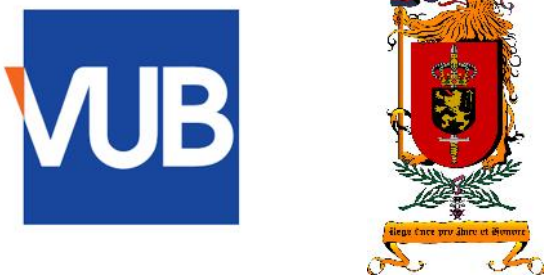
A MULTIDISCIPLINARY APPROACH TO PERIODIC BREATHING: OBSERVATION, QUANTIFICATION AND MATHEMATICAL MODELLING



THESIS

submitted to the
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In fulfilment of the requirements for the combined degrees of
DOCTOR OF ENGINEERING SCIENCES
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DOCTOR OF PHYSICAL EDUCATION AND MOVEMENT SCIENCES
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A Multidisciplinary Approach to Periodic Breathing: Observation, Quantification and Mathematical Modelling

Thesis submitted to the **Vrije Universiteit Brussel** and the **Royal Military Academy** in fulfilment of the requirements for the combined degrees of **Doctor of Engineering** and **Doctor of Movement and Sport Sciences** by **Ir Helio Fernandez Tellez**

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SUMMARY

Periodic breathing is a form of sleep-disordered breathing characterised by instability in the respiratory pattern that exhibits an oscillatory behaviour with periods of hyperventilation followed by apneas or hypopneas. Periodic breathing at normal altitude is correlated with higher levels of mortality and can be found, among others, in subjects with damaged respiratory centres; in subjects who are exposed to acute hypoxia or in patients suffering from chronic heart failure. Both experimental and clinical observations seem to support the idea that periodic breathing might be caused by both the combination of a delay in the transport of information within the feedback control loop, together with an augmented ventilatory response (due to enhanced chemoreceptