoituksena oli määrittää unenaikaiset hengityshäiriöt aikaisempaa tarkemmin.

Progressiiviseen virtausrajoitukseen liittyi systemaattisesti $PtcCO_2$:n nousu, huolimatta siitä liittyikö kyseiseen jaksoon lisääntyneitä hengitysyrityksiä vai ei. Hengitysyritykset lisääntyivät kun $PtcCO_2$-arvo ylitti $PtcCO_2$-tasanteen. $PtcCO_2$ tasanne oli korkein $PtcCO_2$-taso, johon liittyi tasaista hengitystä. Progressiiviseen virtausrajoitukseen liittyi yleensä pieni SpO_2-lasku, mutta näin ei tapahtunut systemaattisesti.

Tietyt $PtcCO_2$-tasot liittyivät tiettyihin uniapneatyyppeihin. Sentraalisen ja sekatyyppisen uniapnean aikana $PtcCO_2$ oli samalla tasolla kuin valveen aikana. Obstruktiivisen uniapnea ja hypopnean aikana $PtcCO_2$-taso puolestaan ei eronnut tasaisen yöllisen hengityksen $PtcCO_2$-tasosta. Tasaisen virtausrajoituksen aikainen $PtcCO_2$ puolestaan oli korkeammalla kuin tasaisen hengityksen $PtcCO_2$-taso, mutta SpO_2 eroa ei havaittu näiden kahden jakson välillä.

Raskaana olevat eivät eronneet verrokeista unenaikaisten hengityshäiriöiden suhteen. Virtausrajoitus, kuorsaus, apnea-hypopnea indeksi (AHI) sekä 3%: n SpO_2 lasku (ODI3) olivat yhtä alhaisia molemmissa ryhmissä. Raskaana olevilla esiintyi verrokkeja useammin $PtcCO_2$-käyrässä "piikkejä" (n = 78 vs 5). Näihin piikkeihin liittyi virtausrajoitusta ja hengityksen säätelyn muuttumista. Eri univaiheiden aikana $PtcCO_2$-tasoissa ei havaittu eroja ryhmien välillä, mutta $PtcCO_2$:n varianssi oli pienempi NREM-unen aikana raskaana olevilla.

$PtcCO_2$-mittaus on herkkä hengityksen muutoksille unen aikana. Uneen liittyvä hiilidioksidin nousu voidaan havaita $PtcCO_2$-mittauksella. Progressiiviseen virtausrajoitukseen liittyy $PtcCO_2$:n nousu ja $PtcCO_2$-tasot ovat yhteydessä sekä unen syvyyteen että uniapneatyyppeihin. Raskaudenaikaiset hengitysmuutokset voivat johtaa "$PtcCO_2$ -piikkeihin" joita ei ole aikaisemmin kuvattu.

CONTENTS

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
AI	Apnea index
BMI	Body mass index
CAI	Central apnea index
CPAP	Continuous positive airway pressure
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
$EtCO_2$	End-tidal carbon dioxide
FRC	Functional residual capacity
GABA	Gamma-aminobutyric acid
GG	Genioglossus muscle
HD	High-drive
HI	Hypopnea index
LM	Leg movements
MAI	Mixed apnea index
NonHD	Non-high-drive
NREM	Non-rapid eye movement sleep
OAI	Obstructive apnea index
OSA	Obstructive sleep apnea
$PaCO_2$	Partial pressure of carbon dioxide in arteries
PaO_2	Partial pressure of oxygen in arteries
Pcrit	Critical closing pressure of the upper airway
PLM	Periodic leg movements
$PtcCO_2$	Partial pressure of transcutaneous carbon dioxide
RDI	Respiratory disturbance index
REM	Rapid eye movement sleep
RERA	Respiratory effort-related arousal
RTN	Retrotrapezoid nucleus

SaO_2	Arterial oxyhemoglobin saturation
SCSB	Static-charge-sensitive bed
SpO_2	Arterial oxyhemoglobin saturation measured with pulse oximetry
SDB	Sleep-disordered breathing
T_i	Inspiratory time
TP	Tensor palatini muscle
TST	Total sleep time
UARS	Upper airway resistance syndrome
V_E	Minute ventilation
VLPO	Ventrolateral preoptic nucleus
VRG	Ventral respiratory group
V_T	Tidal volume
WASM	World Association of Sleep Medicine

ORIGINAL PUBLICATIONS

Publication I Rimpilä V, Saaresranta T, Huhtala H, Virkki A, Salminen AV, Polo O. Transcutaneous CO_2 plateau as set-point for respiratory drive during upper airway flow-limitation. Respir Physiol Neurobiol. 2014 Jan 15; 191:44-51. doi: 10.1016/j.resp.2013.10.014. Available online: 2013 Nov 4.

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Publication III Rimpilä V, Jernman R, Lassila K, Uotila J, Huhtala H, Mäenpää J, Polo O. Upper airway flow limitation and transcutaneous carbon dioxide during sleep in normal pregnancy. Sleep Med. 2017 Aug;36:67-74. doi: 10.1016/j.sleep.2017.05.005. Available online: 2017 May 29.

1 INTRODUCTION

Sleep-disordered breathing (SDB) is a major health problem (Peppard, et al. 2013). It is commonly assessed with apnea-hypopnea index (AHI), which describes how many repetitive complete or partial upper airway closure events occur on average within an hour of sleep. This index forms the basis for obstructive sleep apnea (OSA) diagnosis. OSA is associated with reduced quality of life, numerous comorbidities as well as increased mortality. (Punjabi, et al. 2009)

However, even with low AHI, some patients are highly symptomatic and benefit from SDB treatment and adhere to it (Anttalainen, et al. 2007). This implies that AHI cannot be used to describe the full spectrum of SDB. In fact, events with sustained partial upper airway obstruction without arousals or desaturations are not considered to be important. Clinical significance and definitions for partial upper airway obstruction are not well established. While an apnea is defined as complete absence of breathing, it is difficult to establish a solid definition for non-apneic abnormal breathing (Pamidi, et al. 2017).

In addition, measurement of oxyhemoglobin saturation (SaO_2 and SpO_2 when measured with pulse oximetry) is a standard procedure in the assessment of SDB but the measurement of CO_2, which has the major role is respiratory control, is seldomly performed. In this regard, it becomes difficult to understand why SDB has a certain phenotype if major controller and outcome of ventilation is not monitored. An estimate of arterial CO_2 ($PaCO_2$) can be acquired by using transcutaneous carbon dioxide measurement ($PtcCO_2$) (Storre, et al. 2011). $PtcCO_2$ can be used continuously and nocturnal $PtcCO_2$ profile becomes available.

Our aim was to understand how $PtcCO_2$ is affected by SDB. Specifically, we investigated whether respiratory effort during inspiratory flow-limitation was associated with specific $PtcCO_2$ threshold. In addition, association between $PtcCO_2$ and different subtypes of SDB was investigated. SDB can have detrimental effects during pregnancy and the effects of partial upper airway obstruction on $PtcCO_2$ were studied during final trimester in healthy pregnant women and controls.

2 REVIEW OF THE LITERATURE

2.1 Sleep and breathing

2.1.1 Sleep

Some form of rest is vital to most if not all organisms, which speaks for a very early origin in evolution. The main function of sleep/rest could therefore be linked to most primitive functions of an organism such as energy metabolism. (Porkka-Heiskanen, et al. 2002) In humans, the two-process model of Borbely has been proposed to explain the timing, depth, and duration of the sleep (Borbely. 1982). Circadian control, which is called process C, incorporates the time of day to the model, i.e. falling asleep is more likely to occur at night. This process is strongly influenced by the light exposure. Homeostatic control, process S, includes the duration of wakefulness prior to sleep, i.e. the longer an individual stay awake, the more the propensity to fall asleep increases. (Borbely. 1982) The circadian rhythm (process C) is generated by the suprachiasmatic nucleus (Saper. 2013).

Sleep is traditionally divided into different stages. Main types are rapid eye movement (REM) sleep and non-rapid eye movement sleep (NREM). NREM is also subdivided into different stages according to frequency and phenomena observed in electroencephalogram (EEG) during polysomnography (PSG) (Rechtschaffen, Kales. 1968, Iber, et al. 2007). Sleep structure is commonly assessed with 30 second epochs, which are used to build sleep stage profile (hypnogram) for the night. Normally the deepest sleep is observed in the beginning of the night and periods of NREM and REM sleep form cycles that repeat three to five times during the night (Dogas, et al. 2014).

Physiologically wakefulness is maintained by neural pathways that originate from the brainstem. Two major pathways have been identified. The first branch originates from the upper brainstem and projects to the thalamus. These neurons are active during wakefulness and REM, which are characterized by cortical activity and become much less active during NREM sleep. The second branch originates from the upper brainstem and the caudal hypothalamus. These neurons project to the

lateral hypothalamus and basal forebrain, activating the neurons throughout the cerebral cortex. Lesions in these areas can cause narcolepsy or profound sleepiness and coma. (Saper, et al. 2005)

Sleep is promoted by the ventrolateral preoptic nucleus (VLPO), which is located in the anterior hypothalamus and is active during sleep. Neurons in VLPO project to the hypothalamus and nuclei in the brainstem, which are involved in arousal and wakefulness. VLPO neurons contain inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and galanin. Lesions in this area reduce the amount of sleep more than 50%. VLPO is innervated by the nuclei in brainstem, and both noradrenaline and serotonin inhibit the activity of VLPO neurons. (Gallopin, et al. 2000)

2.1.2 Respiratory neurons and control of breathing

Although seemingly simple, breathing is a complex activity of dedicated neurons and adjacent muscles. In humans and mammals in general, the main respiratory centers are located in the medulla (Lahiri, Forster. 2003). The most important group of these is the ventral respiratory group (VRG). The rostral VRG contains the Bötzinger complex, which is active during expiration as well as the pre-Bötzinger complex, which acts as a pacemaker. A group of inspiratory neurons is located caudally in the pre-Bötzinger complex, and this group innervates the spinal motoneurons, which control the activity of the diaphragm and external intercostal muscles. Nucleus ambiguus contains the laryngeal motoneuron cell bodies, and it is located next to this part of the VRG. Moving further caudally is the expiratory region, which projects axons to spinal motoneurons that control the abdominal and internal intercostal muscles. The VRG extends to spinal cord, and groups of inspiratory neurons are found (group C2 and C3). Yet another group of cells called dorsal respiratory group is found in the medulla, which contains inspiratory neurons and receives input from laryngeal and pulmonary receptors. Peripheral and central respiratory inputs are integrated in the pons (pontine respiratory group), which projects to respiratory neurons in the medulla. (Lahiri, Forster. 2003)

2.1.2.1 Chemoreceptors

The carotid body is considered to be the most important peripheral chemoreceptor although other sites are also found in the aorta (Kumar, Prabhakar. 2012, Nurse.

2014). Only the carotid body will be discussed here. Carotid bodies are located bilaterally in the common carotid arteries at the bifurcation to internal and external carotid arteries. Carotid bodies are very small (2 to 3 mm in man), but have probably the greatest blood flow per unit mass in the body (Kumar, Prabhakar. 2012). The carotid body is considered to be primarily an oxygen sensor, but the afferent activity of the organ is modulated by a prevailing pH/CO_2 level (Nurse. 2014).

Afferent activity of the carotid body is not linear. Hypoxia causes hyperbolic response curve with decreasing partial pressure of oxygen (PaO_2). In addition, afferent activity is not completely inhibited with hyperoxia. Contrary to O_2, CO_2 has a threshold value around 20 mmHg below which the afferent discharge disappears during normoxia. If PaO_2 is reduced, the CO_2 threshold value is also decreased. In the physiological range, the afferent discharge for CO_2 is linear and a plateau is reached around 70 to 80 mmHg. However, if PaO_2 is decreased from normoxia, the discharge is increased. (Kumar, Prabhakar. 2012)

Chemoreception that occurs within the brain is commonly referred as central chemoreception. The main functions are the regulation of $PaCO_2$ and regulation of pH. It is generally thought that pH is the main signal for chemoreception. (Nattie, Li. 2012) A Number of different sites within the brain are sensitive to CO_2/pH changes, but retrotrapezoid nucleus (RTN) is the most important since the elimination of two proton receptors (TASK-2 and GPR4) within these cells leads to profound reduction in central chemoreflex. RTN has multiple projections to respiratory neurons, namely to VRG, Kölliker-Fuse, lateral parabrachial nucleus, and nucleus tractus solitarius, which are responsible for expiratory and inspiratory motoneuron activity as well as respiratory rhythm generation. (Guyenet, Bayliss. 2015)

2.1.3 Upper airway

The primary event causing the SDB is the narrowing or full closure of the upper airway (Remmers, et al. 1978). Anatomically, this structure spans from the nares down to the level of epiglottis. In humans, this anatomical structure contains a relatively high amount of soft tissue, which is supported by a limited number of rigid structures. For these reasons, the upper airway is actively kept open by the upper airway dilator muscles. (Wilkinson, et al. 2008) Especially during wakefulness, the upper airway control needs to adapt various activities such as speaking, sneezing and coughing in addition to breathing, but during sleep, airway becomes more

susceptible to collapse as these behavioral influences are no longer active and the activity of the respiratory motoneurons declines (Kubin. 2016).

2.1.3.1 Upper airway anatomy and physiology

During inspiration, the diaphragm generates negative pressure which decreases the airway lumen if not overcome by force generated by the upper airway dilators (Henke, et al. 1990). The most studied airway dilators are the genioglossus (GG) muscle and the tensor palatini (TP) muscle (Pillar, et al. 2000, McSharry, et al. 2013). The GG is an inspiratory active muscle with tonic and phasic activity, and it has been shown that single motor units in the GG start to fire before the single motor units of the diaphragm (Butler, Gandevia. 2008), providing airway support during inspiration. The GG also responds to negative airway pressure (Horner, et al. 1994). Negative pressure in the airway activates the mechanoreceptors in the larynx (de Carlos, et al. 2013), which reflexively increases GG activity (Mathew, et al. 1982, Horner, et al. 1991, Fogel, et al. 2003, Carberry, et al. 2015). Upper airway patency is not solely determined by the activity of upper airway dilators, but it is also dependent on the anatomy of the upper airway (Chen, et al. 2016). An increased neck circumference correlates with the presence of snoring and sleep apnea (Stradling, Crosby. 1991), indicating that an excessive amount of soft tissue reduces the airway size. In a magnetic resonance imaging study, tongue volume was significantly larger in OSA patients (Lam, et al. 2005). Also, bone structures such as a posterior position of the mandible may limit the airway size and predispose to airway collapse (Jamieson, et al. 1986). A concept of critical closing pressure (Pcrit) has been developed in order to characterize the patency of the upper airway to keep open (Schwartz, et al. 1988). In a healthy individual, the critical closing pressure during passive condition is around -5 cmH2O (Isono, et al. 1997). This means that when the airway muscles are not responding, a negative pressure is needed to close the airway, and therefore at a normal atmosphere (zero pressure difference) the airway stays open.

Pregnancy proposes an added challenge for upper airway. Reduced lung volume increases the upper airway collapsibility (Owens, et al. 2010). The upper airway is affected by increased adipose tissue related to weight gain. Mucosal edema may also be present, which could be the result of estrogen (Hegewald, Crapo. 2011) or increased blood volume (Sanghavi, Rutherford. 2014). In addition, progesterone stimulates breathing, which could be destabilizing, but it also increases the GG activity under inspiratory resistive load, which on the other hand is stabilizing

(Popovic, White. 1998). However, despite pregnancy-related weight gain, a normal singleton or multiple pregnancy does not predispose to SDB (Brownell, et al. 1986, Nikkola, et al. 1996, Maasilta, et al. 2001).

2.1.4 Effects of sleep on breathing

Sleep is associated with reduced ventilation (hypoventilation) and therefore imposes a challenge to ventilatory control stability and homeostatic regulation of O_2 and CO_2 transport (Dempsey, et al. 2004). Areas within the brain that are responsible for wakefulness and sleep are anatomically linked to those responsible for control of breathing (Nattie, Li. 2010, Nattie, Li. 2012). Therefore, state changes are linked to changes in ventilation and vice versa. During sleep, the activity of "wakefulness"-neurons is greatly reduced as reviewed by Saper (Saper, et al. 2010), which leads to reduced ventilatory output as well as reduced sensitivity for blood gases (Nattie, Li. 2010). These normal physiological processes predispose to SDB.

During NREM sleep the activity of the respiratory neurons decrease. This is presumably caused by the reduced activity of noradrenergic and serotonergic neurons in the pons and medulla as well as histamine and orexins in addition to increased activity of GABA-ergic neurons (Kubin. 2016). One study showed that 87% of studied respiratory neurons were less active during NREM. In addition, populations of "strong" and "weak" respiratory neurons were found, and it was discovered that weak cells reduced their activity more than strong cells during NREM (Orem, et al. 1985).

On average, the respiratory neurons located in the brainstem are more active during REM than during NREM. Cholinergic, GABA-ergic, and glutamate containing neurons are active during REM. A large breath variability during REM occurs in parallel with other REM specific phasic phenomena, such as muscle twitches and rapid changes in heart rate and blood pressure (Kubin. 2016).

In addition, during wakefulness, the orexinergic neurons in the lateral hypothalamus stimulate neurons in the RTN and rostral medullary raphe, which probably contributes to the wakefulness drive for breathing. During sleep, the activity of orexinergic neurons is inhibited, which leads to decreased activity of the connected areas and reduced chemosensitivity and ventilatory output (Nattie, Li. 2010, Nattie, Li. 2012).

During sleep onset, the minute ventilation (V_E) decreases and the onset of this change occurs before stage 2 sleep. Most of the reduction results from the decrease

in tidal volume (V_T) (Colrain, et al. 1987). Furthermore, ventilation during sleep is characterized by instability if changes between sleep stages occur frequently. EEG frequency change from alpha (8-12 Hz) to theta (3-7 Hz) is characterized by reduction in ventilation and vice versa. The number of breaths during state changes has an effect on ventilatory response, i.e. the longer time spent in theta, the bigger the ventilatory response when switching to alpha, possibly due to a $PaCO_2$ increase. Similarly, going from alpha to theta, the ventilation change decreases parallel to alpha duration, possibly reflecting the ventilatory overshoot in the alpha state which attenuates with time. (Trinder, et al. 1992)

The transition from wakefulness to NREM-sleep has varying effects on the upper airway dilators. Studies that looked at the finite transitions from alpha to theta demonstrate that there is a sudden drop in total inspiratory electromyography (EMG) activity in the GG and the TP of which the GG recovers within a couple of breaths and exceeds the baseline EMG, while the TP EMG decreases further. (Worsnop, et al. 1998) It was later shown that it is the inspiratory motor units that cease to fire at sleep onset (Wilkinson, et al. 2008). Altogether, upper airway resistance increases during sleep (Henke, et al. 1990). The resistance is increased both in non-snorers and snorers during sleep, whereas inspiratory flow rates are reduced and maximal resistance is increased along with deepening sleep only in snorers (Skatrud, Dempsey. 1985). When sleep stages are considered, a recent study shows that the GG activity (peak and tonic EMG) is the highest during wakefulness, followed by slow wave sleep (SWS) and stage N2 sleep, and lowest during REM sleep. The TP EMG is decreased during sleep with no difference between sleep stages (N2, SWS and REM) (Carberry, et al. 2016). Increased GG activity during SWS (McSharry, et al. 2013) has been attributed to increased reflex activity (Hicks, et al. 2017). When external negative pressure is applied with an iron lung, the GG activity is increased during wakefulness but diminished in NREM sleep (Fogel, et al. 2003), indicating that the negative pressure-reflex (a reflex that activates the muscles of the airway to prevent collapse) in general is diminished during sleep. Specifically, the reflex diminishes at sleep onset as a function of sleep depth when transitions from alpha to theta EEG frequency occur (Gora, et al. 1998). During REM, the negative pressure-reflex is reduced even more (White. 2005).

Also, lung volume contributes to upper airway collapsibility. During sleep, the functional residual capacity (FRC) is reduced (Hudgel, Devadatta. 1984), and it has been shown that peak and tonic GG EMG activities were increased with a lower lung volume. However, despite this activation of the GG muscle the pharyngeal collapsibility increased (Stanchina, et al. 2003).

Altogether, reduced neuronal activity of the respiratory centers as well as chemoreceptors along with the upper airway dilators makes the airway more susceptible to collapse. Airway patency becomes more dependent on the anatomical properties, as part of the dilator muscle activity is lost during sleep. As a result, ventilation is reduced and slight CO_2 retention occurs.

2.2 Sleep-disordered breathing

2.2.1 Definitions and scoring

Sleep-disordered breathing is an umbrella term for various forms of respiratory disturbance that are encountered only during sleep (Mohammadieh, et al. 2017). A spectrum of these disturbances varies from minor inspiratory flow-limitation, which reduces the maximum flow during one breath, to a severe obstructive sleep apnea characterized with upper airway closure for extended periods of time in parallel with a severe hypoxia and hypercapnia (Berger, et al. 2000), frequent arousals and blood pressure changes throughout the night (Peppard, et al. 2013, Randerath, et al. 2018).

In clinical practice, common criteria to address SDB is that provided by the American Academy of Sleep Medicine (AASM) (Iber, et al. 2007, Berry, et al. 2012). These scoring criteria are different for adults and children and only criteria that apply for adults are presented here. For an apnea event the criteria states that there should be an at least 90% drop in the flow sensor from the pre-event baseline and the duration of the event must be 10 seconds or more. In addition, apnea is classified as obstructive, mixed or central according to the presence or absence of respiratory effort. If respiratory efforts are present throughout, the event is labeled "obstructive". If there are no respiratory efforts during the apnea, the event is labeled as "central". An apnea is scored "mixed" if there is no respiratory effort in the beginning, but efforts emerge before the end of the apnea. For hypopnea (reduction, rather than absence of airflow) rules exist, but there is a continuing debate as to how these events should be defined. Currently, it is stated that in order to score hypopnea, there should be an at least 30% reduction in flow amplitude from the pre-event baseline, the event duration is 10 seconds or more, and the event is associated with a 3% oxygen desaturation from baseline or is associated with arousal. (Berry, et al. 2012) Different criteria yield different AHI values, which in some cases determine whether a patient receives reimbursement for treatment or not. The AHI is

determined by counting the number of apnea and hypopnea events together and dividing it by the hours of sleep. It is usually thought that the AHI should be more than 5 in order to be considered abnormal. AHI ≥ 5 and < 15 is considered mild sleep apnea, AHI ≥15 but < 30, moderate sleep apnea and severe sleep apnea when index is ≥ 30.

A Class of events that does not fulfill the criteria for apnea or hypopnea may be called respiratory effort-related arousals (RERAs). RERAs are defined as respiratory events with increasing respiratory effort or flattening of the inspiratory signal denoting flow-limitation, which leads to arousal. Event duration is at least 10 seconds. (Iber, et al. 2007) Previously (Iber, et al. 2007), the use of esophageal manometry was the preferred method to determine respiratory effort, which greatly reduced the number of centers which would analyze this type of event, although inductance plethysmography could be used also. Snoring is part of the SDB continuum and three methods are recommended by the recent AASM manual: acoustic sensor, piezoelectric sensor or nasal pressure transducer (nasal cannula). (Berry, et al. 2017) Nasal cannula however had limited sensitivity compared to two other methods (Arnardottir, et al. 2016). Scoring RERA and snoring remains to be optional in clinical practice as their clinical significance is not completely resolved. The approach of counting the AHI seems straightforward, but the problem is that it does not recognize individuals who are affected by partial upper airway obstruction which does not fit into hypopnea or RERA criteria. The respiratory disturbance index (RDI) may be counted as the sum of AHI + RERA. However, this metric is not commonly used, and a number of different definitions for the RDI has been used, which has been confusing. (Berry, et al. 2012)

2.2.2 Prolonged partial upper airway obstruction, inspiratory flow-limitation and snoring

The evolution of pulse oximeters in the 1970s made sleep apnea a visible and potentially serious disease with repetitive episodes of desaturation. The innovation of nasal continuous positive airway pressure (CPAP) made sleep apnea a treatable condition. These innovations resulted in great interest in diagnosing and treating patients with increased AHI.

The innovation of the static-charge-sensitive bed (SCSB) in Finland in the 1980s (Alihanka, et al. 1981) aroused interest in another form of sleep-disordered breathing, which was called partial upper airway obstruction. These events associate

with increased respiratory effort and have a characteristic high frequency movement signal (spiking) (Polo, et al. 1991, Himanen, et al. 2018). Since these episodes could not be counted as any index such as the AHI and were not associated with arterial oxyhemoglobin desaturation, they were not considered severe and symptomatic enough to be treated. These episodes were medically neglected as "simple snoring". However, research interest in non-apneic form of sleep-disordered breathing has continued alongside conventional sleep apnea for at least 30 years (Polo, et al. 1989, Pamidi, et al. 2017). Research has demonstrated that prolonged partial upper airway obstruction alone, even in the absence of sleep apnea, may cause symptoms and respond and adhere to CPAP therapy (Anttalainen, et al. 2007). In fact, in women the excessive daytime sleepiness and daytime fatigue have been found related to snoring (but not to the AHI) independent of the AHI, age, obesity, smoking or sleep parameters (Svensson, et al. 2008). Self-reported snorers are also three times more likely to report excessive daytime sleepiness when compared to non-snorers (Zielinski, et al. 1999). A Recent study by Schöbel suggests that snoring was associated with lower baroreceptor sensitivity and reduced baroreceptor gain indicating reduced parasympathetic tone during the daytime (Schöbel, et al. 2014).

Partial obstruction is a common finding and similar concepts have evolved in other countries, including the upper airway resistance syndrome (UARS) and upper airway flow limitation, which are not completely overlapping with prolonged partial upper airway obstruction. UARS was initially described as repetitive respiratory arousals with increased respiratory efforts (Guilleminault, et al. 1993). As a term, flow limitation encompasses different conditions irrespective of the concomitant respiratory drive. Whether a mild OSA should be treated is still an open question (McNicholas, et al. 2016), with a notion that at least those who are symptomatic should be treated (Engleman. 2002). The distinction in concepts is crucial because mild OSA means a low AHI (usually 5 – 15/h), which by itself does not tell anything about the amount of partial obstruction during the night.

Contrary to sleep apnea, prolonged partial obstruction is harder to quantify. Apneic or cyclic episodes in general are easily counted, whereas in partial obstruction, a measure of inspiratory flow amplitude, V_T, V_E or effort measurement is needed. Unfortunately, reliable measurement of these parameters makes the recording technically more challenging. Prolonged partial obstruction is not commonly reported and remains to be largely undiagnosed (Anttalainen, et al. 2016). In sleep studies, pulse oximetry is used to assess adequate ventilation, whereas CO_2 is usually not measured. This is problematic because during partial obstruction, ventilation is sufficient to maintain relatively normal oxygen levels, but $PaCO_2$ levels

may increase and lead to increased ventilatory efforts (Rauhala, et al. 2007). It has also been shown that sleepiness is associated with snoring, rather than with oxygen dips (Stradling. 1995). When CPAP was titrated so that also flow limitation was eliminated in addition to apneas, hypopneas and snoring; smaller scatter in vigilance parameters was observed (Meurice, et al. 1998). A population study from Brazil showed that only 5% of asymptomatic individuals will have more than 30% total sleep time with inspiratory flow limitation (Palombini, et al. 2013). Finally, even a low AHI is associated with an increased risk for hypertension (Peppard, et al. 2000). Whether these findings could be explained with the presence of partial obstruction and related increased work of breathing remains to be studied. Perhaps by combining the AHI with an index for flow-limited breaths with increased effort, it could be better addressed whether the symptoms of the patient are a result of SDB or not. Existing problems for disease definitions and practices were recently reviewed (Randerath, et al. 2018).

2.2.3 Sleep-disordered breathing during pregnancy

The prevalence for habitual self-reported snoring varies from 12% to 23% in pregnant women vs. 4% in non-pregnant premenopausal women (Loube, et al. 1996, Franklin, et al. 2000, Guilleminault, et al. 2000). The SDB risk during pregnancy is increased in obese pregnant women (Maasilta, et al. 2001, Pien, et al. 2014). In a large cohort study, SDB was associated with preeclampsia and hypertensive disorders after the effect of weight was controlled, suggesting a direct link between these conditions (Facco, et al. 2017). Prolonged flow limitation and partial upper airway obstruction are common during pre-eclampsia (Edwards, et al. 2001, Connolly, et al. 2001). It is associated with nocturnal blood pressure increase, but it is reversible with CPAP (Edwards, et al. 2000). SDB during pregnancy may lead to the delivery of infants that are small for gestational age (Pamidi, et al. 2016). Nasal CPAP treatment is safe and effective during pregnancy (Polo, Ekholm. 1995, Edwards, et al. 2000), but in order to evaluate the effect of SDB treatment on fetal and maternal outcomes, randomized controlled trials are needed (Pamidi, Kimoff. 2018).

2.2.4 Pathophysiology and mechanics of sleep-disordered breathing

A number of different factors determine whether an individual will have episodes of sleep apnea during different times at night. These factors include: 1) the anatomical

properties of the upper airway, 2) ventilatory control system, often modelled with loop gain, 3) neuromuscular responses to respiratory stimulation, and 4) the arousal threshold. (Wellman, et al. 2011, Owens, et al. 2015) It is now thought that determining the relative contribution of these factors in affected individuals will help to determine which kind of treatment modality would be most effective. For example, patients with a relatively non-collapsible upper airway (Pcrit, -5 to -2 cmH2O) had higher loop gain than patients with a clearly collapsible airway (Pcrit > -2 cmH2O) (Eckert, et al. 2013). However, determining these factors is generally not part of current clinical practice.

2.2.4.1 Anatomy

OSA patients as well as snorers have a smaller airway size compared to normal (Polo, et al. 1991), with the reduction occurring mostly in the lateral diameter of the airway. This reduction is best explained by an increased lateral pharyngeal wall width (Schwab, et al. 1995). In addition, the tongue area was also enlarged in apneic patients but not in snorers or those with a milder disease. Furthermore, the soft palate area was larger in the apneic patients but similar between snorers and controls. This effect was related to a longer length of the soft palate. The amount of subcutaneous fat was also higher in OSA patients as demonstrated with increased fat width both laterally and posteriorly, resulting in an increased neck size. (Schwab, et al. 1995) These anatomical differences render the airway of OSA patients more susceptible to collapse.

Obesity and SDB are tightly connected: increasing weight increased the amount of SDB events. The effects of obesity on SaO_2 desaturation was modeled, and it has been shown that the body mass index (BMI) is an independent predictor of desaturation severity, after controlling the effects of age, gender, sleeping position, event duration, and baseline SaO_2. It was also shown that the effects on desaturation are greater during REM compared to NREM. Also, the effect of V_T reduction increases with the BMI. (Peppard, et al. 2009)

2.2.4.2 Airway control

During sleep, the upper airway becomes vulnerable to collapse as outlined in section 2.1.4. Normally, this leads initially to decreases in V_T and V_E, but the effect of this mechanical load is fully compensated, and V_E as well as V_T are reserved. (Badr, et al.

1990) With inspiratory flow-limitation during sleep, the maximal flow is limited, and increases in effort only decrease the intra-thoracic pressure (Schneider, et al. 2009). Once an obstructive event has begun, the only way to increase the flow is to increase the activity of pharyngeal dilators, which is diminished during sleep (Younes. 2008). In order to compensate, inspiratory time (T_i) and breathing frequency are increased, and it has been shown that the inspiratory duty cycle (proportion of T_i of total ventilatory cycle duration) increases linearly as the upper airway obstruction worsens (Schneider, et al. 2009). Increases in frequency lead to increased dead space ventilation, which decreases the alveolar ventilation. However, in women, the frequency response is more pronounced than in men, but its effect is diminished due to a smaller dead space, resulting in comparable alveolar ventilation. The duty cycle and frequency responses vary between subjects, and they might help to determine the quantitative trait of the individual. (Schneider, et al. 2009) Upper airway obstruction increases the respiratory drive (Badr, et al. 1990).

During inspiration, negative intraluminal pressure is generated, which activates the genioglossus. Patients with OSA are able to recruit the GG muscle, but the recruitment is not adequate to keep the airway open (Fogel, et al. 2005). It was shown that in OSA patients the peak phasic and tonic EMG is higher during wakefulness, suggesting that the airway patency is compromised. Despite the increased activity, the supraglottic resistance was still higher in the OSA patients. Applying CPAP reduced the GG activity considerably in the patients while no effect was observable in controls. (Mezzanotte, et al. 1992) It is noteworthy that OSA patients do not necessarily have apnea events throughout the night, and spontaneous stable flow-limited breathing and snoring occurs. These periods are characterized by increased GG muscle tone, whereas TP activity or end-expiratory lung volume do not seem to play a role. GG activity is reduced during REM, which could explain the common notion that apnea episodes are more severe (in terms of SaO_2 drop) during REM. (Jordan, et al. 2009)

2.2.4.3 Control of breathing, loop gain and the role of CO_2 during sleep-disordered breathing

The respiratory system like many other systems in the body is controlled by feedback loops. Feedback systems have an inherent property to become unstable under certain conditions, and engineering concept of loop gain has been used to model the instability relating to sleep apnea. (Khoo, et al. 1982, Younes, et al. 2001) Effectively, loop gain describes the magnitude of the system's response. High loop gain leads to

a fast and effective response, whereas low loop gain gives a slower and more dampened response. (Khoo, et al. 1982) Loop gain has three important parts: controller gain, plant gain, and communication. In the respiratory system, the central and peripheral chemoreceptors constitute the controller gain, which determines the optimal ventilation in the given environment. Plant gain describes how the system performs these actions. In practice, plant gain describes the ratio between CO_2 change and ventilatory change, i.e. effectiveness of ventilation. Communication between these two occurs via circulation. It is important to note that the anatomy produces an inevitable delay to the system as it takes a few seconds from blood to travel from the lungs to the carotid body. In general, loop gain is low in healthy volunteers, and breathing is very stable during sleep. (Wellman, et al. 2003) Increased gains are present in OSA patients (Salloum, et al. 2010).

In order for ventilation to become unstable, there has to be a phase shift between the controller gain and plant gain (White. 2005). As stated above, this is a property of the respiratory system. In addition, it is required that the response to a stimulus such as hypercapnia or hypoxia is larger than the initial stimulus itself (ratio > 1). Under these conditions, the system produces an amplified response in the wrong time, and instead of dampening, the disturbance is also amplified, and the system cycles between extreme states such as episodes of apnea and hyperpnea.

There are a number of factors that have an effect on controller gain and plant gain. Plant gain is the ratio $\Delta CO_2/\Delta V_E$. Plotted ventilation (V_E) and $PaCO_2$ form a hyperbola at stable CO_2 production (Dempsey. 2005). If the chemoresponse remains unchanged, it holds that a change in ventilation that is needed to produce central apnea changes according to a prevailing CO_2 level. (Figure 1, panel A) This means that during hypercapnia (going right on the hyperbola), the ventilatory change needed to produce central apnea is reduced because the slope of the hyperbola is reduced. Consequently, the plant gain increases, reducing the system stability. The opposite is true during hypocapnia (going left), as the slope of hyperbola increases and a higher ventilatory change is required in order to reach an apneic threshold (a situation when central ventilatory output is zero and ventilation ceases). Some of the conditions that cause high plant are: high $PaCO_2$ as explained above, low cardiac output, low metabolic rate, low dead space, and low FRC (White. 2005).

Controller gain is the ratio $\Delta V_E/\Delta CO_2$, and it essentially describes the chemosensitivity. Plotted chemosensitivity forms a line in the V_E/CO_2 plot. Conditions such as hypoxia increase the controller gain, which means that the slope of the chemoresponse becomes steeper (Figure 1, panel B) (Dempsey. 2005). When the isometabolic hyperbola is used as a model, it can be seen that with a steeper

slope, a smaller change in ventilation is needed in order to reach the apneic threshold, and the system instability increases. Therefore, high loop gain conditions reduce $PaCO_2$ from the eupneic level more easily, which destabilizes the respiratory control and emphasizes the importance of the correct CO_2 level. A classic example of this is the Cheyne-Stokes breathing during heart failure, where the circulation time is increased (Tkacova, et al. 2001) and overt sympathetic activity increases the chemoreceptor activity, and a characteristic ventilatory pattern is seen where apnea and hyperpnea follow each other.

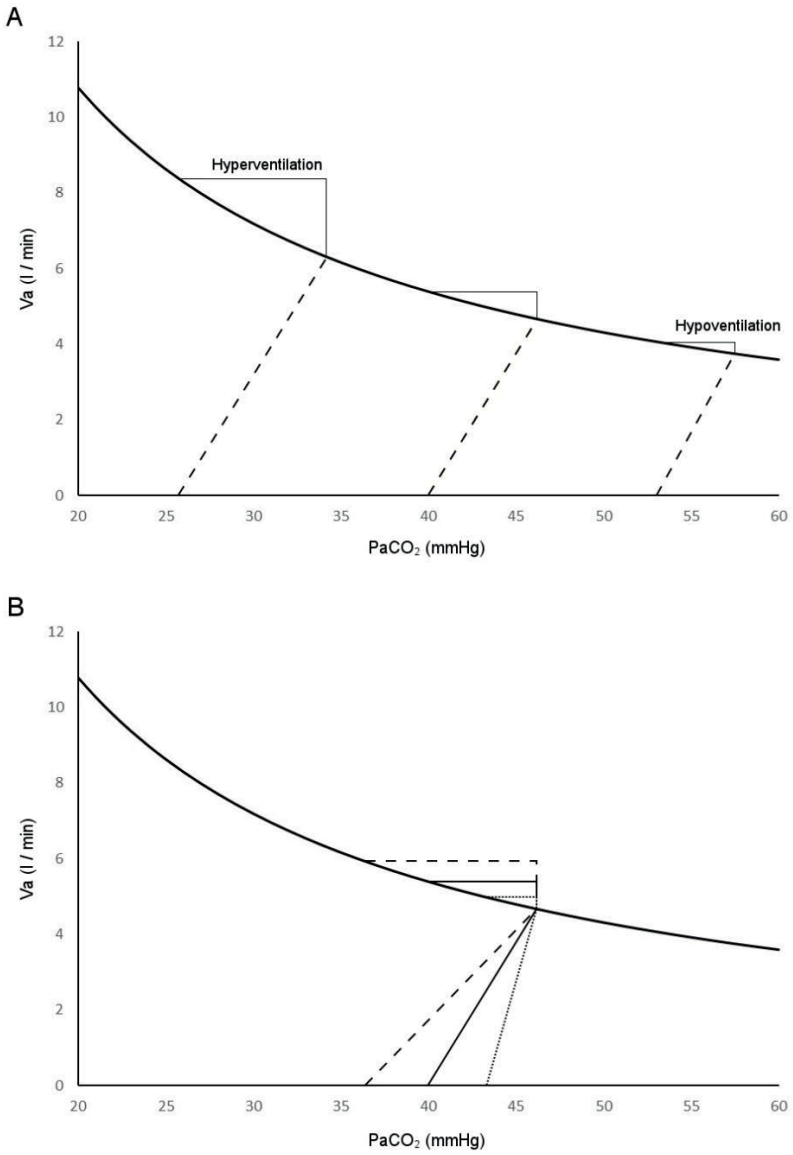

Figure 1. Visualization of loop gain. A) Plant gain, Changes in ventilation lead to movement on the metabolic hyperbola, which decrease (hyperventilation) or increase (hypoventilation) the plant gain. B) Controller gain, Changes in slope correspond to ventilatory change needed to cross the apneic threshold, thus linking the ventilatory sensitivity with stability of the ventilatory control. Image created according to data and concepts presented in Dempsey et al, Exp Physiol 2005, 90(1) 13-24.

The control of breathing plays an important role in maintaining the vicious cycle during sleep apnea. This applies both to obstructive apnea as well as central apnea.

During an apneic event, CO_2 accumulates and O_2 is consumed as usual, leading to increased respiratory drive. At the end of an apnea, airway is opened and hyperventilation occurs (Berger, et al. 2000). For ventilation, there are two important CO_2 levels; first is the eupneic CO_2 level which is the target level and synonymous to stable homeostasis. The other level is usually called an apneic threshold as it represents the CO_2 level below which ventilation ceases. The distance between these two is the CO_2 reserve. It follows that any condition which reduces the CO_2 reserve also increases the ventilatory instability. If loop gain is high, the hyperventilation drives $PaCO_2$ too low which leads to ventilatory inhibition, increasing the probability of having another apnea. (Salloum, et al. 2010) In addition, during sleep, hypocapnia associates with increased upper airway expiratory resistance. As a result, inspiratory flow-limitation is demonstrated with hypocapnia (Sankri-Tarbichi, et al. 2011).

In patients with severe sleep apnea, the CO_2 accumulation that occurs during an event may not be compensated with the resulting ventilatory overshoot even in the absence of overall hypoventilation that commonly occurs in sleep (Salepci, et al. 2015). The duration of the inter event interval may limit the effect of compensatory hyperventilation, which leads to CO_2 accumulation (Gislason, et al. 1989, Berger, et al. 2000). Also, patients with severe OSA are more prone to develop periodic breathing compared to patients with mild to moderate OSA when assessed with proportional assist ventilation, which increases the controller gain (Younes, et al. 2001). Tracheotomy can convert obstructive apneas to central ones as the obstruction is removed but the loop gain is still high. Obstructive apneas can transform into central ones if hypoxia is present. And conversely, increased oxygen levels can convert central apneas to obstructive ones (Longobardo, et al. 2008). Increased controller gains predispose both obstructive and central apneas (Salloum, et al. 2010). There was no difference in loop gain between N2 and N3 sleep in OSA patients, but loop gain during N2 sleep increased during the night (Landry, et al. 2018)

It is clear that CO_2 is an important respiratory controller if not the most important, and studies where inhaled gas levels are manipulated give insight to respiratory control. For example, CO_2 inhalation abolishes central apneas in congestive heart failure patients, while O_2 only has a modest effect. An increase in SaO_2 to a similar level as during administration of CO_2 did not increase $PtcCO_2$ or reduce apneic events. (Lorenzi-Filho, et al. 1999) Similarly, adding CO_2 to inhaled air almost completely abolishes central apneas in idiopathic central sleep apnea; the $PtcCO_2$ increase was 1.3 mmHg (39.3 to 40.6 mmHg) (Xie, et al. 1997). Isocapnic and hypercapnic treatment regimens reduce the AHI by approximately 30%, while

the hyperoxia response cannot be predicted from the controller or plant gain, CO_2 reserve or Pcrit. It can even lengthen individual apnea episodes. Non-responders (CO_2) had a narrower CO_2 reserve and smaller gains in addition to disadvantaged craniofacial anatomy. (Xie, et al. 2013) Minor hypercapnic exposure can be effectively used to treat refractory SDB as an adjunct to CPAP therapy (Thomas, et al. 2005). However, increasing CO_2 in the inspired air increases plasma noradrenaline compared to air (Andreas, et al. 1998). Also, high CO_2 levels (7.0%) increase muscle sympathetic nerve activity (Somers, et al. 1991). It was shown as early as in 1988 that CO_2 inhalation decreases the duration and frequency of obstructive apneas when 3 to 6% CO_2 is used. An increase in chin/chest wall EMG was observed, and it was postulated that CO_2 stabilizes the upper airway. Also, 50% oxygen causes lengthening of apneas, and there was a small decrease in phasic and tonic chin EMG. (Hudgel, et al. 1988) These studies show the critical role of CO_2 in the ventilatory control, although O_2 has a profound effect when hypoxia is severe enough. During obstructive event, an increase in the pump muscle activity cannot increase the flow, and pharyngeal dilator activity is needed. Therefore, metabolically the outcome of obstruction is determined by the ventilatory response of the pharyngeal dilators to changes in $PaCO_2$ and PaO_2. (Younes. 2008)

2.2.4.4 Role of arousal in sleep-disordered breathing

Arousals are an integral part of SDB, especially in obstructive conditions where upper airway patency is compromised and cannot be restored by simply increasing the respiratory effort. A review by Berry (Berry, Gleeson. 1997) showed that arousal occurs at a certain level of respiratory effort regardless of the stimulus (hypoxia, hypercapnia or added resistive load). Another study showed that not all obstructive apneas are resolved with arousal, but are followed by arousal (meaning that upper airway opening is provoking the arousal) or there may not be an arousal at all, which led to conclusion that arousals are not needed for upper airway opening and that the association is incidental. (Younes. 2004) These studies show that the threshold for recruiting the upper airway dilators is different from that of arousal. If the airway dilators are recruited, the arousal is not needed, but it may still occur since the information about blood gases is delayed and arousal may be triggered by the blood gas levels even though the airway is already open. In this situation, the arousal acts more as a destabilizing factor because the ventilatory response is more vigorous with arousal than without it, leading to an excessive CO_2 reduction, diminished respiratory drive, and reduced upper airway tone all of which predispose to

obstruction and may worsen the condition. (Eckert, Younes. 2014) Arousal threshold is not a fixed value, and a number of factors can increase it, such as: deeper sleep, prior sleep fragmentation, depressants (such as ethanol) and the presence of OSA. (Berry, Gleeson. 1997)

2.2.5 Consequences of sleep-disordered breathing

SDB has many negative effects on an individual level, and because the condition is fairly common, these effects are also seen on a population level. OSA increases the risk of stroke and death from any cause independent of known risk factors with a hazard ratio of 1.97. (Yaggi, et al. 2005) SDB is an independent risk factor for mortality, especially in men between 40-70 years. Nocturnal hypoxemia was an independent factor for mortality, whereas arousal frequency or central apneas were not. Men were also at risk of dying from coronary artery disease. (Punjabi, et al. 2009) Untreated severe (AHI > 30) SDB is associated with an increased risk of all-cause mortality with a hazard ratio of 3.0, and the results did not change after daytime sleepiness was taken in to account (Young, et al. 2008). A Busselton health study showed similar results; mild OSA (RDI 5 to 15/h) was not an independent risk factor for mortality, whereas moderate to severe (RDI > 15) was with an adjusted hazard ratio of 6.24 (Marshall, et al. 2008). A controlled observational study showed that in men with AHI > 30/h, the risk of a fatal or non-fatal cardiovascular event is increased. Simple snoring (AHI < 5) was not associated with increased risk. (Marin, et al. 2005) Incident cardiovascular disease is associated with worsening SDB during five years of follow-up if SDB is already present (Chami, et al. 2011). It is likely that OSA contributes to the development and progression of cardiovascular diseases such as hypertension through its physiological consequences which include: increased sympathetic activation, blood pressure fluctuation, decreased heart rate variability, increased intra-thoracic pressure, hypoxia-reoxygenation cycles, and hypercapnia. (Shamsuzzaman, et al. 2003)

2.3 Clinical methods

2.3.1 Transcutaneous carbon dioxide

The respiratory status of the patient is commonly measured with arterial blood gases. This measurement can be painful and it only provides a single value. Blood gases can, however, change rapidly in clinical situations and therefore continuous non-invasive measurements are of great interest. (Storre, et al. 2011) One of the methodologies is $PtcCO_2$. Commercially available $PtcCO_2$ sensors were introduced in the 80's and were mainly used in neonatology together with transcutaneous oxygen ($PtcO_2$) (Midgren, et al. 1984, Midgren, Hansson. 1987). Nowadays, $PtcCO_2$ measurement is used to accompany many clinical settings such as mechanical ventilation, bronchoscopy, and sleep studies (Eberhard. 2007). $PtcCO_2$ measurement is used to measure the partial pressure of carbon dioxide that diffuses through the skin (Clark, et al. 1992). Measured $PtcCO_2$ reflects the CO_2 tension at the level of epidermis and does not equal to $PaCO_2$. CO_2 penetrates the thin membrane on the sensor and changes the pH of the liquid used on the sensor. This pH change is measured and a partial pressure of CO_2 can be determined. $PtcCO_2$ measurement has an inherent time lag which is influenced by capillary volume and blood flow and tissue diffusivity. (Clark, et al. 1992) Measurement is also hindered when there is a strong peripheral vasoconstriction. Increasing the temperature shortens the response time, but may cause skin burns. 43°C seems to be a good compromise. (Nishiyama, et al. 2006)

$PtcCO_2$ measurement can give useful information regarding the control of breathing. $PtcCO_2$ levels from wakefulness to sleep according to sleep depth, being the lowest in stage 1 and the highest in REM sleep. (Andreas, et al. 1998, Holmedahl, et al. 2014) Accordingly, younger subjects are more sensitive to CO_2 than older ones since they present lower $PtcCO_2$ levels during wakefulness, SWS and REM sleep but the absolute changes between stages are similar between groups (Naifeh, et al. 1989). Postmenopausal women have a higher $PtcCO_2$ during sleep, compared to premenopausal women, which supports this finding (Aittokallio, J., et al. 2006). However, postmenopausal estrogen users have also higher $PtcCO_2$ levels during sleep compared to non-users, an unexpected effect which could be a result from peripheral vasodilation caused by estrogen since ventilatory and sleep parameters between groups are very similar (Aittokallio, J., et al. 2009). An increase in $PtcCO_2$ during sleep is characterized by flow-limitation and prolonged spiking on the Emfit

sensor, which is a marker of increased respiratory effort (Rauhala, et al. 2007). $PtcCO_2$ during OSA is higher than during central sleep apnea in patients with a heart failure (Tkacova, et al. 2001). In addition, patients with idiopathic central sleep apnea hyperventilate during wakefulness (Xie, et al. 1995). The treatment of hypercapnic OSA patients with non-invasive positive pressure ventilation (volume-cycled ventilator) reduces the sleep related $PtcCO_2$ increase (Piper, Sullivan. 1994). Nocturnal $PtcCO_2$ patterns can be used to predict vascular parameters such as flow-mediated dilatation and nitroglycerin-mediated dilatation as well as metabolic status (Aittokallio, J., et al. 2008, Virkki, et al. 2008, Aittokallio, J., Saaresranta, et al. 2009).

Results obtained from $PtcCO_2$ measurement are sometimes (Janssens, et al. 2001), but not always, concordant with $PaCO_2$. The limits of agreement can be too wide, and therefore the $PtcCO_2$ should not be used as a surrogate of $PaCO_2$ (Rauch, et al. 1999, Weaver. 2007). A study by Chin showed that $PaCO_2$ correlates with $PtcCO_2$ during hypercapnia, but not during normocapnia (Chin, et al. 1997). The correlation with capillary CO_2 appears to be good (Randerath, et al. 2010, Pinnola, Bastos. 2014). In patients with a respiratory failure undergoing non-invasive ventilation, $PtcCO_2$ has unacceptable wide limits of agreement; $PtcCO_2$ underestimates high $PaCO_2$ values (Kelly, Klim. 2011). Newer devices show a better correlation and limits of agreement to arterial $PaCO_2$ values than the TCM4 device (Storre, et al. 2011). This implies that the data from the new devices can be used as a surrogate of $PaCO_2$. Continuous nighttime monitoring allows detecting fluctuations in $PtcCO_2$, which are not detected with a single morning measurement of arterial blood gases (Storre, et al. 2011). Regardless of the correlation, the transcutaneous monitor measures PCO_2 in the heated skin and not the $PaCO_2$, and the measurement should be interpreted in that light (Stock. 1988). It could be feasible to use $PtcCO_2$ as a measure of tissue CO_2 level. Studies using $PtcCO_2$ in primarily OSA patients and healthy controls are shown in Table 1.

Table 1. Selected publications of SDB patients and healthy subjects with $PtcCO_2$ measurement

Author	Study design	Subjects (n, M/F)	Age (mean, y)	Condition	Findings	Comments
Salepci et al. 2015	Cross-sectional	n = 97, M/F = 59/38	47	OSA	Eucapnic OSA patients may have hypercapnia during sleep	Higher AHI during hypercapnia was evident (p = 0.078)
Pinnola et al. 2014	Cross-sectional	n = 53, M/F = 21/32	43	AHI < 5, healthy	Normative mean value for $PtcCO_2$ was 41.3 mmHg, with range of 32.4 - 49.5 mmHg	Drift corrections were not made
Randerath et al. 2010	Cross-sectional	n = 29, M/F = 12/17	35	Healthy	$PtcCO_2$ correlates closely with capillary CO_2	Drift not observed
Aittokallio et al. 2009	Cross-sectional	n = 18, M/F = 0/18	56	Healthy	Estrogen users have higher $PtcCO_2$ during night compared to non-users	Placebo-controlled study is needed
Aittokallio et al. 2009	Cross-sectional	n = 22, M/F = 0/22	55	Healthy	Nocturnal $PtcCO_2$ variables predicted metabolic variables	SaO_2 and demographic features were poor predictors
Tamisier et al. 2009	Prospective	n = 20, M/F = 14/6	25	Healthy	Intermittent hypoxia induced $PtcCO_2$ decrease and increased ventilatory responses and BP	Number of central apneas increased considerably
Aittokallio et al. 2008	Cross-sectional	n = 103, M/F = 0/103	46	Healthy	$PtcCO_2$ variables had greatest prediction accuracy for vascular impairment	SaO_2 features had weak predictive power
Virkki et al. 2008	Cross-sectional	n = 108, M/F = 63/45	53	suspected SDB	$PtcCO_2$ could be used to classify subjects according to their HDL and TSH levels	$PtcCO_2$ descend was an important predictor
Rauhala et al. 2007	Cross-sectional	n = 19, M/F = 14/5	46	OSA	$PtcCO_2$ increase was associated with increased activity (spiking) on Emfit sensor	Patients with spiking have tendency for hypercapnic respiratory failure
Aittokallio et al. 2006	Cross-sectional	n = 26, M/F = 0/26	n = 13, 46 n = 13, 56	Healthy	sleep related $PtcCO_2$ increase is greater in post- compared pre-menopausal women	$EtCO_2$ levels were not different between groups
Thomas et al. 2005	Cross-sectional	n = 6, M/F = 6/0	54	OSA	CPAP with added low concentration of CO_2 was effective in patients with severe mixed disease	CO_2 concentrations were 0.5% - 1.5%.
Tkacova et al. 2001	Cross-sectional	n = 12, M/F = 11/1	63	CHF with OSA/CSA	$PtcCO_2$ reduction associated with OSA shift to CSA	Reduced cardiac function and circulatory delay may explain this finding

Author	Study design	Subjects (n, M/F)	Age (mean, y)	Condition	Findings	Comments
Andreas et al. 1998	Cross-over, single-blind	n = 9, M/F = na	59	CHF with CSR	O_2 + CO_2 improves CSR	Sleep was not improved and plasma noradrenaline increased
Chin et al. 1997	Cross-sectional	n = 30, M/F = 29/1	53	OSA	$PtcCO_2$ increase correlated with $PaCO_2$ increase in hypercapnic but not in normocapnic patients	Hypercapnic patients had greater $PtcCO_2$ increase during sleep
Xie et al. 1997	Prospective	n = 6, M/F = 6/0	60	ICSAS	Apneas were abolished by adding CO_2 to inhaled air or increasing dead space	Patients were normoxic and mildly hypocapnic while awake
Xie et al. 1995	Cross-sectional	n = 18, M/F = 18/0	60, controls 61, patients	ICSA	Patients had lower $PtcCO_2$ levels during sleep and augmented CO_2 responses	Low CO_2 predisposes to respiratory control instability
Piper et al. 1994	Cross-sectional	n = 13, M/F = 9/4	54	OSA with hypercapnia	NIPPV for 7 to 18 days improved daytime blood gases and ventilatory control	Improved central respiratory drive is proposed
Fukui et al. 1993	Cross-sectional	n = 16, M/F = 16/0	52	OSA	$PtcCO_2$ levels were highest during REM sleep, but decreased with CPAP	No change in $PtcCO_2$ was observed during stage 2 sleep with CPAP
Naifeh et al. 1989	Cross-sectional	n = 34 M/F = 15/19	36, n = 17 70, n= 17	Healthy	In the elderly the hypercapnic ventilatory response does not decrease during sleep	Younger subjects have more sensitive CO_2 response compared to older subjects
Gislason et al. 1989	Cross-sectional	n = 22, M/F = 21/1	51	OSA	Each apnea associated with $PtcCO_2$ increase and long apneas caused CO_2 retention	Patients with lowest ventilatory response have highest CO_2 retention during sleep
Midgren et al. 1987	Cross-sectional	n = 33, healthy M/F = 21/11 n = 21, 23, 10, 15	15 – 74, Range	Healthy, OSA, COPD, scoliosis, LD	Sleep was associated with 0.8 kPa $PtcCO_2$ increase in healthy and OSA patients	Scoliosis was associated with 1.5 kPa increase
Midgren et al. 1984	Cross-sectional	n = 7, M/F = 6/1	41, OSA 64, CRI	OSA, CRI	$PtcCO_2$ increase was observed apnea patients	Supplemental oxygen increased the $PtcCO_2$ in CRI patients

Abbreviations: AHI: apnea-hypopnea index; BP: blood pressure; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CRI: chronic respiratory insufficiency; CSA: central sleep apnea; CSR: Cheyne-Stokes respiration; Emfit: electromechanical film; $EtCO_2$: end-tidal carbon dioxide; HDL: high density lipoproteins; ICSA/S: idiopathic central sleep apnea/syndrome; LD: lung disease; NIPPV; nasal intermittent positive pressure ventilation; OSA: obstructive sleep apnea; $PaCO_2$: arterial CO_2; $PtcCO_2$: transcutaneous CO_2; REM: rapid eye movement; SaO_2: oxyhemoglobin saturation; SDB: sleep-disordered breathing; TSH: thyroid-stimulating hormone.

2.3.2 Arterial oxyhemoglobin saturation

Oximeters have been standard equipment for PSG for decades, and they provide an easy, affordable and accurate way to monitor the relative amount of oxygen in the blood. The method is based on the difference in the absorbance of oxyhemoglobin and deoxyhemoglobin at a certain visible light and near-infrared wavelengths (Mendelson. 1992). Desaturation events that associate with apnea or hypopnea episodes are easily detected with oximeter.

Like all measurements, oximetry has its own caveats. Measurement works best when SaO_2 is above 90%. In these conditions, the measurement bias is below 2% and precision is above 97%. Below 90% the bias and precision worsen, which is of interest in patients with long apneas, where SpO_2 is reduced well below 90%. Low perfusion caused by vasoconstriction, or low cardiac output may also result in inaccurate SpO_2 values. Nail polish can interfere with the measurement, as well as movement of the measurement site, as reviewed by Jubran. (Jubran. 2015)

2.3.3 Airflow detection

The detection of an apnea is a relatively straightforward procedure both visually and with automated methods, if clear cut-offs are easily determined for absent flow. If the breathing is monitored with nasal cannula only, mouth breathing may still be present and breathing events may be mislabeled as apneas when they are actually hypopneas. The detection and characterization of inspiratory flow-limitation is even harder because it is a quantitative variable by nature. Factors that determine the presence of flow-limitation are the negative pressure generated by the lungs and the resistance in the upper airway (Henke, et al. 1990). Patients with SDB usually have an anatomically compromised upper airway (Schwab, et al. 1995) which increases the resistance leading to inspiratory flow-limitation. Nasal pressure is nowadays commonly measured with nasal cannula/prongs and transformed to nasal flow (Farre, et al. 2001). The determination of resistance would require the measurement of pressure from the upper airway, but these measurements are invasive and therefore not commonly used in clinical practice (Mansour, et al. 2004). Inspiratory flow-limitation can be detected visually from the nasal flow signal (Ayappa, et al. 2000), but it remains subjective and prone to errors. Various computational methods have been developed to detect flow-limitation and increase the accuracy (Aittokallio, T., et al. 2001, Mansour, et al. 2004, Morgenstern, et al. 2008). Developments of these methods are needed in order to determine the clinical correlates to inspiratory

flow-limitation. A nasal cannula and the pressure transducer system can be used to detect all types of SDB, and it is sensitive enough to detect the same events as esophageal manometry, having the advantage of being non-invasive (Ayappa, et al. 2000). Even though nasal cannula can provide good flow signal, it is still not quantitative. Amplitude of the signal may also be affected if the position of the cannula changes. Nasal secretions may interfere with the cannula and affect the signal. Low sampling frequency makes the assessment of snoring difficult and prone to errors, as reviewed by Arnardottir. (Arnardottir, Gislason. 2016)

3 AIMS OF THE STUDY

The aim of these studies was to determine how different types of sleep-disordered breathing affect the transcutaneous carbon dioxide measurement. Primary focus of CO_2 measurements has previously been the detection of hypercapnia caused by hypoventilation (Iber, et al. 2007, Berry, et al. 2012). It was already known that $PtcCO_2$ is sensitive for respiratory phenomena but more information was needed because the $PtcCO_2$ signal can be difficult to interpret. Ventilation is primarily controlled by CO_2 and the implementation of this information to SDB analysis is of interest. Anatomical and physiological changes occur during pregnancy, which predispose to SDB. We wanted to know if these changes are reflected in $PtcCO_2$ already during normal pregnancy. Our aim was also to develop a working model for SDB, which could helpful in research as well as clinical work. The following hypotheses were presented:

I It was hypothesized that there is an optimal level for $PtcCO_2$ during sleep. If that is the case then respiratory effort during flow-limitation should be different on different sides of this level.

II It was hypothesized that different types of SDB present at different levels of $PtcCO_2$. Aim of this study was to determine the association between $PtcCO_2$ and subtypes sleep apnea (central, mixed, obstructive), hypopnea, steady flow-limitation, wakefulness and normal breathing during sleep.

III It was hypothesized that pregnant women have more flow-limitation and snoring and that these would be associated with higher $PtcCO_2$ levels compared to non-pregnant controls. It was also hypothesized that sleep stage specific $PtcCO_2$ differences should be present between pregnant and controls given the altered physiology (anatomic changes, hormonal changes) during pregnancy.

4 SUBJECTS AND METHODS

Studies I and II were performed with retrospective data and therefore the approval of the ethics committee was not required for these studies. The protocol for Study III was approved by the ethics committee of the Tampere University Hospital district, and all participants provided an informed consent.

4.1 Subjects

4.1.1 Characteristics of the patients in retrospective studies (I and II)

The patients in these two studies come from a population with suspected SDB who were referred to the Tampere University Hospital to verify the suspicion. A cardio-respiratory sleep study was performed in order to find SDB. The patients' medical history was not used in these studies and only the information derived from the recording file was used.

For the first study (I), 425 cardiorespiratory sleep recordings from the time period between 3/2004 – 4/2007 were initially screened for the presence of inspiratory flow-limitation. 137 were selected for a detailed analysis, and data from 36 subjects was studied in detail. For the second study (II), data from 6/2005 to 5/2007 consisting of 555 patients was screened for the presence of normal breathing and sequences of apnea, hypopnea and flow-limitation. After screening, 44 patients with 88 sequences were studied in detail. These study populations overlap, but the scoring and data analysis was performed independently for each study.

4.1.2 Characteristics of the subjects in the prospective study (III)

A group of 18 healthy pregnant women was recruited from maternity clinics in Tampere region as well as from the antenatal outpatient clinic and the antenatal ward of Tampere university hospital. Inclusion criteria for the study were, age between 18

and 45, gestational age 33 ± 1, and a singleton pregnancy without fetal demise. Pre-eclampsia or other complications requiring monitoring were used as exclusion criteria. Twelve non-pregnant healthy women were recruited as controls from the Department of Obstetrics and Gynecology of the Tampere University Hospital, the medical school of University of Tampere and the Tampere University of Applied Sciences. Controls were included in the study if they were generally healthy and had a normal BMI.

4.2 Methods

4.2.1 Demographic measurements and obstetrical examination

For studies I and II, gender, age, and BMI were available from the sleep recording files. In the third study, initial weight, height, BMI, and blood pressure were collected from the maternity cards of pregnant subjects. In addition, ultrasound was performed to assess fetal movements, weight estimate, amniotic fluid index, and umbilical artery blood flow. Supine blood pressure and a urine test for protein and glucose were also analyzed.

4.2.2 Sleep studies

4.2.2.1 Cardio-respiratory sleep studies

Cardio-respiratory sleep studies included the measurements of SpO_2 (1 Hz, no filter), nasal flow (200 Hz, no filter) from the nasal cannula connected to pressure transducer, anterior tibial EMG(200 Hz, low frequency filter (LF) 10 Hz, high frequency filter (HF) 70 Hz), body position (1 Hz, no filter), respiratory movements from the uncalibrated thoracic and abdominal inductance plethysmography (10 Hz, no filter), snoring from piezoelectric sensor (200 Hz, no filter), and electrocardiogram (200 Hz, no filter). An Embletta recorder using the Somnologica software from Medcare Flaga hf (Reykjavik, Iceland) was used to record the signals. A TCM4 device (Figure 2) from Radiometer (Copenhagen, Denmark) was used to record $PtcCO_2$ (1 Hz, no filter) and $PtcO_2$ (1 Hz, no filter). A Custom written

software by PhD Jussi Virkkala (TCM4ebm) was used to import the data from the TCM4 device to Somnologica online.

Figure 2. A TCM4 device from Radiometer that was used in the studies to record the transcutaneous carbon dioxide and oxygen levels.

4.2.2.2 Polysomnography

PSG was performed in study III. EEG was recorded with eight channels (A1, A2, O1, O2, F3, F4, C3, and C4 referenced to Fz (200 Hz, LF 0.3 Hz, HF 35 Hz)), electrooculography (EOG) with 2 channels (200 Hz, LF 0.3 Hz, HF 35 Hz), submental EMG with 3 and tibialis anterior EMG with 2 channels (200 Hz, LF 10 Hz, HF 70 Hz). Nasal pressure was measured with a cannula (200 Hz, no filter) and respiratory effort with inductance plethysmography belts placed around the abdomen and chest (10 Hz, no filter). Body position was recorded with an accelerometer within the patient unit placed on the abdomen of the subject (1 Hz, no filter). An Embla recorder using the Somnologica software from Medcare Flaga

hf (Reykjavik, Iceland) was used to perform the PSG, and a TCM4 device was used to record $PtcCO_2$ and $PtcO_2$ (1 Hz, no filter). TCM4ebm was used for data import.

4.2.3 Scoring of the respiratory events, leg movements and $PtcCO_2$ plateau

Conventional scoring criteria for SDB (Iber, et al. 2007) with slight modifications were used in conjunction with the development of new scoring criteria for the purpose of the study. In the first study, hypopnea was scored when a 50% reduction of nasal flow was observed for 10 seconds and accompanied with a 3% desaturation from the pre-event baseline. In the second and third study, a 30% reduction of flow for 10 seconds was used to score hypopnea. No desaturation criterion was used, but desaturation for 3% or more was tabulated. Apneas were scored according to the AASM manual (Iber, et al. 2007).

Since there are no commonly accepted criteria how to score inspiratory flow-limitation (Pamidi, et al. 2017), such set of rules was developed for the first study. In the first retrospective study (study I), episodes of flow-limitation were included if progressive pattern of inspiratory flow-limitation was observed for at least 2 minutes. Two minutes was an arbitrary value, but it is considerably longer than an average hypopnea or flow limitation part of obstructive hypopnea usually. Progressive deterioration of flow contour was used as it was postulated that diminished flow would lead to decreased V_E and increase in $PtcCO_2$. The differentiation between episodes was based on respiratory effort measured with thoraco-abdominal bands (both signals viewed independently, combined signal of the two was not used); episodes with an increasing amplitude were marked as high-drive (HD) and episodes with a steady or decreasing amplitude were marked as non-high-drive (NonHD). Rounded flow contour was preferred at the beginning of episode, but not required as long as the flow-limitation was progressively increasing. The presence of snoring was used as a supportive criterion for increased respiratory effort for HD episodes (Figure 3). NonHD and HD scoring was done blind to $PtcCO_2$ signal. Sudden termination of the episode was required in order to have clear end for the episode.

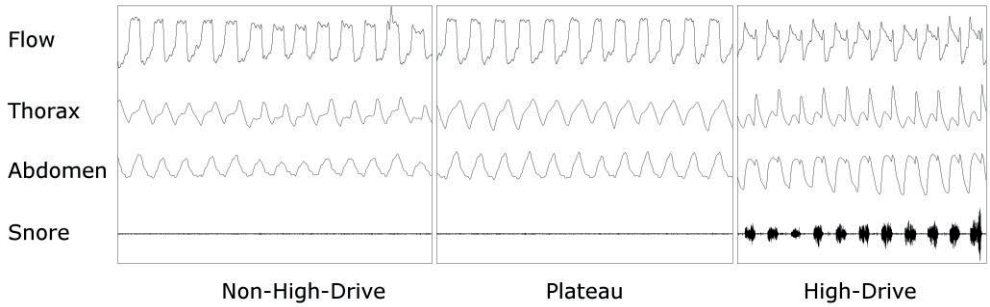

Figure 3. Characteristics of flow and effort patterns for flow limitation episodes determined in study I. Nasal cannula was used to determine the flow. Thoraco-abdominal inductance plethysmography was used to determine the respiratory effort. Plateau represents a breathing sequence during which the $PtcCO_2$ level remains stable and the breathing is minimally obstructed. Characteristic of Non-High-Drive (NonHD) event is shown on the left where the flow deteriorates but increased effort is not seen. Notice the change in abdominal pattern during High-Drive (HD) event on the right indicating increased effort. Mean $PtcCO_2$ values during NonHD, plateau and HD were 5.74 kPa, 5.75 kPa and 5.92 kPa, respectively. Reproduced with permission from Respir Physiol Neurobiol. 2014;191:44-51.

In the second study (study II), sequences of apnea and hypopnea were investigated. In order to include sequences that are sufficiently long to represent given SDB type, it was required that the sequence length is at least 5 minutes or contains ten or more individual respiratory events. Also, consecutive events within the sequence had to resemble each other in terms of ventilatory pattern and length so that 50% of the events had the same classification (central apnea, mixed apnea, obstructive apnea or hypopnea). Sequences were labeled according to the most frequent event type. In order to be included, the patient was required to have at least one of the mentioned apnea/hypopnea sequences, and also sequence of wake and steady breathing for reference. Sequences were scored blind to simultaneous $PtcCO_2$ signal.

In the third study (III), a proprietary scoring utility of Somnologica was used to score inspiratory flow-limitation. A default flattening index of 0.13 was used. Flow-limited and non-flow-limited breaths were determined for each sleep stage.

In the third study (study III), it was also noticed that pregnant subjects had distinctive $PtcCO_2$ peaks during sleep which are not seen in control subjects (or previous patient files). These peaks were considered worth reporting, and a set of rules to characterize the events and to perform a post hoc-analysis was established. The peaks seemed to have an amplitude of more than 0.1 kPa, and that was chosen as a cutoff point. In order to avoid scoring the effects of single episodes of apnea

and hypopnea, the event duration was given a minimum length of 90 seconds with no upper limit. In these populations long apneas or hypopneas are rare and flow-limitation is more common. Presence of flow limitation was determined manually for peak episodes. If episodes of apnea or hypopnea were detected, they were tabulated. The requirement for sleep was not strict, and an epoch of wakefulness was allowed, but two consecutive wake epochs led, however to exclusion from the analysis. REM sleep was excluded as it is common for $PtcCO_2$ to fluctuate during this state due to ventilatory instability. Arousals and respiratory arousals associated with the events were also scored. The start and end points of the events were visually determined to time points where the $PtcCO_2$ slope started to progressively increase and when the start value was reached again after the peak or slope returned to zero.

Leg movements (LM) and periodic leg movements (PLM) were scored according to the criteria of the World Association for Sleep Medicine (WASM) (Zucconi, et al. 2006) with the exception that the EEG criterion had to be omitted in cardio-respiratory studies. In the second study, LMs within 10 seconds on both sides of the apnea/hypopnea termination were excluded from the PLM index, as it was observed that leg movements synchronized with apneas beyond the limits described by Zucconi et al. (Zucconi, et al. 2006) and including these events to PLM index was thought to distort the index.

It was postulated that increased CO_2 during sleep combined with steady unobstructed breathing is a desired condition. The term "$tcCO_2$ plateau" was used to reflect this idea and it was based on the observation that in an overnight $PtcCO_2$ profile the $PtcCO_2$ is sometimes almost horizontal. In the first study, the plateau was defined as a stable breathing sequence for at least 2 minutes with a normal or near normal inspiratory flow contour with the highest $PtcCO_2$. Minor snoring was allowed. Plateau candidates were initially scored from overnight $PtcCO_2$ profile. The sequence closest to flow-limitation episodes was used in the analysis in the first study in case there were multiple stable sequences available. In the second study, a sequence of stable breathing with an at least 5-minute duration with the greatest stability was chosen, and the $PtcCO_2$ values during this period were assigned as "$PtcCO_2$ plateau". Unobstructed breathing was preferred, and only minimal flow limitation was allowed.

4.2.4 Data analyses

$PtcCO_2$ signals were analyzed with an R-based (Transient Pattern Analyzer, TPA) software developed by PhD Arho Virkki. The software version of the TCM4 device contained an error and caused the $PtcCO_2$ signal to oscillate.

In the first study, the $PtcCO_2$ signal was advanced 30 seconds in order to compensate the circulatory delay between the observed ventilatory event and blood gas change in the peripheral tissue. A linear regression line was fitted to the signal with the least squares method, and the start/end point was used in the analysis. The $PtcCO_2$ plateau was assigned 100% and relative values from the episodes were used in the analysis.

In the second study the $PtcCO_2$ signal was not adjusted because the analyzed sequences where longer and stable, and it was thought that an adjustment would only have a negligible effect. Since there are considerable inter-individual differences in $PtcCO_2$ values, wakefulness was set as 0 kPa and absolute differences (ΔkPa) between sequences were used in the analysis. The analysis was also performed with relative values by setting the wakefulness as 100%. In addition, the effect of using wakefulness or steady breathing as reference level was explored by setting the steady breathing ($PtcCO_2$ plateau) as 100%.

In the third study, $PtcCO_2$ was determined for each sleep stage. With sampling rate of 1 Hz, each sleep epoch produced 30 $PtcCO_2$ data points, which were then pooled to determine the median values for each sleep stage. For the flow limitation analysis, the $PtcCO_2$ signal was advanced 30 seconds because individual breaths were studied. Normal breathing and flow limitation were analyzed separately. All data points recorded during inspirations (1 to 3 per inspiration) received a $PtcCO_2$ value and sleep stage label. If less than 75 data points (seconds) were available for given condition, that sleep stage was excluded from the respiratory analysis. This was done in order to limit the effect of very short episodes of flow-limitation on overall results if a subject had only few detected flow limitations within a sleep stage.

In the first study, nocturnal mean, median and minimum values were determined for SpO_2. SpO_2 values in the beginning and in the end of each flow-limitation episode were collected. In the second study, median values were determined from stable breathing sequences (wakefulness, plateau/steady breathing and flow-limitation). For cyclic sequences, pre-event peak values of SpO_2 were determined and the nadir values and mean values of these per sequence were used in the analysis. Overnight SpO_2 mean and minimum values were determined as well. In the third study ODI3 and the overnight SpO_2 mean and minimum values were determined.

4.2.5 Statistical analyses

In the first study, three groups of patients were formed based on the presence of event types (1) only HD events, 2) only NonHD events and 3) both HD and NonHD present), and demographics were analyzed with the Kruskal-Wallis test and episode duration with the Mann-Whitney U-test. Body position, snoring, LM and PLM were treated as qualitative measures, and the Chi-Square test was used to assess the differences between NonHD and HD episodes. The presence of $PtcCO_2$ slope was analyzed with the one sample t-test, and the comparison between episodes slope with the Mann-Whitney U-test. $PtcCO_2$ comparison against the plateau was assessed with a pairwise t-test, and a linear mixed model was used to test whether the starting or ending levels of episodes differed from each other. Spearman's correlation was used to assess the connection between $PtcCO_2$ increase and SpO_2 decrease during episodes. SpO_2 change during the episodes was assessed with the Wilcoxon signed rank test, the Mann-Whitney U-test was used to compare the SpO_2 change between episodes, and a linear mixed model was used to test whether the starting or ending levels of episodes differed from each other. A paired samples T-test and Pearson correlation were used to compare nocturnal mean SpO_2 and plateau mean SpO_2.

In the second study, the effect of gender on $PtcCO_2$ was tested with the Mann-Whitney U-test and the effect of age with a univariate analysis of variance. The Kruskal-Wallis test with the Bonferroni correction was used to assess the $PtcCO_2$ and SpO_2 differences between sequences. Levene's test for equality of variances was used to test the effect of using wakefulness or steady breathing as a baseline for breathing sequences.

In the third study, the Mann-Whitney U-test was used to determine differences in age, BMI and PSG measures. The prevalence of $PtcCO_2$ peaks between groups was tested with Pearson´s Chi-Square test. The variance of $PtcCO_2$ during different sleep stages was tested with non-parametric Levene´s test.

SPSS (IBM SPSS statistics for Windows. Armonk, NY; IBM Corp.) versions 19, 20, and 24 were used to analyze the statistics. P-value of less than 0.05 was considered significant.

5 RESULTS

5.1 Patients and subjects

After screening, the final study population was 36 patients for the first study. Half of the patients had AHI less than 5/h. The mean age of this population was 48 years with a mean BMI of 27.7 kg/m^2. There were no significant differences in demographic variables between the three patient groups.

In the second study, data from 44 patients was analyzed after screening. The mean age was 53 with a mean BMI of 30.5 kg/m^2. The mean AHI was 21.8/h of which 13.4/h consisted of hypopnea. Study populations differ between studies I and II because in the first study the inclusion was based on presence of flow limitation events whereas in the second study the selection was based on the presence of apnea/hypopnea sequence.

The third study differed from the two other studies in that the subjects were all healthy. Altogether, eighteen pregnant women and twelve controls were studied. The controls were younger than the pregnant ones (26 vs. 30, $p < 0.001$), but had a similar BMI to pregnant women in the beginning of pregnancy (22.0 kg/m^2 vs. 21.7 kg/m^2, $p = 0.245$). Pregnant women were normotensive and had no proteinuria. Ultrasound examinations showed normal bioprofiles.

Table 2. Characteristics of patients and subjects from the three studies

	Study I	Study II	Study III	
			Pregnant	Controls
	Median (Min – Max)	*Mean*/Median (*SD*/IQR)	Median (Q1-Q3)	Median (Q1-Q3)
N (M:F)	36 (23:13)	44 (34:10)	18	12 (0:12)
Age	48 (26 - 74)	*52.8 (11.0)*	30 (26-36)	26 (24-31)
BMI (kg/m^2)	26.8 (20.5 – 41.4)	*30.5 (5.9)*	22.0 (19.0 – 29.4)	21.7 (18.8 – 25.4)
AHI (#/h)	4.9 (0 – 42.3)	*21.8 (13.2)*	1.6 (0.7 – 3.3)	0.8 (0.2 – 0.5)
AI (#/h)	0.8 (0 – 22.2)	*8.4 (8.4)*		
CAI (#/h)		*1.7 (2.9)*		
OAI (#/h)		*5.5 (6.2)*		
MAI (#/h)		*1.2 (2.9)*		
HI (#/h)	3.4 (0 - 40.7)	*13.4 (10.0)*		
ODI3 (#/h)			0.4 (0 – 2.1)	0.2 (0 – 0.4)
SaO_2 mean (%)	95.0 (88.3 – 97.6)	*93.8 (2.0)*	95.9 (91.5 – 96.3)	97.5 (96.1 – 97.9)
SaO_2 min (%)	84 (67 – 91)	*82.4 (6.4)*	93.0 (91.5 – 94.0)	94.5 (93.3 – 95.8)
$PtcCO_2$ wake (kPa)		5.18 (0.45)		
$PtcCO_2$ set-point/ plateau (kPa)	5.72 (4.84 – 6.73)	5.47 (0.61)		
PLM index (#/h)	4.9 (0 – 88)	10.9 (28.7)	2.4 (0 – 5.2)	0.5 (0 – 1.4)
LM index (#/h)	11.7 (1.6 – 94)			
FL index			11.3 (6.1 – 23.6)	10.10 (6.3 – 18.4)
Snore time			0 (0 – 0.33)	0 (0 – 0.08)

Mean values in study II are shown with italics. AHI: apnea-hypopnea index; Abbreviations: AI: apnea index; CAI: central apnea index; OAI: obstructive apnea index; MAI: mixed apnea index; HI: hypopnea index; ODI3: 3% oxyhemoglobin desaturation; SaO_2: oxyhemoglobin saturation; $PtcCO_2$: transcutaneous carbon dioxide; PLM: periodic leg movement: LM: leg movement; FL: flow-limitation.

5.2 Sleep-disordered breathing and non-invasive blood gas measurements

5.2.1 Progressive flow limitation (study I)

In the first study, seven patients had only NonHD episodes, 25 patients had only HD episodes, and four patients had both types. Episode characteristics are shown in Table 3. A supine position during an episode was equally common in NonHD and HD. LM and PLM were more frequent during HD episodes, but the differences were not significant. Both flow-limitation types were associated with a $PtcCO_2$ increase that differed from zero. The average slope was 4.04 kPa/h (5.11 kPa/h for NonHD and 3.61 kPa/h for HD, $p < 0.001$). A $PtcCO_2$ increase was also observed during the plateau, but the slope was considerably smaller (0.33 kPa/h, $p = 0.045$

for slope and $p < 0.001$ between plateau and NonHD/HD episodes). On average, NonHD episodes started below the plateau and terminated near $PtcCO_2$ plateau, whereas HD episodes started from the plateau level and terminated above it. However, neither starting levels nor termination levels of $PtcCO_2$ differed from each other. Altogether, a trend towards higher $PtcCO_2$ levels during HD episodes was observed but not significant difference between episodes. Sometimes flow limitation evolves over several minutes, and the transition in effort is clearly seen (Figure 4).

Flow limitation episodes were commonly associated with decrease in SpO_2. The median decrease was 2.0 % ($p < 0.001$) in both episodes. There was no statistical difference in the starting levels of SpO_2 in NonHD and HD episodes, but HD episodes terminated at lower SpO_2 level. A Flow limitation episode was not always associated with a SpO_2 decrease; 77.3 % NonHD and 75.9 % of HD episodes had a SpO_2 decrease. A small but significant correlation was observed between a SpO_2 decrease and a $PtcCO_2$ increase. (NonHD: $\varrho = -0.382$, $p = 0.004$ and HD: $\varrho = -0.460$, $p = 0.031$). The mean nocturnal SpO_2 correlated highly with the plateau SpO_2 ($r = 0.939$).

Table 3. Progressive flow-limitation episodes

	NonHD	HD	p
N	22	55	
Episode duration (s)	177 (131 – 221)	397 (242 – 594)	<0.001
$PtcCO_2$ (% of plateau)			
Episode start (%)	95.8 (0.036)[a]	99.3 (0.029)	0.071
Episode end (%)	100.1 (0.029)	105.2 (0.044)[a]	0.055
Slope (kPa/h)	5.11 (4.88)	3.61 (3.28)	0.182
SaO_2 (%)			
Episode start (%)	96.50 (95.75 – 98)	95 (93 – 96)	0.212
Episode end (%)	94 (93-95.25)	93 (90.75 – 94)	0.03
ΔSaO_2 (end – start)	-2.00 (-4.0 to -0.75)	-2.00 (-3.25 to -0.75)	0.871
Supine position, n (%)	10 (45.5)	26 (50)	0.80
Snore, n (%)	0 (0)	28 (50.9)	<0.001
LM, n (%)	3 (13.6)	14 (25.5)	0.37
PLM, n (%)	1 (4.6)	11 (20)	0.10

Abbreviations: $PtcCO_2$: transcutaneous carbon dioxide; SaO_2: oxyhemoglobin saturation; LM: leg movement; PLM: periodic leg movement. [a], $p < 0.001$ compared to plateau (100%)

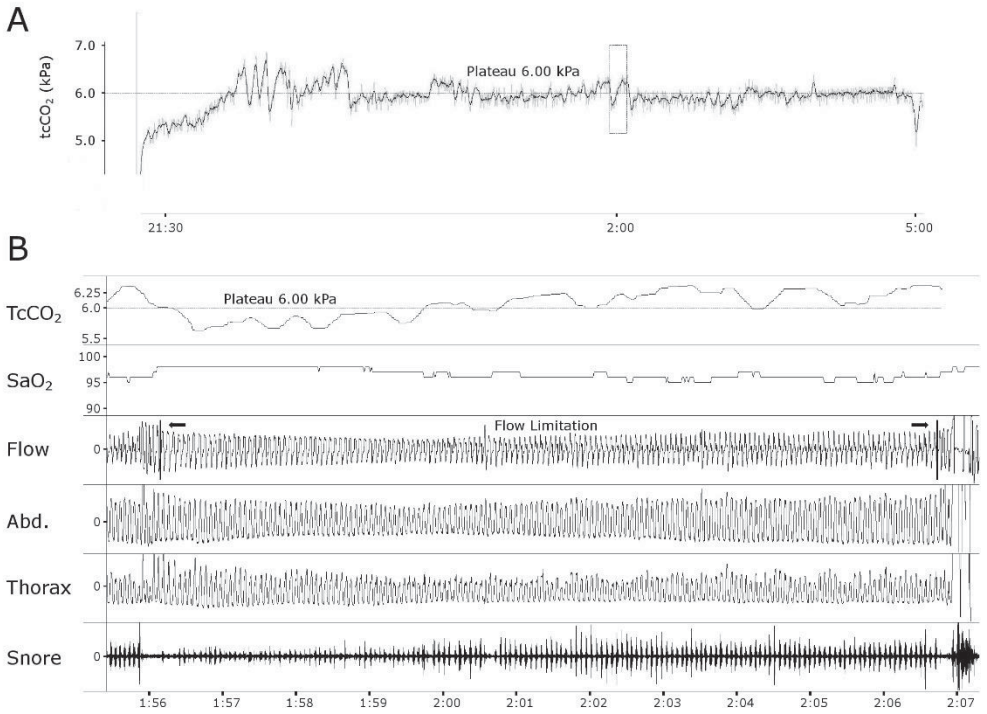

Figure 4. An overnight view of $PtcCO_2$ and a detailed view of a flow limitation event containing both low and high-drive elements. A) Evening wakefulness level of $PtcCO_2$ is seen in the beginning. The plateau level for $PtcCO_2$ is determined from stable breathing in the morning just before awakening. Dashed box shows the flow-limitation event. B) Progression of flow-limitation is seen on the flow channel. Transition in effort and increased snoring is seen between 1:59 – 2:00, which corresponds to $PtcCO_2$ crossing the determined plateau level. $PtcCO_2$ signal was advanced 30 seconds to compensate the measurement delay. Reproduced with permission from Respir Physiol Neurobiol. 2014;191:44-51.

5.2.2 Sleep apnea and steady flow limitation (study II)

Eighty-eight SDB sequences were detected in the second study. Episode characteristics are shown in Table 4. Flow-limitation and hypopnea sequences were most common; 32 sequences of both were found. Only three sequences of mixed apnea were found and these were pooled together with seven central apnea sequences for the analysis. One-third of flow-limitation and steady breathing sequences occurred in a supine position, whereas at least 70% of the cyclic SDB

sequences occurred while supine. 608 individual SDB events from apnea (central, mixed and obstructive) and hypopnea sequences were included. Of these events, 87.8 % were associated with oxyhemoglobin desaturation of 3 % or more. There was only a small variation in the events within sequences; 41 SDB events (6.7 %) did not match with their sequence classification. The range of observed mean values of $PtcCO_2$ for the sequences was from 3.85 kPa to 6.54 kPa. When wakefulness $PtcCO_2$ (5.18 kPa, 100%) was used as a reference value, central and mixed apnea sequences showed no difference in the $PtcCO_2$ levels, whereas all other sequences assumed a higher level of $PtcCO_2$. Obstructive apnea and hypopnea sequences had the same level of $PtcCO_2$ (0.29 kPa, 5.8 % and 0.27 kPa, 5.4 % increase from wake) as $PtcCO_2$ level observed during steady breathing (0.41 kPa, 8.4 % increase from wake). Steady flow-limitation sequences had the highest $PtcCO_2$ levels (0.60 kPa, 12.2 % increase from wake), other sequences being significantly below this level. Figure 5 shows overnight $PtcCO_2$ and SpO_2 profiles with insets from different levels of PtcCO2 associated with wakefulness, steady breathing during, hypopnea and flow limitation (Figure 5). Figure 6 shows the $PtcCO_2$ and SpO_2 results from the second study with episodes arranged according to hypothesized CO_2 increase (Figure 6). Figure 7 shows individual $PtcCO_2$ values for each episode (Figure 7). The variance of $PtcCO_2$ became smaller when steady breathing was used as a reference value instead of wakefulness (Figure 8).

The median wakefulness SpO_2 levels did not differ from that of steady breathing, but SpO_2 was lower during flow limitation. Further, there was no difference between SpO_2 values during steady breathing and flow-limitation. During cyclic SDB sequences, the peak SpO_2 levels did not differ from each other. SpO_2 nadirs during hypopnea sequences (91.6 %) were shallower than during central or obstructive sequences (Figure 6).

Table 4. Sleep apnea and flow-limitation sequences

		Cyclic breathing				
Sequence (n)	Wake	CA + MA	OA	Hypopnea	Steady breathing	Flow-limitation
N	44	7 + 3	14	32	44	32
$PtcCO_2$ (kPa)	5.18 (0.45)	5.11 (1.00)	5.31 (0.37)	5.50 (0.75)	5.47 (0.61)	5.64 (0.66)
$PtcCO_2$ Δwake (kPa)		0.10 (0.43)	0.29 (0.25)	0.27 (0.47)	0.41 (0.43)	0.60 (0.32)
$PtcCO_2$ (%), (%-units)	100 (0)	102.0 (8.5)	105.8 (5.5)	105.4 (9.4)	108.4 (8.6)	112.2 (6.8)
SaO_2, event start (%)	-	96.4 (1.4)	96.6 (1.9)	95.9 (1.8)	-	-
SaO_2, event desat (%)	-	89.9 (5.6)	88.8 (7.0)	91.6 (3.6)	-	-
	95.0 (2.0)	-	–	-	94.0 (3.0)	94.0 (3.0)
Sequence length (min)	4:41	7:48	8:46	7:00	5:56	7:06
Supine (%)	69.8	70.0	92.9	74.2	31.0	32.3

Values presented as medians with interquartile range in the parenthesis. Sequence lengths are shown as mean values. Abbreviations: CA: central apnea; MA: mixed apnea; OA obstructive apnea; $PtcCO_2$; transcutaneous carbon dioxide; SaO_2: arterial oxyhemoglobin saturation.

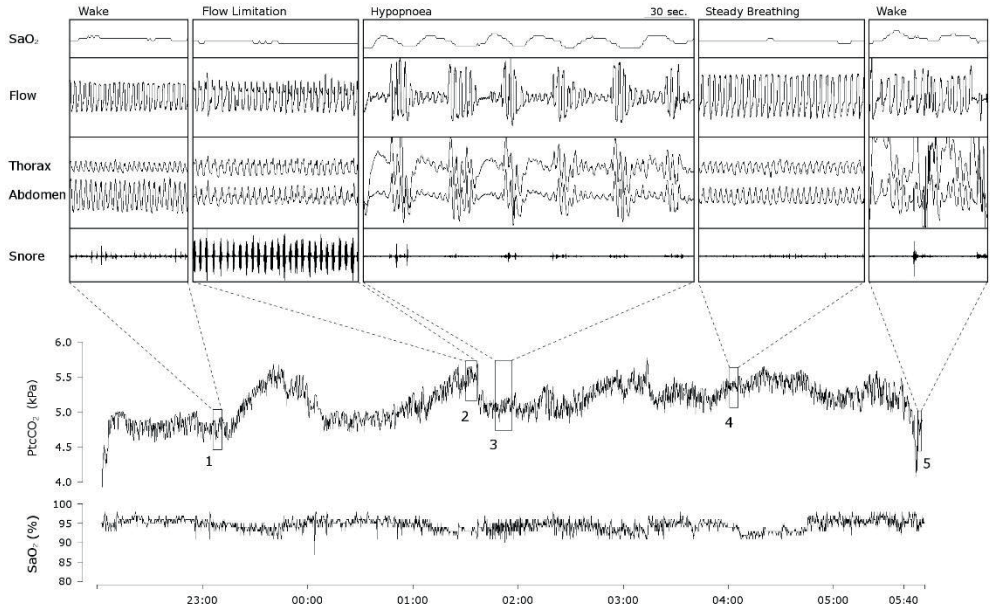

Figure 5. An overnight $PtcCO_2$ and SaO_2 profile and expanded views from selected parts of the night showing the correspondence between $PtcCO_2$ and respiratory phenomena. Evening and morning $PtcCO_2$ levels are very similar suggesting minimal signal drift (1 and 5). Notice how hypopnea episode (3) is below flow-limitation (2) in terms of $PtcCO_2$.Notice also that $PtcCO_2$ level during steady breathing with minimal flow-limitation (4) is above hypopnea episode and below flow limitation episode in terms of $PtcCO_2$. Reproduced with permission from Respir Physiol Neurobiol. 2015;219:95-102.

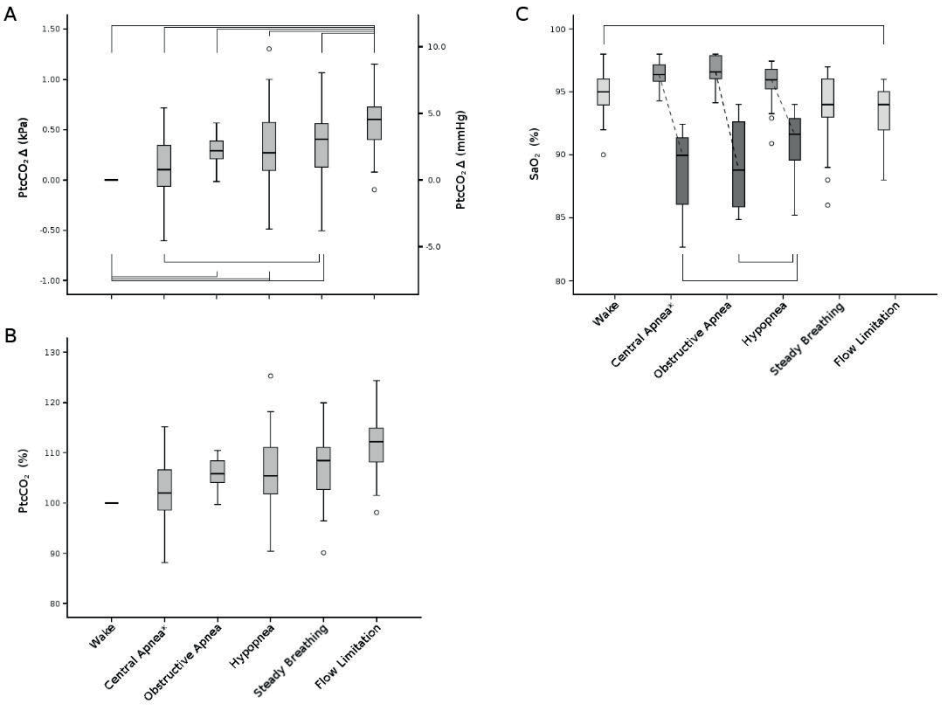

Figure 6. $PtcCO_2$ and SaO_2 during wakefulness, steady breathing (plateau) and SDB episodes. A) Change in $PtcCO_2$ compared to wakefulness. Lines indicate significant difference between episodes. Flow-limitation is higher than other episodes. Notice that obstructive sleep apnea and hypopnea sequences do not differ from steady breathing. X-axis is similar to B panel but omitted for better view. B) Similar to A), but shown with percentages using wakefulness as baseline. Lines removed as they are the same as in A panel. C) SaO_2 levels during flow limitation are lower than in wakefulness but not during steady breathing in sleep. Max. and min. values for SaO_2 are shown for cyclic events. Multiple comparisons adjusted with Bonferroni correction (significant p-value = 0.0033) Reproduced with permission from Respir Physiol Neurobiol. 2015;219:95-102.

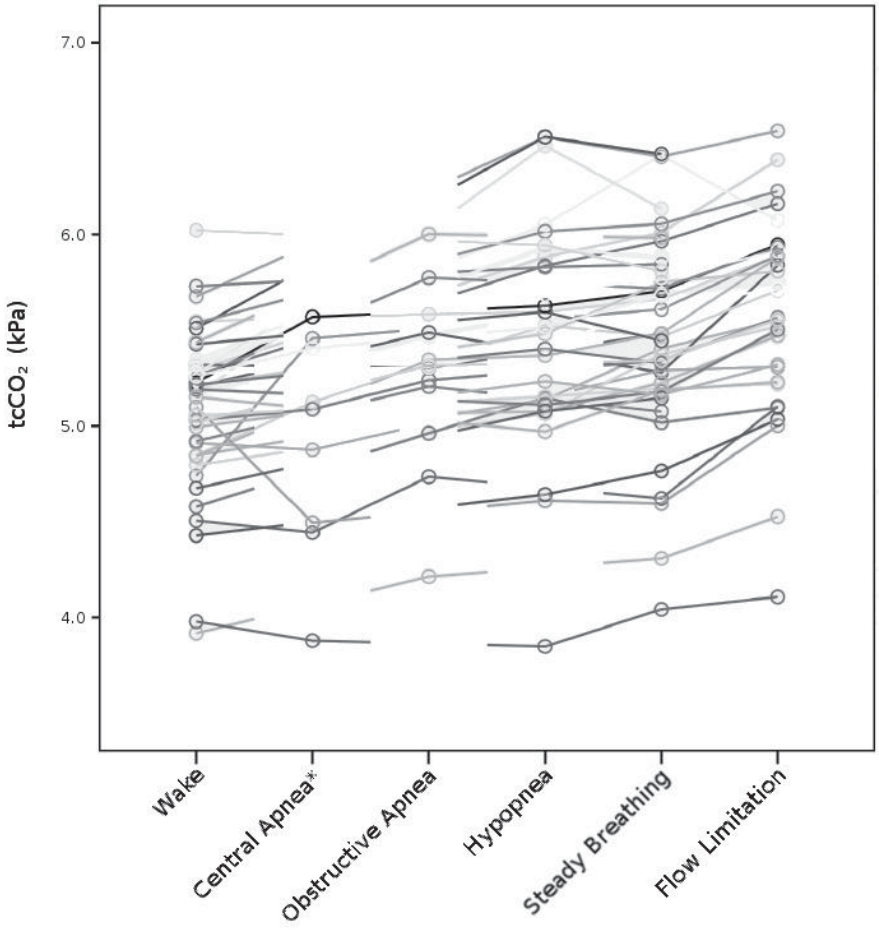

Figure 7. Individual $PtcCO_2$ values for each episode. Episode order is arranged according to hypothesized increasing $PtcCO_2$ value. Open circles represent the $PtcCO_2$ value and lines that connect the circles indicate that the episodes are from the same patient. If the patient does not have an episode, the lines point to next episode that is found. For example, the patient with lowest $PtcCO_2$ values does not have an obstructive apnea episode, but has all the other types. Reproduced with permission from Respir Physiol Neurobiol. 2015;219:95-102.

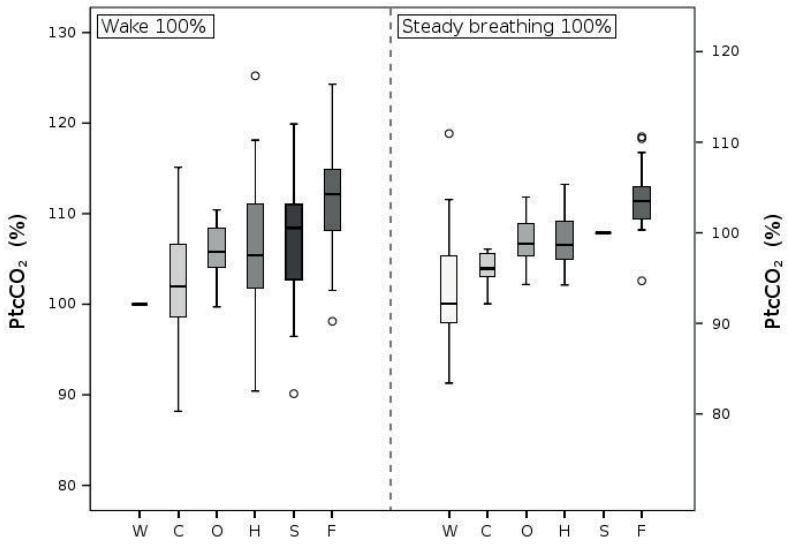

Figure 8. $PtcCO_2$ distributions shown with different baselines. If steady breathing during sleep is used as the reference value the variance of SDB events becomes smaller. W = wakefulness, C = central and mixed apnea, O = obstructive apnea, H = hypopnea, S = steady breathing, F = flow-limitation. Note that the y-axis on the right panel is moved upwards to allow better comparison between panels. Reproduced with permission from Respir Physiol Neurobiol. 2015;219:95-102.

5.2.3 Pregnancy and sleep-disordered breathing (study III)

Conventional SDB parameters AHI and ODI3 showed no difference between pregnant and controls. In addition, FL-index (percentage of flow-limited breaths during sleep) and snore time, showed no difference between groups (Table 3). Only three subjects (two pregnant, one control) from the whole population were identified as snorers. In addition, a systematic analysis (flow limitation determined by the algorithm) did not reveal a greater $PtcCO_2$ increase during flow limitation in the pregnant women in any of the sleep stages.

An unexpected feature of $PtcCO_2$ peaks was more common in pregnant women (78 vs. 5, $p = 0.028$). The mean amplitude of peaks was 0.20 kPa with a mean duration of 241 s. The number of peaks per person ranged from 1 to 22. Inspiratory flow-limitation was associated with 52 peaks (62.7%). The peaks were also associated with arousals (N =51) of which 14 were respiratory arousals. Flow amplitude

reduction to hypopnea was associated with 24 peaks and one peak was associated with apnea. It was common that flow limitation pattern developed gradually and was equally resolved. A SpO_2 drop of 3-4 % was associated with 8 $PtcCO_2$ peaks (Figure 9). Two of the pregnant women had oscillating $PtcCO_2$ as seen in Figure 9B, but only in the other the peaks were above amplitude criterion. This cyclic $PtcCO_2$ pattern was not associated with flow limitation but minimally fluctuating ventilation over time.

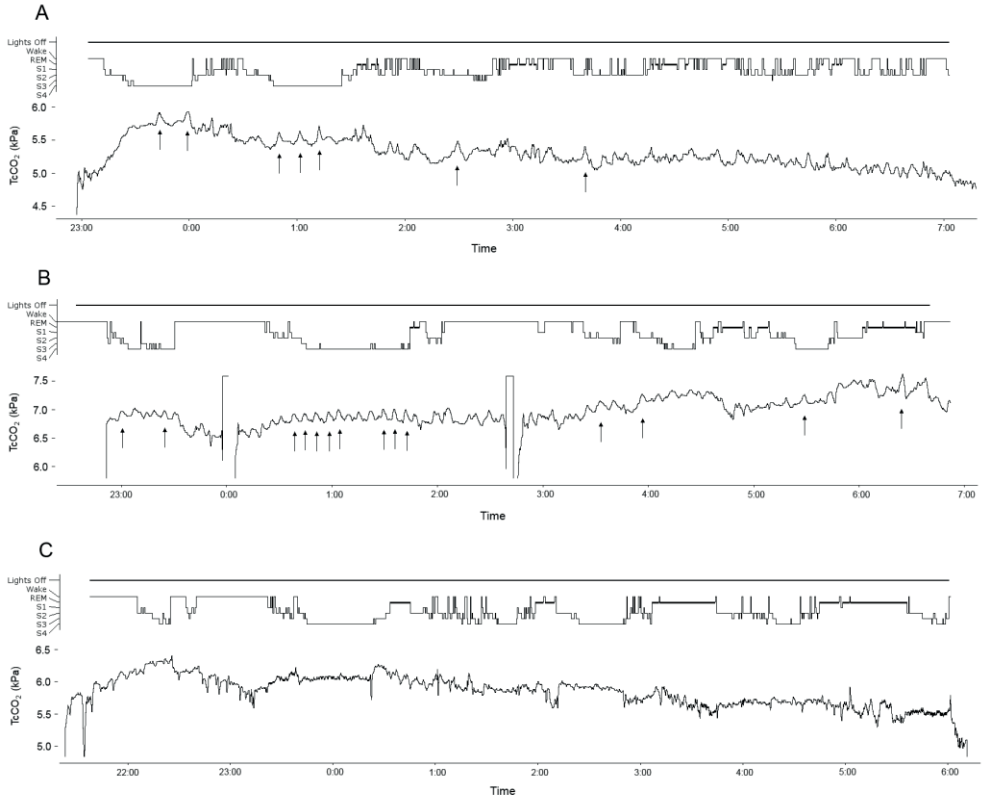

Figure 9. Overnight profiles showing hypnogram and $PtcCO_2$ from two pregnant women and one control. A) Pregnant woman with inspiratory flow limitation events associated with $PtcCO_2$ "peaks" (arrows). B) Pregnant woman with $PtcCO_2$ peaks not associated with flow-limitation. C) A control subject without $PtcCO_2$ peaks. Notice the stable $PtcCO_2$ levels during deep sleep as well as decreasing signal trend suggesting technical drift. Reproduced with permission from Sleep Med. 2017;36:67-74.

5.3 Pregnancy and sleep

Clear changes in sleep were observed between pregnant and control populations (Table 5). In comparison, pregnant women had a reduced total sleep time, sleep efficiency, N3 sleep and REM sleep duration and increased N1 sleep duration as well as increased wake after sleep onset. Pregnant women also had a lower mean SpO_2 (95.9% vs. 97.5%, $p < 0.001$) and minimum SpO_2 (93.0 vs. 94.5%, $p = 0.008$) compared to controls. Heart rate during the night was also increased in pregnant women.

$PtcCO_2$ measurement showed no difference between pregnant and controls in any of the sleep stages (Table 6). The use of absolute or relative values made no difference. It was observed, however, that the variance in $PtcCO_2$ during NREM sleep was smaller in pregnant women than in controls. A $PtcCO_2$ analysis for the sleep stages was possible only for 15 pregnant women and eight controls due to signal drift or otherwise bad quality data.

Table 5. Polysomnography data

	Pregnant (N = 18)	Controls (N = 12)	p
TST (min)	361.0 (330.5-418.9)	415.5 (391.5 – 429.4)	0.007
Sleep onset (min)	17.5 (11.5 – 27.6)	21.5 (15.1 – 27.0)	0.518
WASO (min)	110.5 (58.5 – 151.1)	39.7 (21.8 – 77.0)	0.003
Sleep efficiency (%)	76.7 (68.3 – 88.6)	91 (85.0 – 95.0)	0.002
N1 sleep (min)	30.3 (25.5 – 45.3)	21.0 (16.3 – 30.8)	0.004
N2 sleep (min)	141.8 (96.0 – 168.0)	140.5 (109.9 – 174.0)	0.884
N3 sleep (min)	118.5 (97.5 – 143.6)	156.5 (133.3 – 190.8)	0.009
REM sleep (min)	53.0 (40.3 – 69.5)	91.5 (73.5 – 99.6)	0.001
Average heart rate (bpm)	71.7 (64.3 – 79.0)	59.6 (55.7 – 66.9)	0.002

Values presented as medians and interquartile range. Abbreviations: TST: total sleep time; WASO: wake after sleep onset; N1, N2, N3; non-rapid eye movement (NREM) sleep stages 1,2 and 3; REM: rapid eye movement.

Table 6. Transcutanenous CO_2 during sleep

	Pregnant	Controls	p	p (variance)
N	15	8		
$PtcCO_2$, absolute (kPa)				
Wake	6.19 (5.41 – 6.65)	6.16 (5.96 – 6.51)	0.776	
N1 sleep	6.28 (5.35 – 6.75)	6.49 (6.04 – 6.74)	0.428	
N2 sleep	6.28 (5.43 – 6.75)	6.57 (5.97 – 6.89)	0.392	
N3 sleep	6.32 (5.92 – 6.65)	6.52 (5.97 – 7.08)	0.506	
REM sleep	6.41 (5.28 – 6.95)	6.39 (5.72 – 6.78)	0.825	
NREM sleep	6.29 (5.48 – 6.67)	6.56 (5.98 – 7.01)	0.357	
ΔPtcCO2 (kPa)				
Wake (reference)	0	0		
N1 sleep	0.08 (- 0.03 – 0.18)	0.20 (0.03 – 0.61)	0.115	0.323
N2 sleep	0.12 (0.05 – 0.29)	0.24 (- 0.04 – 0.65)	0.506	0.213
N3 sleep	0.15 (0.08 – 0.38)	0.21 (0.04 – 0.53)	0.825	0.075
REM sleep	0.15 (0.08 – 0.43)	0.16 (- 0.15 – 0.49)	0.925	0.067
NREM sleep	0.11 (0.07 – 0.22)	0.24 (0.03 – 0.62)	0.506	0.038

Values presented as medians and interquartile range. p (variance) denotes the Levene's test. Abbreviations: $PtcCO_2$; transcutaneous carbon dioxide; NREM: non-rapid eye movement; N1, N2, N3; NREM sleep stages 1,2 and 3; REM: rapid eye movement.

6 DISCUSSION

This study focused on associations between SDB, control of breathing, and $PtcCO_2$ measurement. Since carbon dioxide is one of the main controllers of ventilation during sleep, we wanted to know how sensitive the simple $PtcCO_2$ measurement is for these phenomena. Essentially, the study can be divided into two parts. In the first, observational part of the study, cardio-respiratory sleep recordings were analyzed retrospectively in studies I and II to study the associations between $PtcCO_2$ and different classes of SDB, namely progressively developing and stable inspiratory flow-limitation, snoring, and sleep apnea in its various forms. In the third study (III), pregnant women on their third trimester were studied to see the effects of flow-limitation on $PtcCO_2$. The aim of these studies was to understand the phenomenology related to SDB in the context of $PtcCO_2$.

There are three main findings. First, in the context of progressively worsening flow-limitation (NonHD and HD episodes), which decreases V_E and increases CO_2, increased ventilatory effort (HD episode) is clear only after a certain threshold CO_2 level ($PtcCO_2$ plateau) is exceeded. Ventilatory efforts are also evident below the threshold level because the CO_2 level is above the apneic threshold but the efforts are not augmented (NonHD episode). Second, in sleep apnea patients capable of normal breathing, steady flow-limitation leads to significantly higher $PtcCO_2$ levels during sleep than what is observed during normal breathing or during apnea or hypopnea sequences. The SpO_2 level was not different between normal breathing and flow-limitation, which probably explains why these events have drawn less interest compared to apneic events because no change is observed with the routinely used methods. Third, healthy pregnant women have practically no SDB when assessed with conventional parameters AHI and ODI or even with snore time or percentage of flow-limited breaths. Yet it was discovered that distinctive $PtcCO_2$ peaks are more common in pregnant women and that these peaks are mostly characterized with inspiratory flow limitation. It could be speculated that anatomic and hormonal changes such as reduction of functional residual capacity of the lungs and mucosal edema increase the probability of upper airway obstruction and prohibit the effect of ventilatory response, leading to augmented $PtcCO_2$ increases. No difference was observed between pregnant subjects and controls in $PtcCO_2$ during

wakefulness and sleep. However, it was found that the variance of $PtcCO_2$ during NREM sleep was smaller in pregnant women compared to non-pregnant women, suggesting a stricter ventilatory control or diminished CO_2 increase due to lighter sleep.

6.1 Progressive inspiratory flow limitation and $PtcCO_2$ plateau (Study I)

Number of patients that were analyzed was small compared to initial population that was screened. Only 8.5% of the initial population had predetermined events. Given the strict criteria for events this was no surprise. When the characteristics of the final population are compared to those in other studies, resemblance to UARS patients is seen (Gold, et al. 2002). Interesting, yet anecdotal finding in our study was that half of the patients had AHI below 5/h, even though we did not have any kind of cut-off criteria for AHI. Patients with more severe obstruction may not be able to have flow limitation events of this length, but instead develop obstructive apnea, hypopnea or shorter flow limitation event.

At the time of the study there was no commonly accepted criterion (such as AASM) how to score flow limitation per se. RERA could be scored if the event did not meet the criterion for hypopnea, but arousal was required and without EEG arousal could not be determined by definition. Therefore, these events could not be called RERAs. Flow limitation may present with different forms that associate with different upper airway dynamics (Aittokallio, T., et al. 2001). It has been shown that when CPAP pressure was decreased to suboptimal levels the progression of flow limitation was observed (Owens, et al. 2012). It was also shown that inspirations with rounded breaths were followed by breaths showing initial peak flow, which then deteriorated towards the end of the inspiration (Owens, et al. 2012). Progressive pattern for flow limitation was chosen in our study so that the increase in effort could be seen due to increasing $PaCO_2$ that should stimulate the breathing (Johnson, et al. 2005). Progressive pattern was also evident during negative effort dependence as increased respiratory effort over consecutive breaths lead to deterioration of flow (Owens, et al. 2012). Two-minute minimum for sequence length was decided in order to limit the analysis to flow limitation as the majority of apnea/hypopnea events are considerably shorter and with this duration the $PtcCO_2$ dynamics can be visualized (Gislason, et al. 1989). It was previously shown that prolonged flow limitation associates with increasing $PtcCO_2$ (Rauhala, et al. 2007). It was also shown

that flow limitation may also occur without increased respiratory effort (Ayappa, et al. 2000). It was postulated that there is a target level for optimal $PtcCO_2$ level, since long horizontal $PtcCO_2$ levels ($PtcCO_2$ plateaus) are observed during sleep recordings. Since the control of ventilation is mostly dependent on $PaCO_2$ (Dempsey. 2005), this level might be crucial in the determination of respiratory effort, which could explain the observed differences in respiratory effort during flow limitation. Esophageal pressure measurement is the gold standard for determining respiratory effort, but due to its invasiveness, inductance plethysmography is more commonly used. Both methods are accepted for effort measurement (Berry, et al. 2017). Changes in inductance plethysmography correlate with esophageal measurement (Masa, et al. 2003)

Number of events that were found was relatively low. This could be the effect of requiring rather long periods of flow limitation. Falling asleep associates decreased upper airway muscle support as shown with Pcrit (Carberry, et al. 2016), increased resistance (Skatrud, Dempsey. 1985) and diminished negative pressure-reflex (Gora, et al. 1998) leading to reduced ventilation. It is speculated that simultaneous reduction in $PaCO_2$ sensitivity (Teran, et al. 2014) could enable situation where increasing $PaCO_2$ due to flow limitation does not have stimulating effect because the $PaCO_2$ threshold is increasing also. HD events were found more often and they were longer than NonHD events. Both events had increasing $PtcCO_2$, which shows that progressive flow limitation had a clear effect on $PtcCO_2$. We could not show that the events are at different levels of $PtcCO_2$ because there was no difference between start or end levels, suggesting that there is an overlap between the events. However, interesting finding was that NonHD events started below the plateau level and ended at the plateau level whereas HD events started from the plateau level and ended above it. Without EEG it is only possible to speculate the sleep stage, but it seems probable that NonHD events occurred during lighter sleep because the events were terminated near the plateau level, indicating that increases in effort and arousal threshold might play a role. HD events on the other hand may have occurred during deeper sleep since increase in $PtcCO_2$ occurred above the plateau level and despite increased respiratory efforts the HD events were significantly longer than NonHD events. With deepening sleep the sensitivity to $PaCO_2$ changes is reduced as reviewed by Teran (Teran, et al. 2014), which could explain this finding. Position may not explain these findings as supine position was equally common. These findings suggest that the degree of flow limitation and $PtcCO_2$ form a continuum. When the ventilation deteriorates, threshold levels for blood gases and respiratory effort are inevitably reached, leading to increased respiratory efforts (Figure 4). Only four

patients had both types of events. Whether this small overlap is a marker of different populations remains to be solved in future studies. We were unable to find any difference between these groups, but the sample was small, which limits the statistical power.

Scoring of the plateau level for $PtcCO_2$ is the most subjective feature of this study. The aim was to find a period of stable $PtcCO_2$ as a marker of stable breathing, a desirable condition during sleep. Normal rounded inspiratory flow shape would have been optimal, but given the population it was not feasible requirement and minor flow limitation was allowed. Term eupnea is also used to describe this level of breathing and associated CO_2 and O_2 during sleep (Dempsey, et al. 2012). $PtcCO_2$ plateau events scored in this manner should represent the highest level that patient was able to have stable breathing. It is likely that these plateaus are from SWS since breathing is most stable during deep sleep, even in OSA patients (Ratnavadivel, et al. 2009). Positive $PtcCO_2$ slope was also observed during plateau episodes, which indicates that breathing has not been in complete balance as some of plateaus had flow limitation. However, the $PtcCO_2$ slopes observed during NonHD and HD events were more than 10-times steeper, indicating that CO_2 accumulation during plateaus was considerably slower. In addition, when short sequences are used the effect is amplified if the slope is expressed as kPa/h.

Oxyhemoglobin decrease during NonHD and HD events had similar magnitude (2%) although there was a difference between event termination levels, HD events being lower. This may be the result of longer episodes and possibly greater reductions in V_T, which ultimately leads to reduced oxygen levels in the blood. Contrary to systematic $PtcCO_2$ increase, SpO_2 decrease was not observed during all of the events. This finding is in line with other studies and reviews showing that flow limitation may (Calero, et al. 2006) or may not (Rauhala, et al. 2007, Arora, et al. 2015) associate with SpO_2 decrease. SpO_2 measurement bias is near 2 %, and therefore small changes in the value should be interpreted with caution (Jubran. 2015).

6.2 Sleep apnea, flow limitation and $PtcCO_2$ (Study II)

Selection of patients in this second study had important implications for interpretation of the results. It was required that the patient had stable breathing during the night. This requirement indirectly excludes most severe patients because they are not able to have normal breathing during the night. So, in parallel to first

study, this population did not represent average sleep apnea population and the results should be viewed in that light. Number of selected patients was rather low compared to initial population (7.9 %), but the inclusion criteria were again quite strict, so small numbers were expected. Number of SDB sequences remained low as well, so the conclusions should be drawn carefully as most of the sequences were hypopneas or flow limitation. However, the sequences were carefully selected and therefore represented their SDB subtype when the individual events are monotonous and repetitive. Known effects of supine position on upper airway collapsibility (Oksenberg, et al. 2000) were clearly seen in the results. Cyclic events occurred mostly in supine position whereas non-supine position predominates flow limitation and stable breathing sequences.

Our results show that the type of SDB has an effect on observed $PtcCO_2$ level. $PtcCO_2$ during central apnea sequence did not differ from wakefulness $PtcCO_2$ levels, whereas the difference between central apnea and stable breathing could be demonstrated (Figure 6). These findings are in line with previous studies which show the connection between the presence of sleep apnea and CO_2. Hypocapnia induced with mechanical ventilation resulted in central sleep apnea (Rowley, et al. 2006). Conversely, increasing the inhaled CO_2 (1-2.3 %) diminishes central apneas (Xie, et al. 1997) and even higher levels of inhaled CO_2 (3-6 %) will effectively remove episodes of obstructive sleep apnea (Hudgel, et al. 1988). We were unable to show the difference between central sleep apnea and obstructive sleep apnea. Tkacova had previously shown that in heart failure patients the proportion of obstructive apneas reduced and central apneas increased overnight in association to $PtcCO_2$ decrease (Tkacova, et al. 2001). However, we did not use proportions but instead one sequence of events was used to describe the event type, which may explain the different findings. Highest $PtcCO_2$ was observed during flow limitation, which may be a result of multiple factors. First, during a sequence of apnea events the $PtcCO_2$ oscillates between hypercapnia and hypocapnia. When median value was used, the result is $PtcCO_2$ value between the two extremes. On the other hand, during the selected flow limitation sequences there was no hyperpnea that would lower $PtcCO_2$. Second, it is likely that apnea sequences and flow limitation sequences occurred during different sleep stages as deepening sleep reduces $PaCO_2$ sensitivity (Teran, et al. 2014) and associates with increasing $PtcCO_2$ (Holmedahl, et al. 2014). However, recent study showed that differences in loop gain between N2 and N3 NREM sleep are not significant in OSA patients (Landry, et al. 2018). Our finding that $PtcCO_2$ was higher during flow limitation compared to stable breathing was not surprising given the results from the first study but also when compared to those of Calero et

al. They showed that suboptimal CPAP pressure resulted in flow limitation and 6 mmHg (0.8 kPa) increase in end tidal CO_2 ($EtCO_2$), increased T_i and esophageal pressure in addition to small, but significant 1% change in SaO_2 (Calero, et al. 2006).

Interesting SpO_2 features were observed as there was no difference between flow limitation and stable breathing. In practice this means that flow limitation, which was associated with $PtcCO_2$ increase, could not be detected with SpO_2 signal (Figure 3). As already mentioned, SpO_2 changes may not occur with flow limitation, even when the effort was increased (Arora, et al. 2015). Peripheral chemoreceptor afferent discharge can be increased by simply increasing the $PaCO_2$ in the carotid body (Kumar, Prabhakar. 2012), which could then ultimately lead to increased respiratory efforts even in the absence of PaO_2 change. There was no difference in SpO_2 between wakefulness and stable breathing. This raises the question whether stable breathing sequences are recorded during wakefulness as there was no EEG to verify sleep. Sleep is associated with CO_2 increase and we observed 0.41 kPa $PtcCO_2$ increase during stable breathing, which is similar to the differences that were previously reported for sleep (Aittokallio, J., et al. 2006, Aittokallio, J., et al. 2009, Holmedahl, et al. 2014)

Variance of $PtcCO_2$ was considerable within SDB subtypes, which was surprising because the physiological threshold for CO_2 is quite narrow. When $PtcCO_2$ during stable breathing was used as reference level, it was observed that the variances of SDB subtypes became smaller and the variance of $PtcCO_2$ during wakefulness increased. This finding underlines the sensitivity of $PtcCO_2$ measurement and supports the idea that recordings should be done in a very standardized manner, which includes also controlling the signal drift after overnight recording.

6.3 Pregnancy, sleep-disordered breathing and $PtcCO_2$ (Study III)

Pregnant women were older, but since all of the subjects were premenopausal the age is not expected to play a major role in the results compared to the effects of pregnancy. Contrary to our expectations, we were unable to find difference in SDB between pregnant women and control subjects. In addition to AHI and related indexes, SDB was previously described by Connolly by means of a "flattening index" showing that inspiratory flow limitation increases with progressing pregnancy (Connolly, et al. 2001). We used similar flattening index, which was available in Somnologica. There could be several reasons for our negative finding. One

possibility is that selection bias occurred with control population, so that those women who had suspicion of SDB might have been more inclined to participate. Other explanation is that the pregnant women were exceptionally healthy in terms of upper airway. It is also possible that algorithms behind flattening indexes were different.

We were also unable to find differences in $PtcCO_2$ levels during flow limitation between pregnant and controls. Successful analysis required that $PtcCO_2$ could be linked to flow limited breaths. $PtcCO_2$ was advanced 30 seconds to achieve synchronization between flow and $PtcCO_2$. Given that this might not be completely accurate, data was not included from a sleep stage if there was not enough data. It was estimated that 75 data points would account for 3 to 5 minutes of breathing, which could be a long enough period to determine $PtcCO_2$ for flow limitation. Automated analysis would pick sporadic breaths also and it was speculated that limiting the data inclusion would exclude sporadic breaths, but if longer sequences were present, they would be included. Small sample size and/or signal drift might explain this negative result. If flow limitation and normal breathing are collected from different parts of the night $PtcCO_2$ signal drift may amplify or dampen the difference in $PtcCO_2$ values, which widens the variance of the sample.

Unexpected finding was also that there was no difference between groups in wakefulness and sleep stage specific $PtcCO_2$ values. This was an interesting finding since $PaCO_2$ levels are clearly lower during pregnancy (Machida. 1981). Sleep related increase in $PtcCO_2$ was observed in both groups, which does not support that $PtcCO_2$ measurement would be insensitive. Inter-individual differences can be considerable as shown already in the second study and previously also by Fukui (Fukui, et al. 1993) but on a group level the difference should be clear. $PtcCO_2$ is not the same as $PaCO_2$ and therefore it could be that $PtcCO_2$ measurement was affected by the increased metabolism in the peripheral tissue (Clark, et al. 1992), which would lead to increased CO_2 production and consequently similar values. Sleep related $PtcCO_2$ increase seemed to be smaller in pregnant subjects, which could be explained by respiratory stimulation by progesterone (Machida. 1981) or increased sensitivity to $PaCO_2$ (Jensen, et al. 2005), but these differences were not statistically significant.

Sleep disturbances are commonly reported during pregnancy (Mindell, et al. 2015) and this was clearly shown by our PSG results also. Almost all sleep related parameters deteriorated. It could be speculated that increased amount of wakefulness and larger proportion of lighter sleep hinder the $PtcCO_2$ increase during sleep. This might explain the smaller variance in $PtcCO_2$ that was observed during NREM sleep.

Frequent $PtcCO_2$ peaks in pregnant women was the novel finding of this study. Association to flow-limitation was expected but "only" 62.7% were associated with inspiratory flow-limitation. This may be explained by the fact that one of the pregnant women had oscillating $PtcCO_2$ not associated with flow limitation which was counted as peaks (n = 22) in order to describe the phenomenon (Figure 9B). Existence of the peaks is confusing because pregnancy is associated with enhanced response to hypercapnia (Jensen, et al. 2005). Explanation could be the increased risk for upper airway obstruction during pregnancy (Bourjeily, et al. 2014), which may be a result of multiple factors such as reduced lung volume (Owens, et al. 2010), increased blood volume (Sanghavi, Rutherford. 2014) or mucosal edema (Hegewald, Crapo. 2011). Fluctuating $PtcCO_2$ which was present in two pregnant women may be the result of unstable respiratory control and increased loop gain as slight fluctuation of ventilation was present. Increased plant gain is supported by the fact that small changes in ventilation associate with increased (Ptc)CO_2 response and on the other hand decreased controller gain is supported because large changes in $PtcCO_2$ associate with small changes in ventilation effectively canceling each other out and resulting in only small fluctuation (Dempsey. 2005). It was shown by Wellman et al. that loop gain is low in healthy normal men and women and periodic breathing did not develop easily even when ventilation was increased experimentally with ventilator (Wellman, et al. 2003). This supports the idea that loop gain may be increased during pregnancy. Given that the studied population was healthy, the $PtcCO_2$ changes are likely to be more pronounced in other populations such as in obese (narrow airway) or those with hypertension (increased sympathetic activity).

6.4 Strengths and Limitations

The studies presented in this book have many strengths as well as limitations. In the first two studies, diagnostic cardiorespiratory polygraphies were used. Therefore, the results represent symptomatic population. However, the patient selection was skewed because the studies were event driven towards more milder patients in terms of AHI, and therefore the results cannot be generalized to average clinical sleep apnea population. In addition, AHI was not determined according to AASM criteria so the reported indexes are likely to contain some errors. However, full spectrum of symptomatic SDB is not captured by AHI, and considering also flow limitation improves the accuracy (Hosselet, et al. 1998). Unfortunately, EEG was not recorded in these studies. Therefore, the important relation to sleep stages can only be

speculated. It can be claimed that $PtcCO_2$ plateau is a very subjective measure. This is true, but inter-individual variation of $PtcCO_2$ is considerably large, while intra-individual changes are usually quite small (Figure 7). During normal sleep, periods of horizontal $PtcCO_2$ are often recorded and using these levels as reference is a feasible approach. Highest levels of stable $PtcCO_2$ were used in the first study to determine the $PtcCO_2$ plateau. Therefore, it is unlikely that these periods are derived from wakefulness since wakefulness is associated with lowest values (Figure 7). Small sample sizes in two retrospective studies limits statistical power, but in order to have good data from clinical population, which is not collected for the purpose, this tradeoff is inevitable. It may be criticized that a 2-minute duration for flow limitation was too long and limited the availability of scorable events, but with this approach the change in $PtcCO_2$ is more reliable. $PtcCO_2$ measurement can be criticized that it does not reflect the $PaCO_2$ accurately as outlined in section 2.3.1. $PtcCO_2$ measures the CO_2 that diffuses through the skin (Stock. 1988) and it is likely that they produce different values even though correction factors can be calculated and the two measurements may correlate. Oscillating $PtcCO_2$ adds noise to the signal, which was corrected by using the linear regression. Used values are therefore not the real $PtcCO_2$ values but estimates in the first two studies. However, since the signal oscillates and the flow limitation episodes are linear it is assumed that significant error is not introduced. $PtcCO_2$ signal is also known to drift overtime. This drift was not controlled and it is another factor that increases the variance of the measured $PtcCO_2$ values. Despite the limitations listed here the sensitivity of $PtcCO_2$ signal to respiratory phenomena was encouraging

Strength of the pregnancy study was that both pregnant and control subjects were healthy and the phenomena that were seen were part of normal pregnancy. This is helpful when $PtcCO_2$ measurements are performed in high-risk populations. Flow limitation was assessed with algorithm, which can be criticized for not being sensitive enough because we could not replicate the previous clear finding of increased flow limitation in the third trimester in a similar population (Connolly, et al. 2001). This approach however removes the unconscious variation that occurs when scoring is done manually. In addition, flow limitation presents differently between individuals in terms of flow shape (Aittokallio, T., et al. 2001) and to this day there is no uniform way to characterize these differences. Post-hoc finding of $PtcCO_2$ peaks and oscillations are valuable markers that serve future studies. Criteria for characterizing the $PtcCO_2$ peaks is biased since it was made after the data was seen, but bias was inevitable since this phenomenon has not been described before. PSGs were

performed, which allowed to see the effects of sleep stage on $PtcCO_2$ as well as objectively verify the deterioration of sleep parameters during pregnancy.

6.5 Clinical significance of the findings

These studies show that $PtcCO_2$ has a strong association to ventilatory changes caused by SDB. Partial upper airway obstruction and flow limitation may associate with increased $PtcCO_2$, which may not be noticed if only SpO_2 is used. Treatment of mild sleep apnea is controversial because the condition is not associated with increased mortality as recently reviewed and the diagnosis requires more sensitive tools for verification in comparison to more severe disease (McNicholas, et al. 2016). On the basis of our results it seems that $PtcCO_2$ measurement is sensitive to flow limitation (both progressive and steady) in comparison to SpO_2 measurement, which might be useful in the characterization of the mild sleep apnea. Presence of sleep apnea or hypopnea is dependent on multiple factors of which CO_2 is one via control of breathing (Owens, et al. 2015). Overnight profile of $PtcCO_2$ may help to understand why SDB has a certain set of events at certain times of the night, which might improve the diagnosis and also treatment.

Increased amount of $PtcCO_2$ peaks associated with SDB were observed during pregnancy compared to controls despite similar amounts of overnight flow limited breathing between groups. Whether these peaks are even more frequent in high-risk populations or have any predictive value in terms of preeclampsia or other pregnancy related complications remains to be studied. Ventilatory and $PtcCO_2$ pattern indicative of increased loop gain was observed in two pregnant women. Central sleep apnea is virtually non-existent in the pregnant (Bourjeily, et al. 2015), but in the presence of obstructive SDB, high loop gain may sustain the respiratory system instability. Role of loop gain in SDB during pregnancy has not been explored.

6.6 Future directions

CO_2 measurements are not performed in large scale during sleep studies like SpO_2 measurements. Only by showing that measuring CO_2 gives useful information the interest will increase and more data would accumulate, which would then lead to development of more robust and affordable devices.

There are a number of important questions that need to be answered. Studying the determinants of the plateau level of $PtcCO_2$ and the impact of different sleep stages would help to determine guidelines. Also, studies with controlled upper airway resistance and collapsibility probably could add on our understanding of the pathophysiological mechanisms. Determining autonomic nervous system responses and local effects of CO_2 on vasculature (vasodilatation / constriction) and on cutaneous circulation during sleep remains an important unexplored field. If symptomatic and asymptomatic mild sleep apnea populations would differ in terms of $PtcCO_2$ dynamics, the use of $PtcCO_2$ could be extended from the detection of hypercapnia based on a fixed value to $PtcCO_2$ changes that are physiologically significant without the need to wait until disease progresses and becomes detectable also with AHI and ODI3.

7 SUMMARY AND CONCLUSIONS

The health burden of sleep apnea is massive, and any means that could improve the diagnostics and make the treatment more specific and therefore effective are welcomed. The use of CO_2 measurements has been largely limited to research purposes mainly because of the lack of a good parameter that could be obtained with relative ease, such as oxyhemoglobin desaturation from pulse oximetry, with an acceptable cost.

The present study characterized the transcutaneous CO_2 during different types of SDB and during pregnancy. The aim was to find out whether it could give information that would be useful not just from a scientific standpoint but also clinically.

The main conclusions from the studies I to III are:

I. Progressively developing inspiratory flow-limitation is associated with a systematic $PtcCO_2$ increase. This suggests that the measurement is sensitive to even small changes in ventilation. In addition, there seems to be a threshold for $PaCO_2$ above which the respiratory effort increases considerably. The increase in effort is probably caused by relative hypercapnia, which should be corrected. Once this threshold is crossed, increased inspiratory efforts are initiated in order to restore the ventilation and return the $PaCO_2$ to normal level. Below the threshold, the CO_2 level can be thought as being hypocapnic and ventilation is not stimulated because CO_2 should increase and increased respiratory efforts are not witnessed. $PtcCO_2$ measurement may have utility in SDB diagnostics if symptoms in the milder OSA population are linked to $PtcCO_2$ changes.

II. Distinct SDB phenotypes associate with different levels of $PtcCO_2$. During sleep, there is invariably a CO_2 increase, so the events of SDB which associate with central ventilatory inhibition, namely the central and mixed apnea, are found between wakefulness and sleep in terms of $PtcCO_2$ levels. While there seems to be a small trend that CO_2 is lower during obstructive apnea and hypopnea than during steady breathing, the difference between these events could not be shown. Steady flow-

limitation was associated with the highest $PtcCO_2$, exceeding the levels observed during steady breathing and all other SDB types. However, there was no difference in SpO_2 between these two events. These findings suggest that the apnea type is connected to the $PtcCO_2$ level and that steady prolonged inspiratory flow-limitation predisposes to relative hypercapnia before SpO_2 is affected.

III. Pregnant women and control women had similar levels of $PtcCO_2$ during different sleep stages although there was a trend towards a lower $PtcCO_2$ in the pregnant ones. Pregnant women showed a smaller variance of $PtcCO_2$ during NREM sleep, which could indicate more rigorous ventilatory control or hindered sleep related $PtcCO_2$ increase due to lighter sleep. In addition, transient $PtcCO_2$ increases were observed more frequently in the pregnant women, and 63% of these "peaks" were associated with inspiratory flow-limitation. This finding suggests that if inspiratory flow-limitation occurs during pregnancy, the resulting CO_2 increase could be more prominent. Remaining $PtcCO_2$ peaks are most likely a result of unstable ventilatory control in the form of increased loop gain. These findings indicate that even though the ventilation is stimulated and $PtcCO_2$ is kept within a (more) narrow range during pregnancy, if flow-limitation occurs, the consequence can be more severe compared to non-gravid women. Even without flow-limitation the CO_2 control might be unstable, leading to fluctuating ventilation.

In conclusion, transcutaneous carbon dioxide measurement is sensitive to ventilatory changes. SDB is heterogeneous, and the sum of various different factors as discussed above. The prevailing $PtcCO_2$ level is affected by the sleep stage and SDB phenomena, and ventilatory output is modulated continuously with feedback loops. For these reasons, $PtcCO_2$ measurement offers a simple way to observe what ventilatory control is trying to achieve once the effect of each type of disturbance on $PtcCO_2$ is known. With SDB, there seems to be an offset of CO_2 with every phenomenon. In central events both the apneic and hypopneic CO_2 levels are too low, which leads to ventilatory inhibition. Obstruction, on the other hand, associates with a CO_2 increase, so these events cycle around the target level or exceed it. During deep sleep and a lateral position, the obstruction is usually not as severe as in light sleep and may manifest as prolonged inspiratory flow-limitation with high CO_2. Output of ventilation is critically determined by $PaCO_2$. Therefore monitoring CO_2 and aiming to stabilize it could be the best way to manage the effects of SDB.

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PUBLICATIONS

PUBLICATION I

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Transcutaneous CO_2 plateau as set-point for respiratory drive during upper airway flow-limitation

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ABSTRACT

Upper airway flow-limitation is often but not always associated with prolonged gradually increasing respiratory effort. We investigated the changes in transcutaneous carbon dioxide tension ($tcCO_2$) during episodes of upper airway flow limitation during sleep with or without respiratory effort response.

Seventy-seven episodes of progressive flow-limitation were analyzed in 36 patients with sleep-disordered breathing. $TcCO_2$ and arterial oxyhaemoglobin saturation (SaO_2) were measured during steady breathing and during episodes of flow-limitation with and without effort response.

After lights-off $tcCO_2$ increased and leveled-off at plateau, when breathing stabilized. During flow-limitation $tcCO_2$ increased at rate of 4.0 kPa/h. Flow-limitation with increasing respiratory effort associated with $tcCO_2$ increase above the plateau (terminating at 105.2%, $p < 0.001$), whereas flow-limitation without effort response associated with $tcCO_2$ increase starting below the plateau (95.8%, $p < 0.001$).

We conclude that the nocturnal $tcCO_2$ plateau indicates the level above which the increasing respiratory effort is triggered as response to upper airway flow-limitation. We propose that flow-limitation below the $tcCO_2$ plateau is an event related to stabilization of sleep and breathing.

1. Introduction

Measurement of inspiratory flow with nasal prongs has become a standard method to screen and diagnose sleep-disordered breathing (SDB) (Johnson et al., 2005). While the clinical significance of repetitive episodes of obstructive sleep apnea (OSA) is well established, there is less agreement about how to analyze or interpret the various non-apneic episodes with significant inspiratory flow limitation (Aittokallio et al., 2001). Development of clinically useful scoring criteria for flow limitation requires better understanding of the underlying pathophysiological mechanisms.

There is evidence that increased inspiratory effort is an important determinant of subjective sleepiness both in obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome (UARS) (Pelin et al., 2003). Heavy snoring is a surrogate for increased respiratory effort, which at least in women seems to be a better predictor of symptoms of SDB than the apnea–hypopnea index (AHI) (Svensson et al., 2008). We have previously shown that transcutaneous carbon dioxide ($tcCO_2$) level increases during flow limitation (Rauhala et al., 2007), which could explain the gradually increasing respiratory effort. However, the clinical significance of the $tcCO_2$ increase during flow limitation is not known and therefore overnight $tcCO_2$ measurement is rarely included in polygraphic sleep studies.

While prolonged episodes of increased respiratory effort are always associated with flow limitation, episodes of flow limitation may also occur without increased effort (Ayappa et al., 2000). Since carbon dioxide is a more potent modulator of respiratory drive than oxygen (Dean and Nattie, 2010), hypercapnia is more likely to drive breathing during sleep than hypoxia. During withdrawal of the wakefulness stimulus for breathing after onset of sleep, the $tcCO_2$ increases and levels off with stabile sleep. We hypothesized that this stabile $tcCO_2$ level is critical for respiratory drive modulation; respiratory events with $tcCO_2$ below this reference are associated with low respiratory drive whereas events with $tcCO_2$

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above this reference level occur with high respiratory drive. We tested this hypothesis with progressively developing episodes of flow-limitation, which are likely to associate with changes in CO_2. Some of the results of this study have been previously reported in the form of an abstract (Rimpilä et al., 2010).

2. Methods

This study is a cross-sectional retrospective database analysis of cardiorespiratory sleep recordings from patient population with suspected SDB. All the patients had been studied according to the standard clinical practice, without any modification for any potential study. Therefore, approval of the institutional ethics committee was not required; according to the Finnish National Medical Research Act (488/1999). The study consisted of two parts: first, the screening of the patient population for partial upper airway obstruction and second, the detailed analysis of inspiratory flow limitation episodes in the selected population.

2.1. Measurements

The cardiorespiratory recordings included overnight measurement of arterial oxyhaemoglobin saturation (SaO_2), $tcCO_2$, transcutaneous oxygen (tcO_2), nasal flow (prongs), anterior tibial electromyography (EMG), body position, respiratory efforts from thorax and abdomen with respiratory inductance plethysmography (RIP) belts and snoring sound (Somnologica, Medcare Flaga hf, Reykjavik, Iceland). The partial pressures of CO_2 and O_2 were measured transcutaneously with a dual sensor, (TCM4, Radiometer, Copenhagen, Denmark). The sensor was fixed parasternally on the chest and warmed up to 43.0 °C, at which temperature the sensor could be kept in the same position for the duration of the night. Demographic features of the patients such as age, gender or BMI were collected from patient records.

2.2. Selection of recordings

Initially, 425 cardio-respiratory sleep recordings performed for screening SDB at Tampere University Hospital were assessed for signal integrity and presence of flow limitation. Recordings were discarded if, (1) contingent progressive inspiratory flow limitation patterns were not observed, or (2) the key signals (nasal flow, thoraco-abdominal belts) were unusable (missing or poor quality at the time of episodes). In order to ensure the $tcCO_2$ signal quality, a physiological range (approx. 1.33 kPa) of $tcCO_2$ throughout the night within recording was preferred starting point. $TcCO_2$ drift corrections per se were not performed because information from other CO_2 measurements such as arterial blood gases was not available.

137 recordings were approved for a more detailed analysis of the respiratory episodes and periodic leg movements (PLM). Finally, 36 recordings contained 77 episodes of flow limitation that fulfilled our inclusion criteria for the study. Episodes of apnea were scored according to the AASM criteria (Iber et al., 2007). Hypopnea was scored if the nasal flow drop was ≥50% of the baseline; event lasted for at least 10 s and was associated with 3% desaturation from pre-event baseline. An arousal criterion was not applied as it cannot be determined accurately without EEG. AHI does not predict the presence or type of flow limitation and therefore it was not used as a criterion for inclusion or exclusion. Leg movements (LM) were scored according to the WASM criteria (Zucconi et al., 2006) adapted for non-EEG recordings.

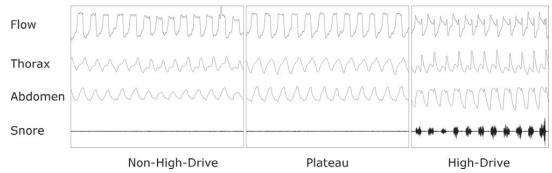

Fig. 1. Common characteristics of plateau, non-high-drive and high-drive episodes. Nasal prongs were used to measure the flow. The determination of the degree of respiratory drive was based on measurements of the respiratory effort with thoraco-abdominal belts and demonstration of absence or presence of heavy snoring on the microphone as supportive criterion. $TcCO_2$ mean values during plateau, non-high-drive and high-drive were 5.75 kPa, 5.74 kPa and 5.92 kPa, respectively, for this subject. For progressive (decreasing or increasing) patterns of effort see Figs. 3 and 4.

2.3. Detailed scoring of the flow limitation episodes

Detailed analysis of the flow limitation episodes was performed in 137 recordings pre-screened for the presence of one or more episodes of inspiratory flow limitation with minimum duration of 2 min per episode. Scoring of the episodes was performed blind to simultaneous $tcCO_2$ readings.

Nasal flow signal from the prongs was used to determine the presence of flow limitation. Breath-to-breath evolution of the nasal flow contour revealed progressively developing pattern of flow limitation. Respiratory effort was visually determined from RIP belts. The effort was determined to be low when amplitude change across the flow limitation episode was decreasing or steady and high when amplitude change was increasing. Episodes with any uncertainty of interpretation were not included. The selected episodes of flow limitation were classified as either high-drive (HD) or non-high-drive (NonHD) episodes. HD episodes were defined to have: (1) progressive inspiratory flow limitation; (2) rounded or flow limited inspiratory contour at the beginning of the episode; (3) sudden termination of the episode; (4) increasing thoracic or abdominal amplitude (crescendo pattern) developing during the episode (waxing and waning pattern not allowed); (5) presence of snoring allowed as a supportive criterion. The NonHD episodes were defined as: (1) progressive inspiratory flow limitation; (2) rounded inspiratory contour at the beginning of the episode; (3) sudden termination of the episode; (4) decreasing or steady thoracic and abdominal respiratory amplitude (5) absence of snoring as a supportive criterion. Table 1 summarizes the classification. When rounded flow contour could not be identified prior to the episode, the starting point was the first breath after which the flow contour started to show a progressive pattern of flow limitation (Fig. 1).

2.4. Defining the $tcCO_2$ plateau

After identification of flow limitation episodes, the overnight $tcCO_2$ signal was uncovered and first visually screened for stabile

Table 1
Classification of flow limitation episodes and plateau.

	Plateau	Non-high-drive	High-drive
Flow limitation	None or stabile	Progressive	Progressive
Effort	Stabile	Stabile or decreasing	Increasing
Snoring[a]	Absent or minor, stabile	Absent	Absent, present or crescendo

[a] Presence and quality of snoring was a supportive criterion only.

levels as candidates for $tcCO_2$ plateau. In this study we defined the $tcCO_2$ plateau as the highest level of $tcCO_2$ that is reached during regular unobstructed or obstructed breathing during the night. Unobstructed breathing is the optimum, but due to the population used, a minor stabile inspiratory flow limitation was allowed: flow limitation needed to be stabile on a breath-by-breath basis in terms of inspiratory flow and respiratory efforts. Minor snoring was also allowed. In case of several possible plateau candidates, the plateau in the closest proximity to the episode(s) was chosen. The validity of the chosen plateau was then confirmed by stabile ventilatory pattern and stabile respiratory effort throughout the plateau as described (Table 1).

2.5. Data analysis

$TcCO_2$ data collected for the duration of the selected episodes was analyzed with software developed by one of the authors (AV) for this purpose (Aittokallio et al., 2008; Virkki et al., 2008). The $tcCO_2$ signal was advanced by 30 s to compensate for the long response time and to reach synchronization with the respiratory episodes. The $tcCO_2$ signal that was available contained oscillation (see raw $tcCO_2$ signals in Figs. 2–4, B panels), which is a technical artifact related to software version of TCM4 device. Therefore a linear regression line was fitted to the signal with least squares method and $tcCO_2$ values in the beginning and termination of this line were used in the analysis. SaO_2 values were determined at the start and at the termination of the flow limitation episodes and plateau.

2.6. Statistical analyses

Demographic variables between patient groups were assessed with Kruskal–Wallis test. Episode durations between the NonHD and HD episodes were compared with Mann–Whitney *U*-test.

$TcCO_2$ slope of the determined plateau and flow limitation episodes was assessed with one-sample *t*-test. Differences between NonHD and HD episode slopes were compared with independent samples median test and Mann–Whitney test. Both absolute (kPa) and relative values (percent of the plateau $tcCO_2$, when plateau was set to 100%) of $tcCO_2$ at the start and at the end of the flow limitation episodes were compared against plateau $tcCO_2$ with pairwise *t*-test, assuming that the episodes were independent. Differences in absolute and relative $tcCO_2$ values between the NonHD and HD episodes were compared with a linear mixed model taking patient as random effect which enables multiple episodes per patient. Inter-patient variation of $tcCO_2$ between the start and at the end of the episodes was compared with independent samples *t*-test in both NonHD and HD episodes.

SaO_2 change (ΔSaO_2) during the flow limitation episodes was assessed with related samples Wilcoxon signed rank test. Distribution of ΔSaO_2 between the episodes was assessed with Mann–Whitney *U* test. Linear mixed model was used to compare the SaO_2 values between the NonHD and HD episodes. Nocturnal mean SaO_2 and plateau mean SaO_2 were compared with paired samples *t*-test.

Spearman's correlation was used to test the connection between $\Delta tcCO_2$ and ΔSaO_2 during the flow limitation episodes. Position, snoring, leg movements and periodic leg movements were treated qualitatively and differences between episode types were addressed with Chi-Square test with the assumption that episodes are independent. SPSS (version 20, IBM, Armonk, NY, US) was used for statistical analyses.

3. Results

3.1. Patient characteristics

Seventy-seven episodes from 36 patients fulfilled the inclusion criteria. The demographic features of the patients are shown in

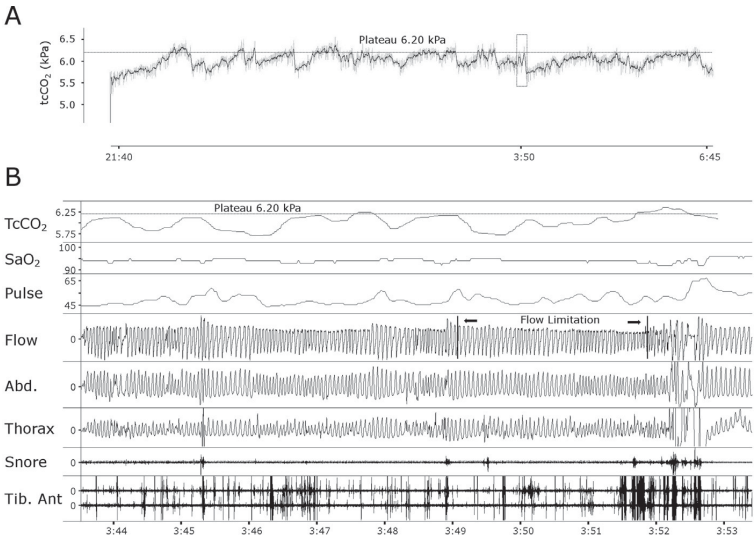

Fig. 2. Example of two consecutive non-high-drive (NonHD) episodes. Only the latter fulfills the duration criteria (minimum of 2 min) of the study. (A) Overnight transcutaneous CO_2 profile. The plateau level is marked with dashed line and the two flow limitation episodes are marked with the dashed box. Signal is averaged and marked with bold line. See text for details. (B) Detailed view of a low drive episode. Width of the panel is 10 min. The evolution of the inspiratory flow contour indicates worsening flow limitation over time. Abdominal and thoracic excursions do not respond despite increasing $tcCO_2$. The episode is terminated with opening of the airway with movement arousal. Leg twitches are present throughout the night. Plateau level is marked with dashed line and the episode selected for analyses is marked with vertical lines and solid arrows. Based on the $tcCO_2$ trace, an alternative plateau could be proposed at around 4:45, but this is rejected because unstable abdominal respiratory signal, not shown in the figure. $TcCO_2$ signal is advanced 30 s to show the correspondence between $tcCO_2$ and respiratory episode. $TcCO_2$ = partial pressure of transcutaneous carbon dioxide; SaO_2 = oxygen saturation from oximetry; Abd. = abdominal band; Tib. Ant. = anterior tibial EMG activity.

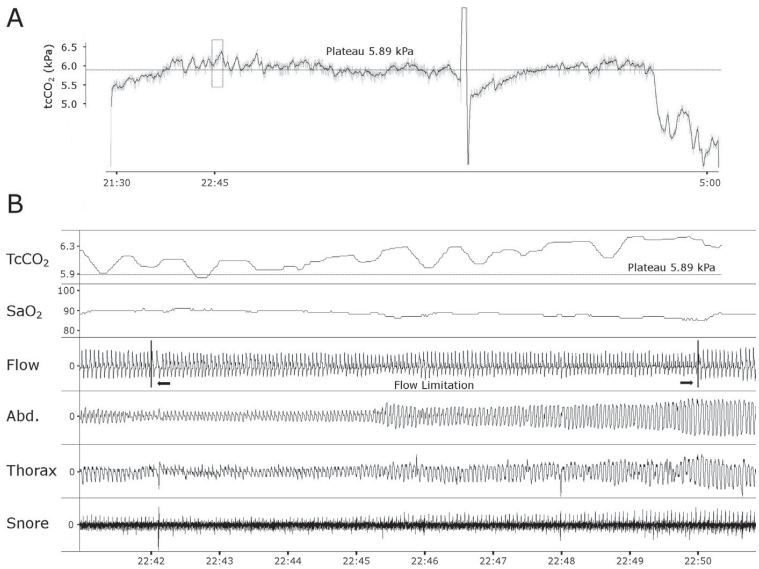

Fig. 3. Example of a high-drive (HD) episode. (A) Overnight transcutaneous CO_2 profile. The plateau level is marked with dashed line and the flow limitation episode is marked with the dashed box. Signal is averaged and marked with bold line. See text for details. (B) Detailed view of the high drive episode. Width of the panel is 10 min. Ventilatory drive responds to increasing $tcCO_2$. After a period of time, flow limitation resolves without movement arousal. Plateau level is marked with dashed line and the episode selected for analyses is marked with vertical lines and solid arrows. Alternative plateau candidates at around 22:00 and around 1:00 are rejected because of respiratory pattern: The first episode contains irregular breathing and movements, the second long episodes of hypopnea. $TcCO_2$ signal is advanced 30 s to show the correspondence between $tcCO_2$ and respiratory episode. $TcCO_2$ = partial pressure of transcutaneous carbon dioxide; SaO_2 = oxygen saturation from oximetry; Abd. = abdominal band.

Table 2. The AHI ranged from 0 to 42 / h of time in bed, but the majority of patients presented with mild SDB: 18 (50%) of the patients had an AHI less than 5/h. Most of the patients were overweight (average BMI 27.7 kg/m^2, range 20.5–41.4 kg/m^2). The median PLM index was 5/h, (range 0–88/h). The number of episodes selected from each subject ranged from one to eight. Twenty-two episodes were classified as NonHD type and 55 as HD type. The duration of NonHD episodes was at median 177 s (interquartile range

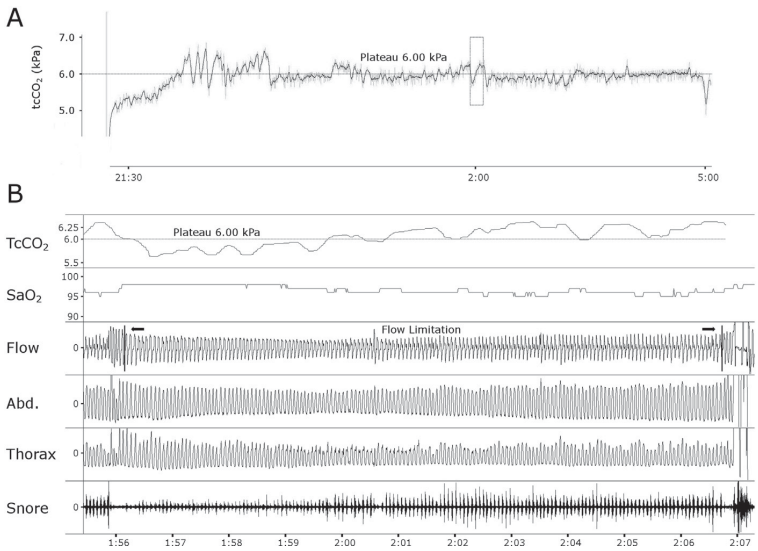

Fig. 4. Example of an episode of flow limitation with mixed drive response. (A) Overnight transcutaneous CO_2 profile. The plateau level is marked with dashed line and the flow limitation episode is marked with the dashed box. Signal is averaged and marked with bold line. See text for details. (B) Detailed view of the episode. Width of the panel is 12 min. Non-high-drive is followed by high-drive. Transition occurs when $tcCO_2$ crosses the plateau level. Increasing respiratory drive is unable to resolve flow limitation before movement arousal terminates the episode. Plateau level is marked with dashed line and the episode selected for analyses is marked with vertical lines and solid arrows. Alternative plateau level observed around 23:30 is rejected because of somewhat irregular breathing. Breathing during the morning period is highly regular. $TcCO_2$ signal is advanced 30 s to show the correspondence between $tcCO_2$ and respiratory episode. $TcCO_2$ = partial pressure of transcutaneous carbon dioxide; SaO_2 = oxygen saturation from oximetry; Abd. = abdominal band.

Table 2
Demographic features of the study population, $n = 36$.

	Mean	SD	Median	Min–max
Females, *n* (%)	13 (36.1)	–		–
Age	48	10.79	48	26–74
BMI (kg/m^2)	27.7	4.52	26.8	20.5–41.4
AHI (#/h)	10.1	11.90	4.9	0–42.3
AI (#/h)	3.5	5.90	0.8	0–22.2
HI (#/h)	6.7	8.36	3.4	0–40.7
SaO_2 mean (%)	94.6	2.39	95.0	88.3–97.6
SaO_2 min (%)	82.6	6.43	84	67–91
$TcCO_2$ set-point (kPa)	5.69	0.42	5.72	4.84–6.73
PLM index (#/h)	10.8	16.77	4.9	0–88
LM index (#/h)	18.2	17.13	11.7	1.6–94

Definition of abbreviations: BMI, body mass index; AHI, apnea–hypopnea index; AI, apnea index; HI, hypopnea index; SaO_2, arterial oxyhemoglobin saturation; $tcCO_2$, transcutaneous carbon dioxide; PLM, periodic leg movements; LM, leg movements.

131–221 s) and HD episodes 397 s (interquartile range 242–594 s, $p < 0.001$). Supine sleeping position was equally common during NonHD and HD episodes. Seven patients had only NonHD episodes (NonHD patients), twenty-five patients had only HD episodes (HD patients), and four patients had both types of flow limitation episodes (mixed patients). Comparison between the three patient groups (NonHD, HD and mixed) with Kruskal–Wallis test did not reveal any significant differences in BMI, AHI, apnea-index (AI), hypopnea-index (HI), mean SaO_2, min SaO_2, $tcCO_2$ plateau, PLM index or LM index (Table 3).

3.2. $TcCO_2$

The $tcCO_2$ increased during both the NonHD and HD episodes at an average rate of 4.04 kPa/h. The slopes of increase were significantly different from zero (5.11 kPa/h during the NonHD episodes and 3.61 kPa/h during the HD episodes, $p < 0.001$) but did not differ from each other ($p = 0.12$). The $tcCO_2$ increased also during the plateau ($p = 0.045$), but with a lower slope (0.33 kPa/h, $p < 0.001$) than that measured during either type of flow limitation episodes.

NonHD episodes (Fig. 2.) occurred at a lower $tcCO_2$ level compared to HD episodes (episode start mean 95.8% vs 99.3% of plateau, $p = 0.071$, episodes termination mean 100.1% vs. 105.2%, $p = 0.055$, Fig. 5). NonHD episodes started with $tcCO_2$ that was on average 0.24 kPa below the plateau ($p < 0.001$) and ended with $tcCO_2$ equal to the plateau (−0.01 kPa; $p = 0.808$). HD episodes (Fig. 3.) started with $tcCO_2$ at around the plateau (−0.04 kPa; $p = 0.076$) but ended with significantly higher $tcCO_2$ (0.30 kPa higher than plateau,

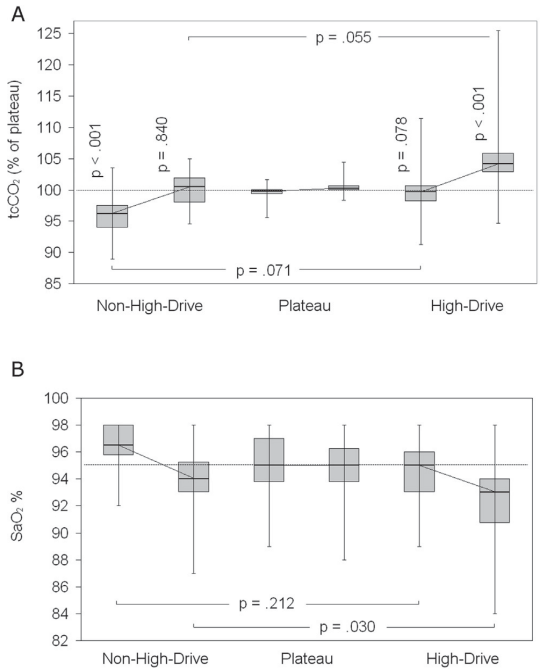

Fig. 5. Summary of flow limitation episodes. (A) Panel shows a box-plot with the median, quartiles and range of $tcCO_2$ at the start and termination (connected with solid lines, start of the episode on the left side) of all analyzed episodes of progressive flow-limitation and plateau. The dashed line indicates the plateau level set to 100%. *P*-values connected with lines denote the differences between the different episode types at the start and termination of episode. Vertical *P*-values denote the difference between plateau level and the particular episode phase. Non-high-drive ($n = 22$) episodes start below the $tcCO_2$ plateau whereas high-drive ($n = 55$) episodes terminate above the plateau. Non-high-drive episodes terminate and high-drive episodes start at around the plateau. There is no consistent trend of $tcCO_2$ during the plateau episodes. (B) Panel shows a box-plot presentation of the corresponding SaO_2. The dashed line indicates the median SaO_2 of 95% observed during the $tcCO_2$ plateau. *P*-values connected with lines denote the differences between episodes at the start and termination of episodes. $TcCO_2$ = partial pressure of transcutaneous carbon dioxide; SaO_2 = oxygen saturation from oximetry.

Table 3
Characteristics of the two types of flow limitation episodes.

	Non-high-drive ($n = 22$)	High-drive ($n = 55$)	*p*
Episode duration (s)	177 (131–221)	397 (242–594)	<0.001
$TcCO_2$ (% of plateau)			
Episode start	95.8[a] (0.036)	99.3 (0.029)	0.071
Episode end	100.1 (0.029)	105.2[a] (0.044)	0.055
Slope (kPa/h)	5.11 (4.88)	3.61 (3.28)	0.182
SaO_2 (%)[b]			
Episode start	96.50 (95.75–98)	95 (93–96)	0.212
Episode end	94 (93–95.25)	93 (90.75–94)	0.03
ΔSaO_2 (end-start)	−2.00 (−4.0 to −0.75)	−2.00 (−3.25 to −0.75)	0.871
Supine position, *n* (%)	10 (45.5)	26 (50)[c]	0.80
Snore, *n* (%)	0 (0%)	28 (50.9%)	<0.001
LM, *n* (%)	3 (13.6%)	14 (25.5%)	0.37
PLM, *n* (%)	1 (4.6%)	11 (20%)	0.10

Episode duration and SaO_2 values are presented as median and quartiles. $TcCO_2$ and qualitative data are presented as mean and SD. ΔSaO_2, episode end-episode start; LM, leg movements; PLM, periodic leg movements.

[a] $p < 0.001$ compared to plateau.
[b] Not available during one high-drive episode.
[c] Not measured during 3 episodes.

$p < 0.001$). Episodes with both NonHD and HD components were treated as HD episodes (Fig. 4).

During NonHD episodes the standard deviation (SD) of relative $tcCO_2$ was 0.0357 at the start and 0.0288 at the end ($p < 0.001$). During HD episodes the opposite was found: SD at the start (0.0293) was lower than at the end (0.0438, $p < 0.001$).

3.3. SaO_2

The arterial oxyhemoglobin saturation decreased (ΔSaO_2) similarly during both NonHD and HD episodes with median decrease of 2.0%-units during both type of episodes ($p < 0.001$), but distribution of ΔSaO_2 did not differ between episodes ($p = 0.871$). The median SaO_2 did not differ between the episodes at the start (96.5 vs. 95.0%, $p = 0.212$) but the HD episodes terminated at lower SaO_2 compared to the NonHD episodes (94.0 vs. 93.0%, $p = 0.03$, Fig. 5).

The SaO_2 measured during the plateau correlated highly with the mean nocturnal SaO_2 ($r = 0.939$, $p < 0.001$). A significant correlation was also observed between the $tcCO_2$ increase and the SaO_2 decrease during the episodes (Spearman's rho for NonHD: $r = -0.382$, $p = 0.004$ and HD: $r = -0.460$, $p = 0.031$). The $tcCO_2$ increased during all but one NonHD episode in a linear function of time, whereas SaO_2 decrease was observed during 75.9% of HD episodes and 77.3% of NonHD episodes.

4. Discussion

Our new data demonstrate that $tcCO_2$ increases during all episodes of progressive flow limitation, irrespective of the degree of respiratory effort. We have previously shown that $tcCO_2$ increases during episodes of progressive flow limitation with high respiratory drive (Rauhala et al., 2007). Our new data demonstrate that $tcCO_2$ also increases during episodes of progressive flow limitation in the absence of progressively increasing respiratory drive. This finding contradicts the common thinking that the respiratory drive during sleep increases as a linear function of increasing CO_2. The novel finding is that during flow limitation the $tcCO_2$ needs to exceed a certain set-point level until respiratory effort starts to increase. This set-point corresponded to the visually determined plateau $tcCO_2$, measured during episodes of stabile breathing during sleep. The NonHD episodes started with significantly lower $tcCO_2$ than the set-point but as the episodes evolved, the $tcCO_2$ gradually increased, terminating at $tcCO_2$ levels close to the set-point. Analogically, the $tcCO_2$ values at the beginning of the HD episodes did not differ from the set-point, but at the moment of termination were significantly above the set-point. Our results confirm the previous finding that episodes of inspiratory flow limitation may occur with both low and high respiratory drive (Ayappa et al., 2000). In the current study we demonstrate that the level of $tcCO_2$ measured during stabile sleep is the set-point, which the control of breathing targets during flow limitation.

Our new finding indicates that the respiratory effort during flow limitation do not increase as a linear function of the $tcCO_2$. Instead, there is a set-point level of $tcCO_2$, measurable through the skin, below which respiratory drive during sleep does not strongly respond to $tcCO_2$ increase. Below this set-point, despite progressive $tcCO_2$ increase, flow limitation is not associated with a crescendo pattern of increasing respiratory effort. We suggest that drive to both respiratory pump muscles and upper airway dilator muscles during transitions between wakefulness and stabile sleep remains low and produces the NonHD flow limitation episode. Low drive to respiratory pump muscles could result from central hypoventilation, aiming at physiological $tcCO_2$ increase up to the set-point. Low drive to upper airway dilator muscles predisposes to flow-limitation, which contributes to $tcCO_2$ increase. Compared to HD episodes, the NonHD episodes were shorter and the $tcCO_2$ increased faster. Because clear marker of event termination was required for event inclusion, a selection bias toward episodes with fast $tcCO_2$ increase terminating at arousal may have occurred. Therefore, we may have missed those NonHD episodes, during which more slowly rising $tcCO_2$ could stabilize at set-point level without disturbance. Whether acceleration of the $tcCO_2$ increase by flow limitation during a NonHD episode has some role in inducing arousal (respiratory effort related arousal, RERA), remains to be studied.

In contrast to NonHD episodes, progressive flow limitation during HD episodes results in vigorous response, producing prolonged episodes of constantly increasing respiratory effort (crescendo pattern) and corresponding $tcCO_2$ increase. Depending on the response of the upper airway dilator muscles, continuing flow limitation with $tcCO_2$ above set-point either stabilizes the upper airway (sufficient response) or initiates a vicious circle of aggravating flow limitation with increasing respiratory effort (insufficient response). The HD episodes may continue for several minutes, since they only occur when the arousal threshold is highest during slow-wave sleep. In literature, this pattern is referred to as increased respiratory resistance (IRR) pattern (Alihanka, 1987; Polo et al., 1991; Anttalainen et al., 2007), obstructive hypoventilation (Isono and Remmers, 1994) or crescendo pattern (Stradling, 1995). Simultaneous measurements of esophageal pressure have confirmed that these events are associated with highly increased intrathoracic pressure variation as a marker of increased respiratory drive (Polo et al., 1991; Rauhala et al., 2007).

Reliable identification of the $tcCO_2$ plateau was critical for the study. The increase of CO_2 is a well-known physiological event while falling asleep, which has been demonstrated by measuring the arterial or end-tidal CO_2 (Henke et al., 1990). However, to our knowledge, the leveling-off of $tcCO_2$ during stabile sleep has not been reported before. The plateau seems more evident on $tcCO_2$ signal than when using other methods of CO_2 monitoring. This is in line with the idea that the plateau is not determined by ventilation alone but by the product of ventilation and perfusion, controlled by the autonomic nervous system. The $tcCO_2$ plateau was unanimously identifiable in most recordings, when the detection was based on high, constant $tcCO_2$ level combined with stabile unobstructed respiratory pattern. However, some degree of stabile flow limitation or snoring was allowed, since flow limitation was common in this population. In some patients this may have led to minor over-estimation of the plateau-level. In case signal drift was suspected, the plateau level was determined as close as possible to the flow-limited episodes. Awareness of potential artifacts and rejection of technically insufficient recordings are essential for obtaining reliable $tcCO_2$ readings.

The $tcCO_2$ method was developed for non-invasive monitoring of the arterial CO_2. Decent performance has been demonstrated in situations where the autonomic state of the patient remained stable (e.g. mechanical ventilation during anesthesia (Xue et al., 2010)). The accuracy of $tcCO_2$ measurements to estimate arterial CO_2 has been questioned because the method is sensitive for vasoconstriction (Healey et al., 1987; Clark et al., 1992). It is possible that slow wave sleep as a hemodynamically stabile vasodilatory state could also stabilize the $tcCO_2$ readings. Despite marked recent advance in the $tcCO_2$ technology regarding calibration and long-term stability (overnight) of the signal, the reliability of the readings are challenged by problems such as drift, air leakage and changes in body position. In our data, body position did not explain the observed $tcCO_2$ differences between NonHD and HD episodes. The consistency of the connection between the respiratory effort driven by the chemoreceptors and the $tcCO_2$ levels measured across the peripheral skin is striking. During wakefulness or during arousals from sleep, surges of sympathetic outflow to the carotid body (Fidone

and Gonzalez, 1986) and to the skin (Morris, 1997) may parallel. We have previously modeled potential modulation of the carotid body sensitivity by changes in carotid body perfusion under control of sympathetic outflow (Virkki et al., 2007). The rapid drops seen at Figs. 2–4 A-panels are most likely arousals. Arousals drop the $tcCO_2$ rapidly toward the levels measured during wakefulness since both the respiratory and circulatory demands are changed from those of sleep to those of wakefulness. In conclusion, the value of the $tcCO_2$ signal as a measure of the product of ventilation and peripheral perfusion should be understood and taken advantage of as a measure of the peripheral acid-base balance.

The validity of the inductance belts used in our study in assessing respiratory drive can be questioned. Esophageal pressure measurement would have been the optimal metrics for measuring respiratory drive and pneumotachography for exact measuring of airflow and flow contour. Taken into account the large patient population that was needed for primary screening of episodes, this approach was not feasible. The thoraco-abdominal belts are a decent surrogate in most occasions for measuring the respiratory efforts (Masa et al., 2003). It is possible, although unlikely, that narrowing of the upper airway may limit the movement of the ribcage or diaphragm in a way that increasing respiratory drive would result in decreasing thoraco-abdominal amplitude. This would have caused mislabeling of an HD episode as a nonHD one. On the other hand, we are not aware of any mechanism that would cause mislabeling of nonHD episodes as HD ones. Failure to distinguish between the types of episodes would have resulted in weakening of our results. The consistent results are in line with sufficiently successful episode labeling. Any improvement in drive measurement should only enhance our findings.

Only cardiorespiratory polygraphic recordings were available for analysis. One could argue that without polygraphic recording of sleep, it would not be possible to differentiate between wakefulness and sleep, or, more importantly, between REM and NREM sleep. There are a number of arguments that make us convinced that the episodes we chose for analyses were all during NREM sleep. First, we started with episodes of clear, long lasting episodes of regular breathing with constant or gradually aggravating flow limitation. It is highly unlikely that these episodes of flow limitation would have occurred while awake. Second, there are a number of clues to suspect REM from respiratory parameters. Episodes of flow limitations were not included when bursts of phasic events typical for REM sleep manifested either as irregular breathing efforts, variable heart rate or twitches in the anterior tibial EMG were present. The muscle atonia of REM affects more the intercostal muscles than the diaphragm, resulting in decreased respiratory movement amplitude that is only seen in the thoracic belt signal. For the purpose of the study we could afford rejecting any episode of flow limitation that did not fulfill all the strict inclusion criteria. Therefore, it is unlikely that any of the chosen respiratory episodes would have occurred during REM sleep. Episodes of flow limitation rejected because of possible REM were short and represented NonHD type episodes, even when the $tcCO_2$ levels increased above the established $tcCO_2$ plateau level. This is in line with the fact that the control of breathing during REM differs from NREM sleep and suggests that the $tcCO_2$ plateau chosen according to our criteria to represent the set-point of respiratory drive is valid only for NREM sleep.

Our study was a retrospective analysis of consecutive cardiorespiratory recordings collected as part of clinical diagnostic procedures. To reveal the existence of a new phenomenon with methodology that was available, we carefully selected patients with sleep recordings of high technical quality, who fulfilled our strict inclusion criteria for flow-limitation. The high number of excluded patients does not mean that these phenomena as such are rare in patients with SDB. In technically successful recordings, the $tcCO_2$ plateau level can be determined in almost all cases. Flow-limitation episodes are particularly common in patients, in whom SDB ranges from non-apneic snoring to mild to moderate sleep apnea. The most common reason for exclusion was the minimum duration of the flow-limitation episodes of 2 min. This resulted in exclusion of many patients, whose inspiratory flow limitation episodes with low respiratory drive were shorter than required. We did not want to compromise with these criteria, since we wanted a clear trend in the relatively slow responding $tcCO_2$ signal. This was only a methodological limitation, without any suspicion that shorter episodes as such would behave differently. We also carefully rejected episodes with potential waxing and waning pattern of the respiratory drive in the background. Many HD episodes were not included because the initial crescendo pattern did not terminate but shifted to stabile HD breathing with stabile flow-limitation or heavy snoring, indicating that inspiratory duty cycle and effort are in balance (Schneider et al., 2009). By careful episode selection, we aimed at uncovering mechanisms that could be generalized to much larger groups of patients.

Identification of the $tcCO_2$ plateau and the set-point for respiratory drive during sleep as part of polygraphic sleep recording or cardiorespiratory recording has significant clinical value and has become a routine practice at our sleep center. The major advantage is that it may help to differentiate between respiratory events that are either of central or obstructive origin. Respiratory episodes during sleep, including episodes of apnea or hypopnea, may result either from unstable sleep with repetitive arousals constantly shifting the respiratory set-point (Wellman et al., 2011) or from unstable upper airway. This results in a mixture of central and obstructive events. The conventional differentiation between episodes of central and obstructive apnea has recently been extended to also include central and obstructive hypopnea (Berry et al., 2012; Mooney et al., 2012). Based on our results, this concept could perhaps be applied also to flow limitation, the NonHD events representing flow limitation from central origin and the HD events flow limitation driven by upper airway obstruction (Rimpilä et al., 2010). Therefore, differentiation between episodes of low and high drive may have clinical implications; since also central and obstructive sleep apnea are treated differently. An analysis of the respiratory events in relation to the $tcCO_2$ plateau may be of interest when patients are symptomatic with low AHI (Anttalainen et al., 2007).

In conclusion, the $tcCO_2$ plateau phenomenon, expressing the level of peripheral CO_2 during which airway stability is balanced with minimal respiratory drive during sleep, may help to assess the clinical importance or understand the clinical manifestation of the symptoms and cardiovascular co-morbidities of the patient. Our novel finding in patient population with suspected SDB suggests that there is a target CO_2 level during sleep, which is dependent on both ventilation and perfusion, and which determines the degree of respiratory drive and the autonomic nervous system state. Optimizing the CO_2 level at this set-point level should be the target of all therapies aiming at improving SDB.

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Transcutaneous carbon dioxide during sleep-disordered breathing

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Transcutaneous carbon dioxide during sleep-disordered breathing

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ABSTRACT

Respiratory drive is tightly controlled by the carbon dioxide levels. We tested the hypothesis that sequences of sleep apnoea (obstructive, central or mixed), hypopnoea and flow limitation are characterized by different levels of transcutaneous CO_2 ($PtcCO_2$). Polygraphic recordings ($n = 555$) from patients with suspected sleep-disordered breathing (SDB) were retrospectively screened to find sequences (5 min or 10 events) of both SDB and steady breathing. Eighty-eight SDB sequences from 44 patients were included and $PtcCO_2$ and SpO_2 values were collected. $PtcCO_2$ values during sequences were normalized by setting wakefulness level as 100%. In terms of $PtcCO_2$, apnoea sequences with central component (central ($n = 7$) and mixed ($n = 3$) apnoea) did not differ from wakefulness (102.0% vs 100%, $p = 0.122$) whereas obstructive apnoea (105.8%, $p < 0.001$) and hypopnoea did (105.4%, $p < 0.001$). $PtcCO_2$ during flow limitation was higher than that during any other sequence, including steady breathing (112.2% vs 108.4%, $p = 0.022$). Continuous $PtcCO_2$ monitoring during sleep adds to the understanding of different SDB phenotypes.

1. Introduction

Recording the arterial oxyhaemoglobin saturation (SaO_2) during sleep is a standard method to monitor the effect of sleep-disordered breathing (SDB) on arterial oxygen content. Monitoring the carbon dioxide during sleep is technically more demanding and its interpretation more complex. Therefore, the carbon dioxide is less frequently monitored during standard polysomnography (PSG) and its physiology less understood. Since carbon dioxide has important physiological roles including controlling pH and local perfusion through nitric oxide production (Lavi et al., 2003), better understanding of carbon dioxide physiology during sleep is needed.

Carbon dioxide is usually measured to detect hypoventilation during sleep (Pautrat et al., 2015). Gold standard is the arterial partial pressure of carbon dioxide ($PaCO_2$), but repetitive samples are difficult to obtain during sleep. Therefore, surrogate measures are used. End-tidal carbon dioxide ($PetCO_2$) provides breath-to-breath measurement, but low tidal volumes or mouth breathing can distort the results. Transcutaneous carbon dioxide ($PtcCO_2$), which reflects both ventilation and perfusion at the periphery (Stock, 1988; Clark et al., 1992), is not directly affected by mouth breathing or mask ventilation, but slow response time affects the timing in the analysis of individual respiratory events (Janssens et al., 1998; Kesten et al., 1991). Comparison between these different methods is difficult since they measure carbon dioxide at different sites and different phases of CO_2 production, diffusion, buffering or transport. Therefore, one CO_2 signal should not only be used as an estimate of another, since each signal has value in its own right. The $PtcCO_2$ signal is closest to the CO_2/pH environment at the tissue level, which in many clinical situations would be more useful than $PaCO_2$, if understood and interpreted accordingly.

We previously introduced the concept of $PtcCO_2$ plateau, defined as steady level of $PtcCO_2$ associated with steady breathing

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during sleep (Rimpilä et al., 2014). This plateau was shown to differentiate two phenotypes of upper airway flow limitation. The aim of the present study was to assess: (1) whether $PtcCO_2$ measurement is sensitive enough to detect differences between SDB types and (2) if so, how the $PtcCO_2$ levels associated with different phenotypes of SDB relate to the $PtcCO_2$ levels measured during wakefulness and the plateau $PtcCO_2$ during sleep. We hypothesized that each breathing type has a distinct $PtcCO_2$ level.

2. Methods

2.1. Ethical approval and patients

Initially, 555 cardio-respiratory sleep recordings with $PtcCO_2$ measurement performed between June 2005 and May 2007 in Tampere University Hospital, Tampere, Finland, were used for the study. All patients had previously been studied according to the standard clinical practice, without any modification for research purposes. Approval of the institutional ethics committee was therefore not required according to Finnish legislation.

2.2. Measurements

The cardiorespiratory recordings included overnight measurement of arterial oxyhaemoglobin saturation from pulse oximetry (SpO_2), nasal flow (prongs), anterior tibial electromyography (EMG), body position, respiratory efforts (uncalibrated thoracic and abdominal respiratory inductance plethysmography) and snoring (piezoelectric sensor) (Somnologica, Medcare Flaga hf, Reykjavik, Iceland). The partial pressures of CO_2 and O_2 were measured transcutaneously with a dual sensor, (TCM4, Radiometer, Copenhagen, Denmark). Device was calibrated with fixed gas composition (CO_2:7.5%, O_2:20.9%, N_2:71.6%) before sleep studies. The sensor was attached to upper chest next to sternum and warmed up to 43.0 °C, at which temperature the sensor was kept in the same location for the duration of the night. Online recording of the digital output of the TCM4 device with custom written software (TCM4ebm by Jussi Virkkala) ensured full synchronization and integration of the $PtcCO_2$ signal with Somnologica. Background information such as age, gender and BMI were collected from patient records. Arterial blood gas values were not available.

2.3. Design

This study is a database analysis of cardiorespiratory sleep recordings from patient population with suspected SDB. The study consisted of two phases. First, screening of the patient population for SDB sequences and normal breathing, and second the analysis of the effect of different types of SDB sequences on $PtcCO_2$ and SpO_2 levels. A recording was included to the study if all of the following sequences were identified: (1) a sequence of undisturbed normal breathing during evening wakefulness, (2) a sequence of steady breathing with minimal flow-limitation during sleep, and (3) one or more sequence(s) of cyclic SDB (central, mixed and obstructive apnoea or hypopnea). After inclusion, the $PtcCO_2$ traces were uncovered and recordings with insufficient $PtcCO_2$ quality: detached sensor or air leak within sensor, extremely low (below 3.0 kPa) or high (above 7.0 kPa) levels, suspicion of excessive overnight signal drift (more than 1.0 kPa difference between evening and morning wakefulness) or incomplete signal (morning/evening values missing), were excluded.

2.4. Sequence selection

Unfiltered nasal pressure signal, nasal flow signal with square root transformation and signal from snoring sensor were used to score the breathing. Wakefulness sequence with normal breathing was identified in the beginning of the recording, before lights-off mark. Sequences of steady breathing with minimal flow-limitation were characterized by breathing with stable amplitude and frequency and selected from period between wakefulness in the evening and clear awakening in the morning. Minimal flow-limitation (the inspiratory flow contour is not completely round) without snoring, and absence of major body movements were required to ensure that the sequence occurred during sleep. Episodes with waxing and waning patterns were not accepted. When more than one sequence of steady breathing was identified, the one with greatest stability was selected.

Inspiratory flow-limitation sequence with or without snoring was also included in the analysis when present. Identification of flow-limitation was based on typical inspiratory peaks and flattening of the inspiratory flow (Aittokallio et al., 2001), associated with signs of increased respiratory effort on the thoraco-abdominal belts.

Sequences of cyclic SDB events, repeating with similar pattern, were scored by using the following criteria: (1) the sequence length should be five minutes or more, or contain ten or more similar individual events; (2) the consecutive events within the sequence had to resemble each other in terms of their length and respiratory pattern. At least 50% of the respiratory events had to have the same classification (central, mixed, obstructive or hypopnea). Sequences were classified according to their most frequent event type. The respiratory events were scored apnoea, if they had a 90% reduction in inspiratory amplitude for a minimum duration of ten seconds. Episodes of hypopnoea were required to have 30% reduction in inspiratory amplitude for a minimum duration of ten seconds with no desaturation criteria. However, desaturation of 3% or more was noted when present. For the purpose of the study, one representative sequence of each type from each patient was included to the analysis. In the case of several candidate sequences the one with greatest stability and highest proportion of events with same classification was selected.

2.5. Data analysis

There is marked inter-individual variation in the $PtcCO_2$ readings (Fukui et al., 1993). Therefore, instead of comparing the absolute levels of the $PtcCO_2$ during various types of SDB, we analyzed the differences between sequences using either absolute ($\Delta PtcCO_2$, kPa) or relative (%) scales by fixing the $PtcCO_2$ levels observed during wakefulness as zero kPa or 100%. Additionally, the relative $PtcCO_2$ levels (%) during sequences were also compared when the $PtcCO_2$ during steady breathing with minimal flow-limitation was set to 100%.

Pre-event SpO_2 levels (SpO_2 start) and desaturations related to individual respiratory events in sequences with cyclic nature were determined and average values were used in the analysis. For stable sequences (wakefulness, steady breathing and flow limitation) median values were used. Once the final study population was confirmed the apnoea–hypopnoea-indices (AHI) were determined according to the latest consensus statement with the exception of arousal criterion for hypopnoea, which could not be used (Berry et al., 2012). Leg movements and PLM were scored according to the WASM criteria (Zucconi et al., 2006) with the exception that leg movements occurring within ten seconds on both sides of apnoea termination were considered to have an association and were excluded from the PLM index.

2.6. Statistical methods

The effect of gender on $PtcCO_2$ values was tested with Mann–Whitney *U* test and the effect of age with univariate ANOVA.

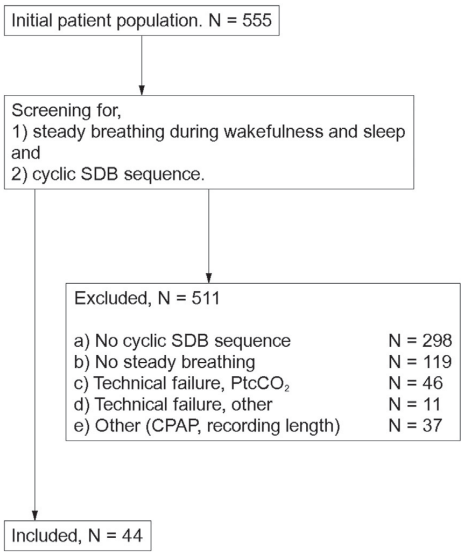

Fig. 1. Selection of the final study population, which included 44/555 (7.9%) of initial patient population. SDB = sleep-disordered breathing, $PtcCO_2$ = transcutaneous carbon dioxide.

Differences in $PtcCO_2$ and SpO_2 values between sequences were assessed using independent samples Kruskal–Wallis test with Bonferroni correction. The effect of using different fixation points for $PtcCO_2$ (wakefulness 100% vs steady breathing 100%) was assessed with Levene's test for equality of variances. *p*-value of less than 0.05 was considered significant. Statistics were analyzed using SPSS software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.)

3. Results

3.1. Characteristics of the study population

Tracings from 44 patients (34 men and 10 women) fulfilled the inclusion criteria of the study and were further analyzed (Fig. 1.). Main characteristics of the population are shown in Table 1. AHI range of this study population was 3.6–53 1/h. Mean increase in $PtcCO_2$ from wakefulness to sleep was 0.41 kPa (3.04 mmHg). Neither gender nor age had an effect on $PtcCO_2$ values.

Table 1
Patient characteristics.

	Mean/median	SD/IQR
Sex, M:F(*n*)	34:10	
Age (years)	52.8	11.0
BMI (kg/m^2)	30.5	5.9
AHI (#/hour)	21.8	13.2
Apnoea index	8.4	8.4
Central apnoea index	1.7	2.9
Obstructive apnoea index	5.5	6.2
Mixed apnoea index	1.2	2.9
Hypopnoea index	13.4	10.0
PLM (#/hour)	*10.9*	*28.7*
Recording length, (min)	443.4	75.9
$PtcCO_2$, wakefulness, (kPa)	*5.18*	*0.45*
$PtcCO_2$, steady breathing, (kPa)	*5.47*	*0.61*
$\Delta PtcCO_2$ (steady breathing-wake), (kPa)	*0.41*	*0.44*
Overnight SaO_2 mean, (%)	93.8	2.0
Overnight SaO_2 min, (%)	82.4	6.4

Indices calculated as #/analyzed hours. AHI, apnoea-hypopnoea index; PLM, periodic leg movements; $PtcCO_2$, transcutaneous carbon dioxide; SaO_2, arterial oxyhaemoglobin saturation. Median and interquartile ranges (IQR) presented in italics.

3.2. Characteristics of SDB sequences

Eighty-eight SDB sequences were detected. Most of these were hypopnoea sequences ($n = 32$) or flow limitation ($n = 32$). Only three sequences of mixed apnoea were detected and they were pooled together with central apnoea ($n = 7$) sequences, with central component of breathing as a common feature. Table 2 shows the SDB sequence characteristics. Most notable differences can be seen in absolute and relative values of $PtcCO_2$ and position distributions: two thirds of the cyclic SDB sequences occurred in supine position (66.7–92.9%), whereas one third of the steady breathing with minimal flow-limitation and flow limitation sequences occurred while supine (31.0% and 32.3%, respectively).

Total of 608 respiratory events were included from central, mixed, obstructive and hypopnoea sequences. 534 events (87.8%) were associated with arterial oxyhaemoglobin desaturation (3% or more). The analyzed SDB sequences were very homogenous; only 41 events (6.7%) in 18 sequences did not match with their sequence classification. Figs. 2 and 3 show examples of overnight tracings.

3.3. Transcutaneous carbon dioxide in SDB sequences

Eight patients showed average $PtcCO_2$ values higher than 6.00 kPa (45 mmHg), highest being 6.54 kPa (49.1 mmHg) during flow-limitation. In three patients the morning $PtcCO_2$ was higher than 6.0 kPa, highest being 6.47 kPa (48.5 mmHg). The other two were 6.02 kPa.

Pairwise comparisons of the absolute and relative changes in $PtcCO_2$ levels during SDB sequences, wakefulness, and steady breathing during minimal flow limitation are shown in Table 3 and Fig. 4. In the absence of SDB, the $PtcCO_2$ was higher during sleep (steady breathing with minimal flow limitation) compared to wakefulness. The $PtcCO_2$ levels during respiratory sequences with central component (central or mixed apnoea) did not differ from those measured during wakefulness, but they were lower than the $PtcCO_2$ levels during stable breathing with minimal flow limitation. The $PtcCO_2$ levels during the other SDB events (obstructive apnoea, hypopnoea and flow-limitation) were higher than those during wakefulness. The highest levels of $PtcCO_2$ were observed during flow limitation, the difference being significant when compared to steady breathing during minimal flow limitation and all other forms of SDB, Supplementary Fig. A.1 and A.2 for individual $PtcCO_2$ values.

When steady breathing was used as a baseline for relative $PtcCO_2$ instead of wakefulness, the variances of $PtcCO_2$ within SDB sequences became significantly smaller, except for obstructive apnoea which had the smallest variance (Fig. 5).

Supplementry material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.resp.2015.10.002.

3.4. Arterial oxyhaemoglobin saturation during SDB sequences

The SpO_2 results are shown in Table 2 and Fig. 4. The levels of SpO_2 at the beginning of desaturation events during cyclic SDB did not differ from each other ($p = 0.066$), but the SpO_2 nadirs during hypopnoea (91.6%) sequences were more shallow than those during central (89.9%, $p = 0.035$) or obstructive apnoea sequences (88.8%, $p = 0.05$). The median SpO_2 during wakefulness (95.0%) was similar to steady breathing with minimal flow limitation (94.0%, $p = 0.078$) but higher than that during flow-limitation (94.0%, $p = 0.006$).

Table 2
Characteristics of the SDB sequences ($n = 88$).

	Cyclic breathing					
Sequence (n)	Wakefulness	Central + Mixed apnoea (10)	Obstructive apnoea (14)	Hypopnoea (32)	Steady breathing	Flow-limitation (32)
$PtcCO_2$ (kPa)	5.18, (0.45)	5.11, (1.00)	5.31, (0.37)	5.50, (0.75)	5.47, (0.61)	5.64, (0.66)
$PtcCO_2$, Δwake (kPa)	0	0.10, (0.43)	0.29, (0.25)	0.27, (0.47)	0.41 (0.43)	0.60, (0.32)
$PtcCO_2$ (%), (%-units)	100 (0)	102.0 (8.5)	105.8 (5.5)	105.4 (9.4)	108.4 (8.6)	112.2 (6.8)
SaO_2, event start (%)	–	96.4 (1.4)	96.6 (1.9)	95.9 (1.8)	–	–
SaO_2, event desaturation (%)	–	89.9 (5.6)	88.8 (7.0)	91.6 (3.6)	–	–
SaO_2 (%)	95.0 (2.0)	–	–	–	94.0 (3.0)	94.0 (3.0)
Sequence length (min)	0:04:41	0:07:48	0:08:46	0:07:00	0:05:56	0:07:06
Supine (%)	69.8	70.0	92.9	74.2	31.0	32.3

Values presented as medians with interquartile range in the parentheses. Sequence lengths are shown as mean values. Pairwise comparisons of $PtcCO_2$ values are shown in Table 3. $PtcCO_2$, transcutaneous carbon dioxide; SaO_2, arterial oxyhaemoglobin saturation.

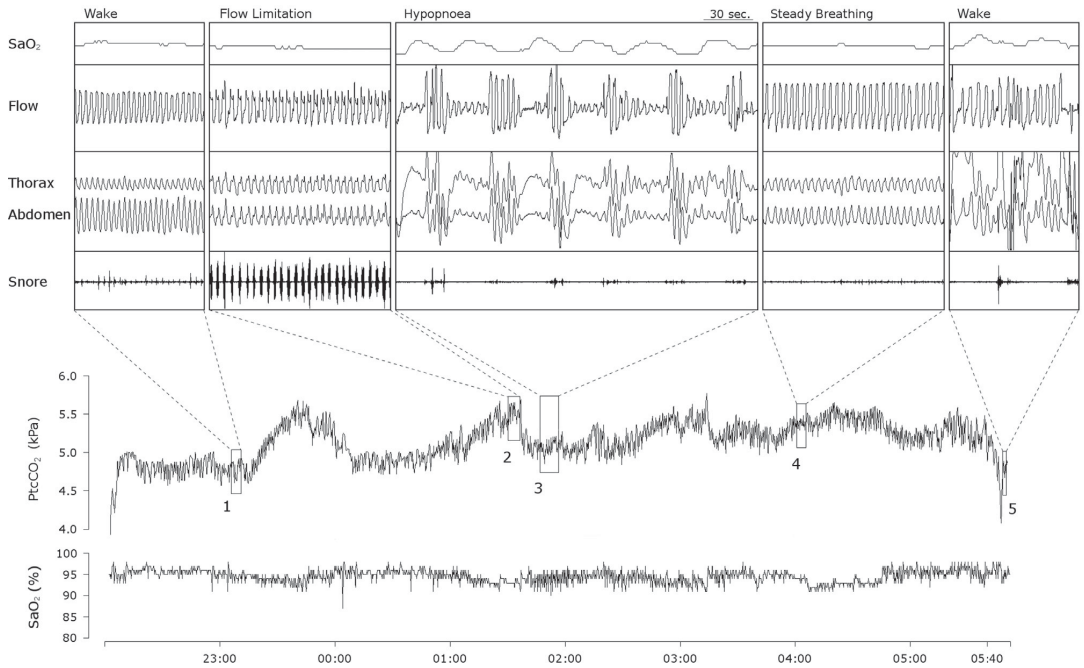

Fig. 2. An example of hypopnoea sequence within an overnight $PtcCO_2$ and SpO_2 profile with expanded views of all included sequences. Lower panel shows the dynamics of $PtcCO_2$ and SpO_2 using the time scale below. Upper panels show part of the (SDB) sequence from the corresponding part of $PtcCO_2$ signal (rectangles and numbers). Scale bar indicates 30 s. Sequences associate with different $PtcCO_2$ levels, the steady breathing (4) being situated between hypopnoea (3) and flow-limitation (2) sequences.

Table 3
Pairwise comparison of absolute and %-units changes of $tcCO_2$ between wakefulness, cyclic SDB sequences, steady breathing and flow limitation.

Pair (n)		$\Delta PtcCO_2$, (kPa)	p	$\Delta PtcCO_2$, %-units	p
Wakefulness (44)	Central apnoea (10)	0,10	0.116	1,987	0.122
	Obstructive apnoea (14)	0,29	**<0.001***	5,822	**<0.001***
	Hypopnoea (32)	0,27	**<0.001***	5,363	**<0.001***
	Steady breathing (44)	0,41	**<0.001***	8,439	**<0.001***
	Flow limitation (32)	0,60	**<0.001***	12,207	**<0.001***
Central apnoea (10)	Obstructive apnoea (14)	0,19	0.181	3,835	0.168
	Hypopnoea (32)	0,16	0.086	3,376	0.086
	Steady breathing (44)	0,30	**0.016**	6,452	**0.015**
	Flow limitation (32)	0,50	**<0.001***	10,220	**<0.001***
Obstructive apnoea (14)	Hypopnoea (32)	-0,02	0.831	−0,459	0.876
	Steady breathing (44)	0,12	0.341	2,617	0.365
	Flow limitation (32)	0,31	**0.012**	6,385	**0.011**
Hypopnoea (32)	Steady breathing (44)	0,14	0.336	3,076	0.326
	Flow limitation (32)	0,33	**<0.001***	6,844	**0.002***
Steady breathing (44)	Flow limitation (32)	0,20	0.026	3,768	**0.022**

Significant pairwise differences are marked with bold ($p < 0.05$). * = Significant difference between sequences after Bonferroni correction ($p < 0.0033$)airwise comparisons marked with bold indicate $p < 0.05$.

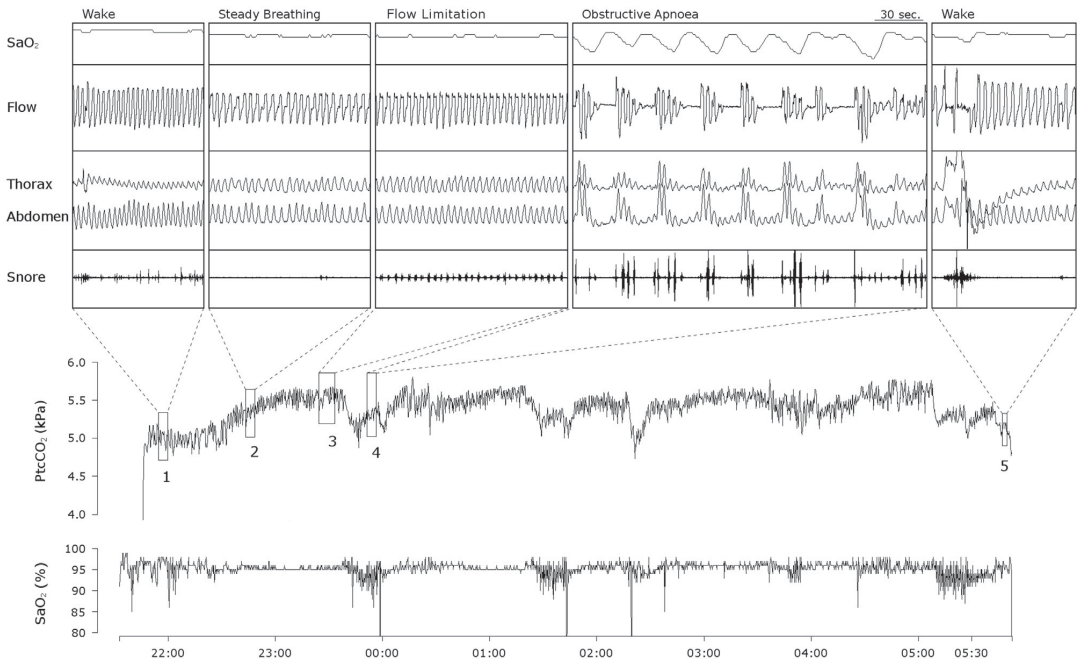

Fig. 3. An example of obstructive apnoea within overnight $PtcCO_2$ and SpO_2 profile with expanded views. Lower panel shows the dynamics of $PtcCO_2$ and SpO_2 using the time scale below. Upper panels show part of the (SDB) sequence from the corresponding part of $PtcCO_2$ signal (rectangles and numbers). Scale bar of 30 s is shown. An obstructive sleep apnoea sequence (4) is associated with low $PtcCO_2$ compared to steady breathing (2) or flow limitation (3). Each sequence type is associated with specific $PtcCO_2$ level.

4. Discussion

Measuring $PtcCO_2$ during sleep is of potential interest, but there are no common guidelines for interpretation. The purpose of the study was to evaluate if the $PtcCO_2$ measurement is sensitive enough to detect differences between different SDB types and to see what those differences are. Sleep is associated with a physiological CO_2 increase but the interaction between this increase and SDB is not fully elucidated. The main findings of this study are as follows: (1) the different types of SDB are associated with different relative levels of $PtcCO_2$, (2) $PtcCO_2$ levels during central or mixed apnoea are close to those observed during wakefulness, whereas during obstructive apnoea and hypopnoea they are higher than during wakefulness and (3) the highest $PtcCO_2$ levels are observed during flow-limitation. There are two major implications of our results. First, it is possible that cyclic SDB inhibits the physiological CO_2 increase which should occur during sleep. Second, flow limitation (non-cyclic SDB) seems to cause CO_2 increase that exceeds the physiological sleep-related CO_2 level and may therefore predispose true hypercapnic conditions.

Our finding that the different types of SDB are associated with different levels of $PtcCO_2$ is in line with previous studies. The type of apnoea tends to change overnight from obstructive to central events (Meer et al., 1992). In patients with chronic heart failure (CHF), the overnight change of apnoea type from obstructive to central sleep apnoea has been associated with $PtcCO_2$ decrease (Tkacova et al., 2001). We also found that the $PtcCO_2$ levels during cyclic SDB sequences are often below steady breathing levels. This predicts that successful treatment of SDB with cyclic breathing results in an increase, not decrease in $PtcCO_2$. This is supported by other studies. A decrease in the frequency of the apnoeic and hypopnoeic episodes as a result of using CPAP for one month was associated with increased $PtcCO_2$ during stage 2 sleep (Naughton et al., 1994). Similar observations have been reported in studies with adaptive servoventilation (ASV) (Teschler et al., 2001). The interaction between sleep apnoea type and $PtcCO_2$ is bidirectional: an increase in inspired CO_2 stabilizes breathing and may completely abolish the episodes of central apnoea (Xie et al., 1997) and reduce the occurrence of obstructive apnoea (Hudgel et al., 1988).

Flow-limitation and "simple" snoring without hypoxemia is often considered as a benign type of SDB, not warranting treatment. However, our study shows that flow limitation is associated with the highest levels of $PtcCO_2$. The increase in CO_2 is probably a result of hypoventilation as the tidal volume is reduced by flow-limitation (Schneider et al., 2009). Patients with symptomatic flow limitation respond well to CPAP therapy and adhere to treatment similar to patients with obstructive sleep apnoea (Anttalainen et al., 2007). In addition to controlling SDB, early treatment of flow limitation may be warranted, since fully developed hypercapnic respiratory failure may be a therapeutic challenge. Opposite to obstructive sleep apnoea, the therapeutic response of hypercapnic respiratory failure to CPAP therapy is decrease of CO_2 (Piper and Sullivan, 1994). When the level of $PtcCO_2$ observed during steady breathing is exceeded, the respiratory effort increases (Rimpilä et al., 2014). This effect can be seen when progressively developing flow-limitation is used as a model. Based on these phenomena we propose that during sleep the $PtcCO_2$ increases from the levels observed during wakefulness to the levels characteristic for stable sleep and breathing, unless prevented by cyclic SDB or flow-limitation.

For the purpose of the study, we included the conventional apnoea classes into the analysis as sequences rather than individual events. This was done because of two reasons. First, the type of SDB and the autonomic background state during SDB may vary as a result of arousals and sleep stage changes. Choosing a sequence of repetitive events of the same type of SDB ensures that the autonomic state during the sequence would remain as stable as possible.

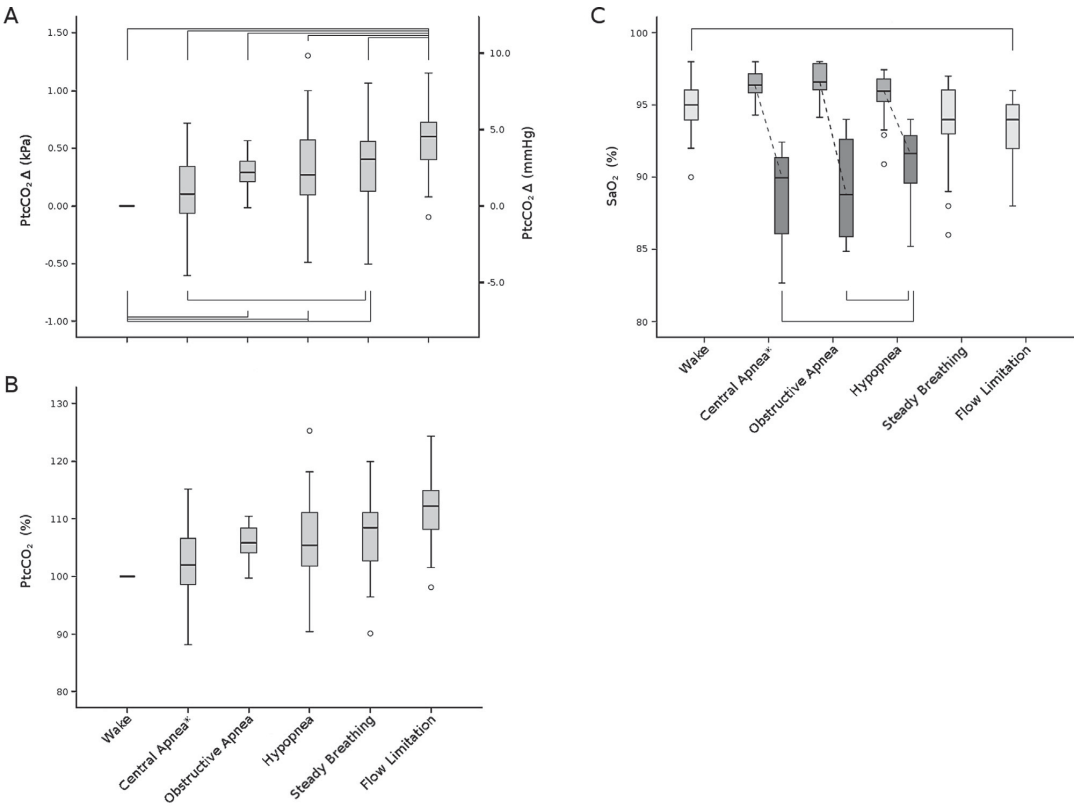

Fig. 4. $PtcCO_2$ and SpO_2 during SDB sequences, wakefulness and steady breathing. Panel A shows absolute differences in $PtcCO_2$ in comparison to wakefulness ($\Delta PtcCO_2$, kPa on left, mmHg on right). The flow limitation differs from all other sequences and the $PtcCO_2$ during the central apnoea sequences (*pooled with mixed apnoea) is lower than that during obstructive apnoea or hypopnoea sequences. The $PtcCO_2$ levels during steady breathing are situated between cyclic and non-cyclic SDB. Panel B shows relative differences in $PtcCO_2$ in comparison to wakefulness (100%). Panel C shows arterial oxyhaemoglobin saturation (SpO_2) during the sequences. For cyclic SDB, the starting level of desaturation is shown with medium dark grey and the nadir of desaturation level is shown with dark grey. The box plot shows the median, interquartile range and the minimum and maximum values. Significantly different pairs are shown with lines. The pairs are the same for panel A and B, the exact *p*-values for $PtcCO_2$ are shown in bold in Table 3 and in the text for SpO_2. Circles denote outliers.

Second, by analyzing longer sequences it was possible to circumvent issues arising from the slow response time related to $PtcCO_2$ technology (Janssens et al., 1998). On the other hand, by doing this, large number of patients had to be screened in order to find individuals showing sequences of both SDB and normal breathing fulfilling our strict inclusion criteria. Only 7.9% out of the originally screened population were finally analyzed, explaining also why a retrospective approach was chosen. The final sample size is a trade-off between having few recordings with uncompromised inclusion criteria or more recordings with more confounding noise.

When steady breathing with minimal flow-limitation was used as a reference point for $PtcCO_2$, the variance of $PtcCO_2$ within SDB sequences became smaller (Fig. 5). This implies that stable $PtcCO_2$ during steady breathing is less affected by external factors than during wakefulness. Such factors include: previous physical activity or emotions, excitement about the sleep study procedure, circadian rhythm, or use of stimulants. The lower variances add to our confidence that the used definition of steady breathing with minimal flow limitation provided a decent estimation of the $PtcCO_2$ level during optimal sleep and breathing. We have previously described the concept of the $PtcCO_2$ plateau, which links stable breathing with minimal flow limitation with stable $PtcCO_2$ level (Rimpilä et al., 2014).

This study has inherent limitations that should be considered. EEG was not available so the determination of wakefulness and sleep is limited. We have previously shown that $PtcCO_2$ increases on average 0.4 kPa between wakefulness and SWS sleep (Aittokallio et al., 2009). The current study did not include EEG, but the difference in $PtcCO_2$ between wakefulness and steady breathing with minimal flow limitation was the same (0.41 kPa), suggesting that these sequences represented steady sleep. Sleep stage effects on apnea severity have been demonstrated (Ratnavadivel et al., 2009) but their relations to CO_2 were not reported. Prospective studies are needed to confirm the links between SDB phenotype, sleep stage and CO_2.

Nasal flow was used to measure air flow. Oronasal flow would have been optimal to detect oral breathing in order to discriminate episodes of apnoea and hypopnoea unequivocally. Misclassification is an issue only for episodes of true hypopnoea, which may have been considered as obstructive or mixed apnoea, when oral breathing was not detected. However, this is unlikely to have affected our results: the distribution of $PtcCO_2$ values during obstructive apnoea is narrow compared to the other forms of SDB (Fig. 4). Mixing episodes of hypopnoea with obstructive apnoea would have widened the $PtcCO_2$ distribution. Long periods of oral breathing which are characterized by poor nasal flow signal were not used

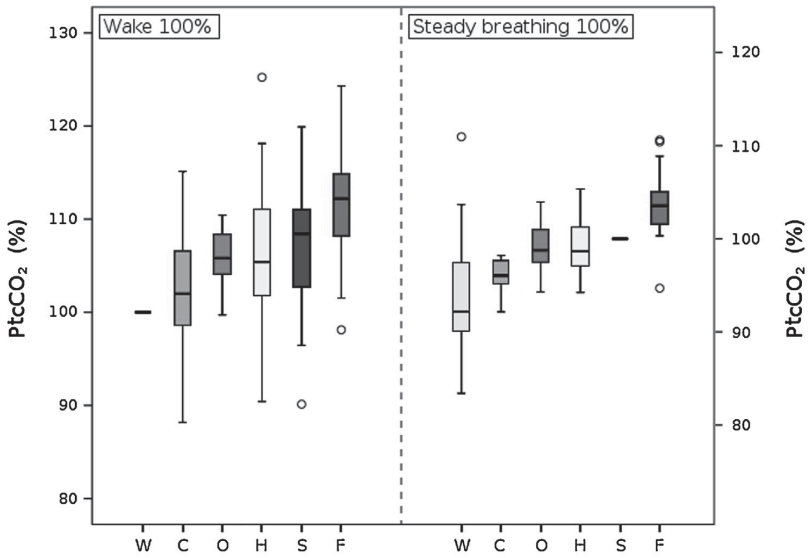

Fig. 5. Difference in $PtcCO_2$ distribution across sequences when different baselines are used. Notice that the *y*-axis on the right is moved upwards so that wakefulness and steady breathing medians are at the same level to allow comparison between panels. Sequence variances are smaller when steady breathing with minimal flow limitation is used as baseline, except for obstructive apnoea. $PtcCO_2$ = transcutaneous carbon dioxide, W = wakefulness, C = central and mixed apnoea, O = obstructive apnoea, H = hypopnoea, S = steady breathing with minimal flow limitation, F = flow limitation. Circles denote outliers.

for $PtcCO_2$ analyses. For AHI, missing oronasal flow could have led to modest underestimation of AHI.

Another major limitation arises from the $PtcCO_2$ technology. Recalibrations of $PtcCO_2$ and drift corrections are usually not performed after sleep study, which prevents the assessment of the exact signal drift during the night and hypoventilation may not be detected. The highest mean $PtcCO_2$ observed during flow-limitation was 6.54 kPa (49.1 mmHg), which does not fulfill the recent AASM guidelines (Berry et al., 2012) for diagnosing hypoventilation. Therefore, sleep-related hypoventilation is unlikely to play a role in this dataset. Although significant differences between the $PtcCO_2$ levels were found between various types of SDB, there was still large within-type variation in $PtcCO_2$ suggesting that other factors such as arousals and the O_2–CO_2-interaction are also involved in determination of the SDB phenotype. Despite these technological limitations, demonstration of significant $PtcCO_2$ differences between SDB phenotypes suggests that the signal quality was sufficient for the purpose of this study.

For good quality overnight recordings, with current $PtcCO_2$ monitoring techniques, there are two important issues to be considered: first, the manufacturers instruct to change the place of the probe every four hours. This may be a relevant instruction for infants or children, but in adults this may not be needed, when using probe temperature of 43.0 °C (Janssens et al., 2001). Reddening of the skin is common but significant burn injuries of the skin under the probe sites are rare and if occur, heal without complications. Common practice in adults is to keep the probe site unchanged for the duration of the sleep study (up to 8 h). This allows an undisturbed signal profile overnight.

Also, at 43.0 °C the $PtcCO_2$ correlates reasonably with $PaCO_2$, but the absolute values may have large limits of agreement, so the use of $PtcCO_2$ as a direct surrogate of $PaCO_2$ is not recommended (Nishiyama et al., 2006). Therefore, even though $PaCO_2$ values would have been useful for sensor calibration, deviations between $PtcCO_2$ and $PaCO_2$ could not have been ruled out during an overnight recording. In the present study, the $PtcCO_2$ was not used as a surrogate of $PaCO_2$.

Patients with obstructive sleep apnoea but without long sequences of steady breathing with minimal flow limitation were excluded from the present study. This does not mean that these sequences do not exist. In clinical setting, when the respiratory and the $PtcCO_2$ signals are simultaneously visible, it is possible to find shorter periods during which steady breathing associates with steady $PtcCO_2$ levels (plateau). In patients with severe OSA, the plateau may only become visible when on CPAP. Therefore, we believe that our findings are applicable also to patients with more severe SDB when $PtcCO_2$ plateau may not be identified.

The control of periodic breathing during sleep has been modelled using a loop gain concept (Khoo et al., 1982; Younes et al., 2001). The loop gain is the ratio expressing, how strong the physiological response triggered by the control loop is compared to the initial disturbance. A high loop gain (>1) amplifies the response and predisposes the system to oscillation. In the context of SDB, high loop gain results in periodic breathing whereas low loop gain stabilizes the respiratory oscillation. In our study the respiratory control during upper airway obstruction was unstable (suggesting loop gain >1) when $PtcCO_2$ was between the wakefulness and steady breathing levels. When $PtcCO_2$ increases above the levels observed during steady breathing, the airway obstruction is associated with flow-limitation, without oscillation of the respiratory command (loop gain <1). Further studies are needed to test whether the relative value of $PtcCO_2$ could be used as a surrogate for the loop gain.

In clinical setting, $PtcCO_2$ is increasingly measured during sleep studies when assessing gas exchange during SDB. $PtcCO_2$ is also often measured as part of research protocols, but the results are rarely reported. In contrast to arterial oxyhaemoglobin saturation, there are no common guidelines for analyzing and interpreting the $PtcCO_2$ phenomena during sleep. Conventionally the $PtcCO_2$ signal has been considered as a noninvasive estimate of the arterial $PaCO_2$, and correction algorithms are used in order to reach a better agreement between $PtcCO_2$ and $PaCO_2$. While $PaCO_2$ measures

the efficacy of the respiratory system in removing CO_2, $PtcCO_2$ is additionally affected by cutaneous vasoconstriction (Clark et al., 1992), determined by the output of the sympathetic nervous system. Therefore, $PtcCO_2$ may be a poor estimate of ventilation, but a useful parameter to assess the CO_2 environment and pH control of the periphery. Our demonstration of the existence of the $PtcCO_2$ plateau during stable breathing and deviations from this level to both directions during different forms of SDB may add new interest to measure $PtcCO_2$ during sleep. In particular, the $PtcCO_2$ increase observed during flow-limitation may imply that the clinical importance of this respiratory abnormality has been underestimated.

5. Conclusion

In conclusion, the different forms of SDB associate with different levels of $PtcCO_2$. The highest levels of $PtcCO_2$ occur during flow limitation. During obstructive apnoea or hypopnoea the $PtcCO_2$ is higher than during wakefulness but lower than during flow limitation. The $PtcCO_2$ levels during central or mixed apnoea are similar to wakefulness. Our findings support the potential of $PtcCO_2$ monitoring in understanding the pathophysiology of different phenotypes of SDB. Treatment of SDB should focus on stabilizing breathing by suppressing the oscillation related to ventilatory overshoots and letting the sleep-related CO_2 increase to occur, but it should also remove the obstruction during flow limitation in order to ensure adequate minute ventilation to prevent hypercapnia. Future studies with prospective design in different patient groups, such as those with severe OSA (high AHI) as well as symptomatic patients with flow limitation (low AHI), are needed in order to better understand sleep-disordered breathing and its health consequences.

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PUBLICATION III

Upper-airway flow limitation and transcutaneous carbon dioxide during sleep in normal pregnancy

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Original Article

Upper-airway flow limitation and transcutaneous carbon dioxide during sleep in normal pregnancy

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ABSTRACT

Objective: Sleep during pregnancy involves a physiological challenge to provide sufficient gas exchange to the fetus. Enhanced ventilatory responses to hypercapnia and hypoxia may protect from deficient gas exchange, but sleep-disordered breathing (SDB) may predispose to adverse events. The aim of this study was to analyze sleep and breathing in healthy pregnant women compared to non-pregnant controls, with a focus on CO_2 changes and upper-airway flow limitation.
Methods: Healthy women in the third trimester and healthy non-pregnant women with normal body mass index (BMI) were recruited for polysomnography. Conventional analysis of sleep and breathing was performed. Transcutaneous carbon dioxide ($TcCO_2$) was determined for each sleep stage. Flow-limitation was analyzed using the flattening index and $TcCO_2$ values were recorded for every inspiration.
Results: Eighteen pregnant women and 12 controls were studied. Pregnancy was associated with shorter sleep duration and more superficial sleep. Apnea–hypopnea index, arterial oxyhemoglobin desaturation, flow-limitation, snoring or periodic leg movements were similar in the two groups. Mean SaO_2 and minimum SaO_2 were lower and average heart rate was higher in the pregnant group. $TcCO_2$ levels did not differ between groups but variance of $TcCO_2$ was smaller in pregnant women during non-rapid eye movement (NREM). $TcCO_2$ profiles showed transient $TcCO_2$ peaks, which seem specific to pregnancy.
Conclusions: Healthy pregnancy does not predispose to SDB. Enhanced ventilatory control manifests as narrowing threshold of $TcCO_2$ between wakefulness and sleep. Pregnant women have a tendency for rapid CO_2 increases during sleep which might have harmful consequences if not properly compensated.

1. Introduction

Pregnancy is a challenge for the cardiorespiratory system, particularly during sleep when the body needs to rest without compromising fetal oxygen supply and carbon dioxide removal. In normal pregnancy, breathing during sleep is well preserved [1]. Plasma concentrations of progesterone are elevated during pregnancy and contribute to the increased ventilatory responses to hypoxia [2] and hypercapnia [3]. Factors compromising breathing during pregnancy are the growing uterus that elevates the diaphragm, resulting in decreased functional residual capacity of the lung. The decreased tracheal traction in turn predisposes to upper-airway narrowing, and hormonal changes increase the upper-airway edema. Obesity during pregnancy is an additional factor predisposing to obstructive sleep apnea (OSA) or snoring [4]. Breathing abnormalities are purported to be common during pregnancy, with partial upper-airway obstruction rather than OSA usually observed [5]. Sleep-disordered breathing (SDB) in pregnant women is associated with intrauterine growth retardation [6,7].

In sleep studies, CO_2 is rarely measured, and little is known about CO_2 control during SDB, but we have previously shown the effect of progressively developing flow-limitation as well as steady flow-limitation on transcutaneous CO_2 ($TcCO_2$) increase [8–10]. CO_2 has been suggested to play a role in hypertension in pre-

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eclampsia [11]. Central chemoreceptor sensitivity to CO_2 is also increased during pregnancy [3], which could destabilize the ventilation when operated near threshold values.

The purpose of this study was to evaluate the differences in SDB and $TcCO_2$ parameters during normal pregnancy compared to non-gravid controls. It was hypothesized that pregnant women may have more flow-limitation and snoring compared to non-pregnant women (1). In addition, flow-limitation in pregnant women may cause greater $TcCO_2$ increase (2), and consequently, $TcCO_2$ values during sleep should differ between pregnant and non-pregnant women (3).

2. Methods

2.1. Participants

We recruited 18 pregnant women from maternity clinics in Tampere and its nearby regions and from the antenatal outpatient clinic and antenatal ward of Tampere University Hospital. Inclusion criteria were 18–45 years of age, singleton pregnancy without fetal demise, and gestational age 33 ± 1 weeks. Women with pre-eclampsia or other complications warranting constant monitoring and/or induction of labor were excluded.

Twelve non-pregnant women with body mass index similar to that of pregnant women in the beginning of pregnancy were chosen as controls. These women were recruited from Tampere University of Applied Sciences, Medical School of University of Tampere, and Tampere University Hospital, Department of Obstetrics and Gynecology, using recruitment posters. The study was approved by the local Ethics Committee (Identification Number R12102), and all women received oral and written information on the trial and signed a consent form before attending.

2.2. Obstetrical examination

The patients were first seen by an obstetrician (R.J.) at the antenatal outpatient clinic or ward. From the maternity card the following baseline information (standard recordings of the first maternity clinic visit in early pregnancy) was obtained: initial weight, height, body mass index (BMI), initial blood pressure, and the results of the oral glucose tolerance test if performed. Fetal ultrasound was performed using Voluson ultrasound equipment (Voluson S6 ultrasound, GE Healthcare, CT, USA) to record a fetal weight estimate, amniotic fluid index (AFI), fetal movements, and to assess the flow of the umbilical artery (uA). After a minimum of 15 min rest in a supine position in the examination room, blood pressure was measured from the right arm using a validated oscillometric technique (Omron automated manometer, M4-I Intellisense, Omron Corporation, Japan) with medium cuff-size. Weight was measured on a regular weighing scale. Urine dip stick test was analyzed for protein and glucose (Combur3 Test, Roche Diagnostics, Germany).

2.3. Sleep recordings

An overnight polysomnography was performed at Unesta Research Centre within a week after the obstetrical examination in the pregnant group. Controls visited the sleep laboratory once and all the information needed was then gathered. Recording montage contained electroencephalogram (EEG) with eight channels (A1, A2, O1, O2, F3, F4, C3, C4), electrooculogram (EOG), submental electromyography (EMG), anterior tibial EMG, nasal flow (prongs/cannula), body position, and inductance plethysmography (RIP) belts, which reflect the respiratory effort of the abdomen and thorax (Somnologica, Medcare Flaga hf, Reykjavik, Iceland). The sleep investigations included also nocturnal measurement of transcutaneous partial pressure of carbon dioxide ($TcCO_2$) and transcutaneous partial pressure of oxygen (TcO_2). A parasternally fixed dual sensor ($TcCO_2$ and TcO_2) warmed up to 43.0 °C was used (TCM4, Radiometer, Copenhagen, Denmark).

2.4. Data analysis

Sleep was scored according to AASM (American Academy of Sleep Medicine) criteria [12], and former stages S3–S4 were used in the breath-by-breath analysis. Proprietary scoring function of Somnologica was used to score flow limitation and snoring (default flattening index of 0.13 was used) and reported as percentage of total sleep time. Episodes of apnea were scored according to AASM rules [13], hypopnea was scored when a 30% reduction of flow was observed for a minimum of 10 s and apnea-hypopnea index (AHI) was calculated. Oxyhemoglobin desaturations of 3% (ODI3) or more were tabulated. $TcCO_2$ values were sampled with the frequency of 1 Hz and the data values during each sleep stage were pooled to calculate the statistics, including the median and quartiles for each sleep stage. This means that each epoch produced 30 data points to the corresponding sleep stage data pool. $TcCO_2$ values were also determined separately during inspirations with and without flow-limitation in each sleep stage. For this respiratory analysis, the $TcCO_2$ data was advanced 30 s in order to correct the physiological delay between breathing and the CO_2 reading on the skin. In addition, to avoid the disproportionately marked effect of individuals with low levels of flow-limited breathing on overall data, the $TcCO_2$ data was excluded from this analysis if less than 75 data points were available in a given sleep stage. One to two data points were available from each inspiration. Accordingly, short episodes (less than 3–5 min, depending on respiratory rate) of flow-limitation were not included. Poor quality $TcCO_2$ data (missing, unphysiological behavior and drift more than 1 kPa between evening and morning wakefulness for sleep stage analysis) as well as data during calibrations were omitted. $TcCO_2$ drift corrections were not done. Technical drift occurs both upwards and downwards, which results in a reduced effect of signal drift on a group level, but at the same time increases the variance of the sample which affects statistical analysis.

2.4.1. Peak analysis

The overnight profile revealed $TcCO_2$ fluctuations, which have not been reported or identified earlier in any other patient population or healthy controls. Based on initial visual observation, a set of rules to identify and numerically characterize these events were established. A $TcCO_2$ peak was scored when a sudden $TcCO_2$ increase followed by decrease to baseline was observed. Since no guidelines exist for scoring this type of event, $TcCO_2$ increase of more than 0.1 kPa was chosen as a loose criterion to score a $TcCO_2$ peak. For exclusion of clear episodes of apnea and hypopnea, minimum event duration was set to 1 min and 30 s. Peaks during rapid eye movement (REM) sleep were excluded due to normal ventilatory instability and fluctuating $TcCO_2$ that is commonly seen. Sleep state was required for the peak to be scored and peak events containing two or more consecutive epochs of wakefulness were excluded. Association to arousal or respiratory arousal was also scored. Respiratory arousal was scored when inspiratory flow shape improved simultaneously with arousal. The start of the peak was marked when $TcCO_2$ slope started to increase. The end of the event was marked when $TcCO_2$ returned to starting value or slope returned near zero (applied when the peak ended at higher $TcCO_2$). Signal drift was considered insignificant during these shorter events.

2.5. Statistics

The data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The differences between pregnant and controls were analyzed with independent samples Mann–Whitney U-test. Non-parametric tests were used due to small sample size and skewed distributions. Results are expressed as medians with interquartile range (IQR) except for age and BMI where full range is shown. Pearson's chi-square test was used to test the prevalence of peaks between groups. Non-parametric Levene's test was used to compare the variance of $TcCO_2$ between groups in different sleep stages. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Obstetrical characteristics

Study enrollment ran from 1 January 2013 to 31 December 2015. Findings on general physical and obstetrical examination were normal. All subjects were normotensive without proteinuria. All fetuses presented with normal bioprofiles in ultrasound examination. The outcomes of the pregnancies were analyzed (possible complications during pregnancy, time and mode of delivery, birthweight, Apgar scores at 1 and 5 min, umbilical artery pH and base excess). Fourteen patients delivered vaginally and four via caesarean section. Gestation at birth ranged from 37 + 3 to 42 + 0 weeks. Obstetrical characteristics are presented in Table 1.

3.2. Sleep and demographics

The control population was younger than the pregnant population (26, range: 24–31, vs 30, range: 26–36, $p < 0.001$). There was no difference in BMI at the beginning of pregnancy compared to controls (22.0, range 19.0–29.4, vs 21.7, range: 18.8–25.4, $p = 0.245$). Sleep quality of the pregnant women was worse compared to controls. Pregnant women had more light sleep (N1) and less deep sleep (N3) and REM sleep. Also, total sleep time (TST) was shorter and wake after sleep onset (WASO) was longer in pregnant women. A clear difference between the groups was seen on oxyhemoglobin parameters (SaO_2), which were lower in pregnant women. Considerable increase in average heart rate was observed in pregnant women also. Common SDB parameters AHI and ODI3 showed no differences. Additional measures that were used (FL-index (%) and snore time (%)) did not show statistical difference. Two pregnant subjects and one control subject were identified as significant snorers with episodes of prolonged flow limitation. Detailed values are presented in Table 2.

Table 2
Polysomnography data.

	Pregnant	Controls	p
	Median (Q1–Q3)	Median (Q1–Q3)	
TST (min)	361.0 (330.5–418.9)	415.5 (391.5–429.4)	**0.007**
Sleep onset (min)	17.5 (11.5–27.6)	21.5 (15.1–27.0)	0.518
WASO (min)	110.5 (58.5–151.1)	39.7 (21.8–77.0)	**0.003**
Sleep efficiency (%)	76.7 (68.3–88.6)	91 (85.0–95.0)	**0.002**
N1 sleep (min)	30.3 (25.5–45.3)	21.0 (16.3–30.8)	**0.004**
N2 sleep (min)	141.8 (96.0–168.0)	140.5 (109.9–174.0)	0.884
N3 sleep (min)	118.5 (97.5–143.6)	156.5 (133.3–190.8)	**0.009**
REM sleep (min)	53.0 (40.3–69.5)	91.5 (73.5–99.6)	**0.001**
AHI (#/h)	1.55 (0.73–3.25)	0.75 (0.23–1.45)	0.124
ODI3 (%)	0.4 (0–2.1)	0.2 (0–0.38)	0.200
SaO_2 mean (%)	95.9 (95.2–96.3)	97.5 (96.1–97.9)	**<0.001**
SaO_2 min (%)	93.0 (91.5–94.0)	94.5 (93.3–95.8)	**0.008**
FL-index (%)	11.3 (6.1–23.6)	10.10 (6.3–18.4)	0.573
Snore time (%)	0 (0–0.33)	0 (0–0.08)	0.914
PLM (#/h)	2.4 (0–5.2)	0.5 (0–1.4)	0.296
Average HR (bpm)	71.7 (64.3–79.0)	59.6 (55.7–66.9)	**0.002**

Data presented with medians and interquartile range. AHI, apnea–hypopnea index; FL-index, percentage of flow-limited breaths during sleep; HR, average heart rate; N1, N2, N3, non-rapid eye movement (NREM) sleep; ODI3, oxyhemoglobin desaturation for 3% or more; PLM, periodic leg movements; REM sleep, rapid-eye movement sleep; TST, total sleep time; WASO, wake after sleep onset. Significant p-values are marked with bold.

3.3. $TcCO_2$

In terms of $TcCO_2$ levels (absolute or relative) there were no differences in $TcCO_2$ between the pregnant and control groups in any of the sleep stages (Table 3). In general, the pregnant women had a wider range for $TcCO_2$ when absolute values were used. However, we discovered that in pregnant women the variance of $TcCO_2$ across sleep stages became smaller for non-rapid eye movement when $TcCO_2$ during wakefulness was used as the reference value (Table 3, Fig. 1). Sleep stage and $TcCO_2$ analysis was possible only for 15 pregnant and eight non-pregnant women due to $TcCO_2$ signal drift and poor data in three pregnant women and four controls. Inspiratory flow-limitation did not cause greater

Table 1
Obstetrical characteristics of 18 healthy pregnant women participating in the sleep study.

Subject	Age	P	US	RR	BMI	Del	Mode	Sex	BW	Apgar	uApH
1	36	2	34 + 6	130/75	25.7	40 + 3	V	Boy	3740	9/9	7.28
2	29	1	32 + 1	108/69	27.3	39 + 4	V	Boy	3605	9/10	7.26
3	29	0	31 + 4	112/72	21.0	42 + 0	V	Girl	3300	9/9	7.28
4	36	2	33 + 2	118/82	NA	39 + 1	CS	Boy	3470	9/9	7.37
5	31	0	33 + 2	102/67	21.6	40 + 6	CS	Girl	3740	9/9	7.34
6	36	0	33 + 0	122/71	25.8	40 + 2	V	Boy	3650	8/9	7.21
7	36	2	32 + 6	124/79	27.7	39 + 0	V	Boy	3120	9/9	7.19
8	29	0	32 + 6	121/72	29.4	40 + 1	CS	Girl	3080	9/8	7.34
9	29	0	32 + 3	99/51	25.0	41 + 3	V	Girl	3260	7/8	7.17
10	29	3	32 + 4	104/58	19.2	39 + 0	V	Girl	3195	9/10	7.24
11	31	1	32 + 4	120/76	33.0	38 + 3	V	Boy	3800	9/9	7.17
12	30	1	31 + 4	112/84	22.0	39 + 3	V	Boy	3920	8/9	7.30
13	29	0	34 + 0	108/72	28.0	41 + 1	CS	Girl	4480	8/8	7.36
14	30	0	31 + 2	118/74	21.6	39 + 6	V	Boy	3255	7/9	7.13
15	35	0	32 + 4	112/70	19.2	37 + 3	V	Girl	2385	8/8	7.17
16	34	0	31 + 5	113/77	19.0	41 + 1	V	Girl	3340	8/9	7.28
17	30	0	33 + 4	110/80	23.0	39 + 4	V	Girl	3250	6/9	7.20
18	26	0	34 + 0	124/74	22.0	42 + 0	V	Girl	4190	9/9	7.20

Apgar, Apgar score 1 min/5 min; BMI, body mass index at the beginning of pregnancy; BW, birth weight (g); CS, ceasarean section; Del, gestation at delivery (weeks + days); Mode, mode of delivery; NA, not available; P, parity; RR, blood pressure at ultrasound visit; US, ultrasound scan; V, vaginal; uApH, umbilical artery pH at birth.

Table 3
Absolute and relative transcutaneous CO_2 data for sleep stages.

	Pregnant ($N = 15$)	Controls ($N = 8$)	p	p (variance)
	Median (Q1–Q3)	Median (Q1–Q3)		
$TcCO_2$, absolute (kPa)				
Wake	6.19 (5.41–6.65)	6.16 (5.96–6.51)	0.776	
N1 sleep	6.28 (5.35–6.75)	6.49 (6.04–6.74)	0.428	
N2 sleep	6.28 (5.43–6.75)	6.57 (5.97–6.89)	0.392	
N3 sleep	6.32 (5.92–6.65)	6.52 (5.97–7.08)	0.506	
REM sleep	6.41 (5.28–6.95)	6.39 (5.72–6.78)	0.825	
NREM sleep	6.29 (5.48–6.67)	6.56 (5.98–7.01)	0.357	
$\Delta TcCO_2$ (kPa)				
Wake (reference)	0	0	–	
N1 sleep	0.08 (−0.03 to 0.18)	0.20 (0.03–0.61)	0.115	0.323
N2 sleep	0.12 (0.05–0.29)	0.24 (−0.04 to 0.65)	0.506	0.213
N3 sleep	0.15 (0.08–0.38)	0.21 (0.04–0.53)	0.825	0.075
REM sleep	0.15 (0.08–0.43)	0.16 (−0.15 to 0.49)	0.925	0.067
NREM sleep	0.11 (0.07–0.22)	0.24 (0.03–0.62)	0.506	**0.038**

Data presented with medians and interquartile range. N1, N2, N3, non-rapid eye movement (NREM) sleep; REM, rapid eye movement; $TcCO_2$, transcutaneous carbon dioxide. p (variance) denotes Levene's test. Significant p-values are marked with bold.

$TcCO_2$ increase in pregnant women compared to controls in any of the sleep stages (data not shown).

3.3.1. $TcCO_2$ peaks

A further look into $TcCO_2$ overnight profiles of the pregnant group showed a number of distinctive peaks (Figs. 2, 3), which are not commonly seen in overnight profiles of non-pregnant subjects. Eleven of 18 pregnant women had these peaks, whereas four of 12 non-pregnant women had similar $TcCO_2$ peaks ($p = 0.136$). Altogether, only five peaks were observed in the control population versus 78 peaks in the pregnant population (0.42 peaks/person in controls vs 4.33 peaks/person in pregnant, $p = 0.028$) rendering the peaks approximately 10-times more frequent in the pregnant population. Mean amplitude of the peak was 0.20 kPa with duration of 241 s (range 92–430 s). Mean slopes were 0.11 kPa/min upwards and 0.09 kPa/min downwards. When present, the number of peaks per person ranged from 2 to 22 in pregnant women. Fifty-two $TcCO_2$ peaks (62.7%) were associated with clear inspiratory flow-limitation (Fig. 2). Respiratory arousal was associated with 14 peaks and arousal with 37 peaks. Amplitude criterion of hypopnea was reached in 24 peaks and apnea in one peak. Oxyhemoglobin desaturation of 3–4% was associated with eight events.

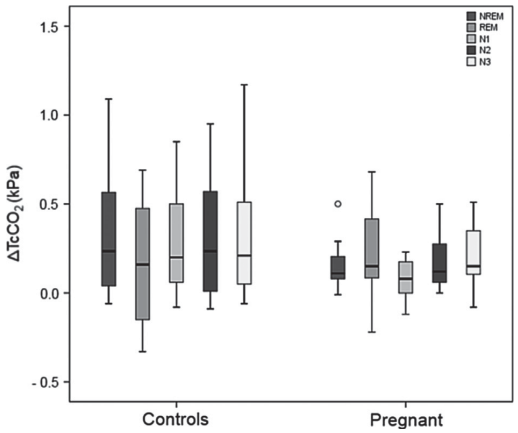

Fig. 1. Relative transcutaneous carbon dioxide ($TcCO_2$) in pregnant women and controls during different sleep stages. Wakefulness was assigned as 0 kPa and sleep stages are relative to that. $TcCO_2$ levels did not differ between groups, but the variance (Levene's test) was different for pooled non-rapid eye movement. Boxplots show median values with interquartile range and min–max. Circle denotes outlier.

4. Discussion

We studied sleep and breathing parameters in 18 healthy women during pregnancy weeks 31–34, and in 12 healthy non-gravid controls. Pregnant women slept less and stayed less time in slow wave sleep and REM sleep. No difference was observed between groups in terms of flow-limitation or snoring, AHI or periodic leg movements. However, pregnant women had lower average and minimum SaO_2 levels and increased heart rate. Unexpectedly, the $TcCO_2$ levels showed no difference between groups during different sleep stages, only the variance of NREM $TcCO_2$ was smaller in the pregnant group. These findings suggest that the $TcCO_2$, which represents the peripheral pCO_2 at the tissue level, remains unchanged and is carefully controlled during pregnancy. The most intriguing finding of our study was that more than half of the pregnant women presented with transient $TcCO_2$ increases in a pattern that to our knowledge has not been previously described in any other control or patient population. Post-hoc analysis showed that most of these $TcCO_2$ increases were associated with transient episodes of inspiratory flow-limitation, although in some pregnant women flow limitation was absent. The transient $TcCO_2$ increases in pregnant women are in contrast with otherwise strictly controlled $TcCO_2$ and may reveal episodes when the maintenance of homeostasis is challenged.

Our study corroborates previous findings that sleep quality is diminished during pregnancy [14]. Total sleep time was shorter with 40-min reductions in N3 and REM sleep and increase in N1 sleep. We showed that breathing is only minimally disturbed in late pregnancy, a finding that has been reported several times before. A recent study performed by Sarberg et al. [15] had a similar, albeit larger, healthy study population with comparable results of very low levels of AHI, ODI and nadir SaO_2 from the respiratory recordings. We observed lower levels of snoring than have been previously reported, but this difference may result from methodological differences.

The average SaO_2 during sleep was lower in pregnant women compared to the controls. This is in line with earlier findings showing progressively decreasing PaO_2 levels [16] from second to third trimester of pregnancy seen in the supine position. The fact that PaO_2 does not decrease during pregnancy in the sitting position [16] suggests that also the lower SaO_2 in our study during sleep is associated with body position and the progressive impact of

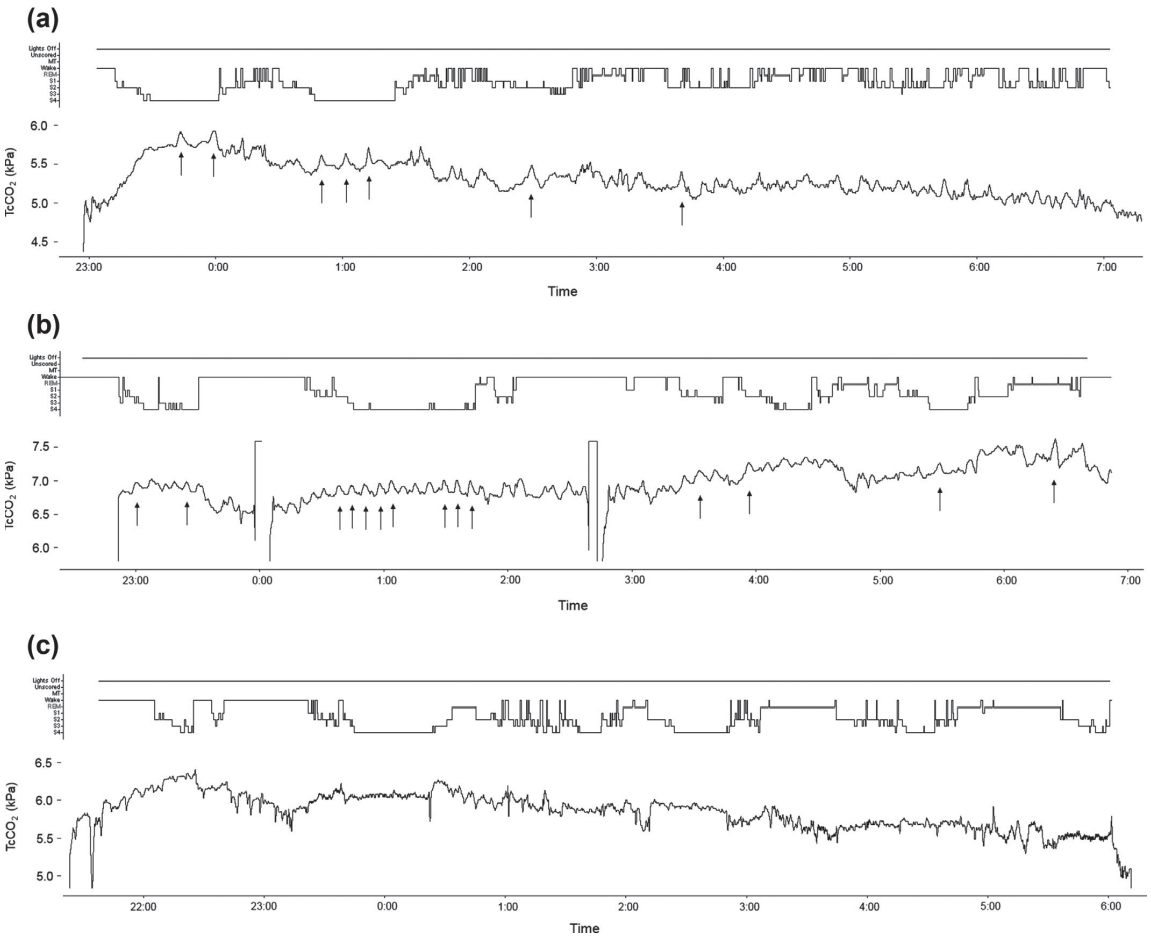

Fig. 2. Three examples of overnight transcutaneous carbon dioxide ($TcCO_2$) profile with hypnogram. For drift assessment, we expect that the wakefulness $TcCO_2$ should be the same in the evening and in the morning. Also, the plateau levels during slow-wave sleep should repeat at about the same levels. (a) A pregnant woman with $TcCO_2$ peaks (arrows) associated with short episodes of flow-limitation. Overnight flow-limitation index was 4.3%. Downward trend of the signal is considered physiological, related to respiratory stimuli from circadian process and/or sleep fragmentation. (b) A pregnant woman with $TcCO_2$ peaks (arrows) without flow-limitation episodes. Overnight flow-limitation index was 4.7%. A minor upwards drift is probable, since the wakefulness levels are higher in the morning. The lower fluctuating $TcCO_2$ level during the early part of the recording seems to hinder $TcCO_2$ increase to the so-called plateau level during slow-wave sleep, so drift may seem more accentuated than what it really is. (c) A control woman without any $TcCO_2$ peaks. Overnight flow-limitation index was 3.1%. Decreasing trend of the plateau levels and evening/morning wakefulness levels suggest a technical drift.

elevating diaphragm on functional residual capacity (FRC) and oxygenation [17]. The cardiac output increases during pregnancy [18] but also becomes sensitive to body position suggesting compression of the inferior vena cava by the uterus [19]. Decreased venous return to the heart could contribute to the observed increasing heart rate in the third trimester since stroke volume decreases from the second trimester [18].

The role of CO_2 in SDB during pregnancy has been speculated [11,20], as well as in pre-eclampsia [11]. CO_2 measurements are not routinely measured during adult sleep studies [21], mainly due to lack of simple, robust and noninvasive methods of CO_2 monitoring. The reference measurement is partial pressure of the arterial CO_2 ($PaCO_2$), which is a reliable measure of ventilation but requires blood samples and is not suitable for sleep studies. End-tidal CO_2 ($EtCO_2$) is noninvasive and allows for continuous monitoring of the mixed venous CO_2 provided that the tidal volumes are sufficient to produce readable end-tidal CO_2-plateau: this may be a challenge in subjects with mouth breathing, SDB, nocturnal hypoventilation or usage of a continuous positive airway pressure (CPAP) mask, which is often the case in subjects in whom this type of measurement is indicated [13].

$TcCO_2$ measurement is probably best adapted for sleep recordings. It reflects both ventilation and peripheral blood perfusion [22,23]. The main issues with $TcCO_2$ are slow response time and potential signal drift during prolonged recording [24,25]. The overnight $TcCO_2$ profiles can display either technical drift or physiological trends. The technical drifts can be related to changes in the contact between the sensor and the skin after changes in body position but may also occur within the sensor. The physiological trends arise from changes in control of breathing and circulation at the system level or changes in metabolism and blood perfusion locally. The $TcCO_2$ signal is a combination of ventilation at system level and perfusion at local level, which are both under the control of the sympathetic nervous system. The sympathetic tone from

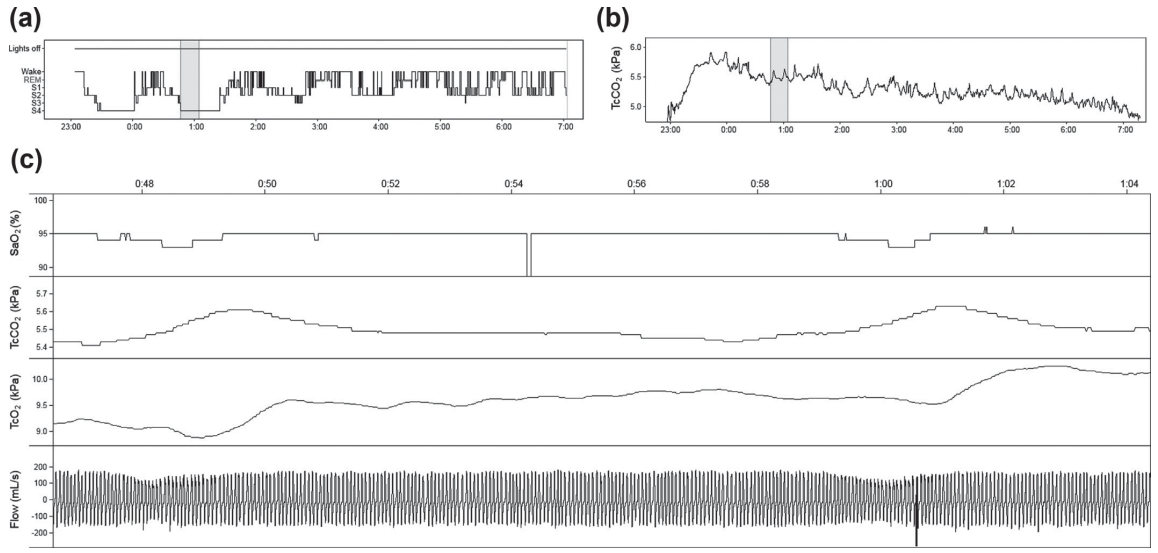

Fig. 3. A pregnant woman with two transcutaneous CO_2 peaks associated with flow-limitation episodes. (a) Hypnogram. (b) The overnight $TcCO_2$. (c) A detailed 18-min time window, from the darkened area shown in (a) and (b). Traces: SaO_2 (%), arterial oxyhemoglobin saturation; TcO_2 (kPa), transcutaneous partial pressure of oxygen; $TcCO_2$ (kPa), transcutaneous partial pressure of carbon dioxide; Flow (ml/s), flow at nasal prongs.

hypothalamic origin displays a circadian rhythm with high tone during wakefulness and a nadir tone around 03:00–04:00 h. During the morning hours this sympathetic tone starts to increase and is potentially reflected as a decreasing trend in $TcCO_2$, as superficial skin perfusion starts to increase. A physiological trend may also occur, if the proportion of slow-wave sleep (SWS) decreases and the proportion of sleep stages N1–N2, REM or wake increase as they often do during the latter part of the night. This is the likely explanation for the decreasing trend in Fig. 2(a), since the wakefulness levels are the same before sleep onset and after sleep. Frequent arousals from sleep decrease the $TcCO_2$ (hyperventilation) whereas periods of upper-airway flow-limitation increase it (hypoventilation). Long or repeated periods of flow-limitation may also cause a physiological $TcCO_2$ increase over time. In the populations of the current study, prolonged flow-limitation was rare and its contribution to $TcCO_2$ trends was unlikely. We conclude that, at present, it is not possible to distinguish between technical and physiological trends. Therefore, we preferred only to exclude cases with extreme trend/drifts but include signals with limited drift.

We are not aware of previous reports of $TcCO_2$ during sleep in pregnancy. Therefore, we can only compare our results with studies using other methods, including also measurement while awake. It is well established that the minute ventilation increases and $PaCO_2$ decreases during pregnancy [26]. This effect is considered as an exaggeration of ventilation to ensure sufficient gas exchange to the fetus and is at least partly driven by increasing levels of progesterone during pregnancy [3]. Against our expectations, we failed to show decreased $TcCO_2$ levels in pregnant women. There are several possible explanations for this observation. First, the sensitivity or accuracy of the $TcCO_2$ method is not sufficient to demonstrate difference. This interpretation is not supported by the observed lower variance in our larger study group (15 pregnant women vs eight controls), which may reflect increased chemoreceptor sensitivity [3]. The $PaCO_2$ increases during sleep [27] but decreases during pregnancy while awake [26]. When using $TcCO_2$, we see sleep-related increase but not pregnancy-related decrease while awake (Table 3), which should be of about similar magnitude. This suggests that the effects of sleep and pregnancy on the $TcCO_2$ are mediated through different mechanisms. One possible explanation for similar $TcCO_2$ values could be that the $TcCO_2$ measures the combination of the increased metabolic rate with increased CO_2 production and decreased $PaCO_2$, resulting in no change. However, the lower partial pressure of CO_2 in the arteries and higher heart rate during pregnancy could represent adaptive measures to maintain constant pCO_2 at the tissue level.

Discovering the $TcCO_2$ peaks in the healthy pregnant women (but not in controls) is new and seems contradictory in relation to the mechanisms mentioned above. One would assume that changes in $TcCO_2$ should be minimal. Yet, visually detectable transient $TcCO_2$ increases are common pregnancy-specific findings. The transient $TcCO_2$ increases with upper-airway flow limitation can be explained as obstructive events. Partial upper-airway collapse decreases minute ventilation, which results in transient CO_2 increase followed by corrective response. We have previously shown that upper-airway flow limitation during sleep is associated with increasing $TcCO_2$ [8,9]. There are several reasons for upper-airway narrowing during pregnancy, including upper-airway edema and decreased tracheal traction due to pregnancy-induced elevation of the diaphragm. On the other hand, tight respiratory control during pregnancy ensures that the minor upper-airway obstructive event is promptly corrected and does not develop into an episode of OSA. Examples of transient $TcCO_2$ increases with flow limitation are presented in Fig. 2(a) and Fig. 3. These episodes may play a role in pre-eclampsia [11].

In contrast to $TcCO_2$ peaks associated with flow-limitation, in some individuals the phenomenon is more likely to be associated with unstable respiratory control. A different type of $TcCO_2$ pattern is seen in Fig. 2(b). This fluctuation was counted as peaks, but since flow-limitation is not observed it can be speculated that ventilatory plant gain is increased (small changes in ventilation cause augmented CO_2/O_2 response). Slight fluctuation of ventilation is observed during these peaks in SWS which indicates an overall increase in loop gain, as ventilation during SWS is usually very stable. Respiratory stimulation during pregnancy probably

prohibits the development of (central) apneic behavior because reaching the apneic threshold would require further increase in ventilation [27]. In fact a recent study showed that central sleep apnea is almost non-existent during late pregnancy [20]. This could also explain why the observed large fluctuations in $TcCO_2$ are accompanied by very little waxing and waning behavior. In our previous studies we have used the concept of $TcCO_2$ plateau to describe optimal $TcCO_2$ during sleep and normal breathing [9]. If this level is exceeded, respiratory efforts increase. Fig. 2(a) represents this idea well during the first sleep cycle; flow-limitation causes upward deviation of the $TcCO_2$ from the target level, but compensatory mechanisms quickly restore the optimal level. On the other hand, if a disturbance such as an arousal decreases CO_2 from the target level, the ventilation is repressed in order to restore that optimal level. An extreme case is the momentary repression to zero when apneic threshold is reached. The pregnant woman in Fig. 2(b) presumably fluctuates around the plateau level since there is neither flow-limitation nor hypopneic breathing present. Our results show the dynamic behavior of CO_2 during sleep in pregnancy, which could benefit the understanding of SDB during this vulnerable state. It remains to be investigated whether the CO_2 events observed here are prolonged or exaggerated in risk populations and how they may contribute to pathophysiological processes.

The strength of this study is the use of overnight $TcCO_2$ measurement and a healthy population. Changes that are seen in $TcCO_2$ profile should be considered as normal findings, which is useful when $TcCO_2$ is measured in high-risk populations or in pre-eclamptic patients. In addition, a full polysomnographic recording allowed detailed determination of sleep. Determination of $PaCO_2$ during sleep would have been informative, but being invasive and uncomfortable procedure it would have disturbed sleep unduly. $EtCO_2$ measurement would have also been useful, but was not available for this study. The number of subjects in this exploratory study is quite small and thus decreases the statistical power. However, recruitment of women for an overnight sleep recording in late pregnancy is challenging, particularly when no previous measurement standards exist for all the events. Hence, a novel method for scoring $TcCO_2$ peaks was developed and used in this study.

Our approach for respiratory analysis has limitations, which should be considered when evaluating the data. First, the use of automated scoring function for breathing may not be optimal, but subject-to-subject variation is minimal and systematic error is similar between subjects. Second, the $TcCO_2$ signal is known to drift and this will have an effect if normal breathing and flow-limited breathing occur at different times during the night. In order to counter this effect, data with large differences between the evening and morning were discarded. Also, large fluctuations in $TcCO_2$ signal without any discernible change in ventilation were considered erroneous. Some individuals had virtually no flow-limitation and in order to avoid overrepresentation in the data, data from sleep stages with small amounts of flow-limited breathing were excluded.

For the analysis of sleep stage $TcCO_2$ the data was pooled from the whole night to give a sleep-stage-specific $TcCO_2$ value. In the case of signal drift, this approach is problematic since it introduces bias. Signal drift downwards will give values that are too low and upward drift will give $TcCO_2$ values that are too high. Technical drift however, occurs in both directions and when the data is analyzed on a group level the effect of drift is diminished to some extent. Unfortunately the variance is increased at the same time, which makes it more difficult to see statistical differences between groups. This may explain why we failed to see differences between sleep stages. Despite of these limitations we see that our data gives a detailed view of overnight CO_2 dynamics that should be further studied.

Our results open new perspectives to cardiorespiratory monitoring during sleep and pregnancy. In healthy individuals, even subtle changes in ventilation may lead to notable changes in $TcCO_2$. Our subjects were healthy and had a relatively low level of SDB, but in individuals with complicated pregnancies, upper-airway flow-limitation could result in marked $(Tc)CO_2$ changes affecting heart and endothelial function. CO_2 increase related to flow-limitation may contribute to overnight increase in blood pressure [11] that is reversible with treatment. Identification of clinically significant $TcCO_2$ patterns could in the future guide to treatment decisions in symptomatic patients with low AHI. Flow limitation can be effectively controlled with CPAP (continuous positive airway pressure), a mode of therapy which helps to stabilize CO_2 levels and sleep.

5. Conclusions

In conclusion, during normal pregnancy SDB is very mild and comparable to non-pregnant controls. In contrast to the earlier findings of decreased $PaCO_2$ during pregnancy, the absolute levels of $TcCO_2$ showed no difference between the groups. However, the variance of $TcCO_2$ is smaller in the pregnant group when relative values are used. We suggest that the decreased $PaCO_2$ during pregnancy is an adaptive measure to maintain constant pCO_2 at the tissue level. Transient changes are seen in overnight $TcCO_2$ profile, which reflect altered respiratory control. Further studies with a larger population are evidently needed in the field of sleep disorders during pregnancy and different pregnancy complications.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.05.005.

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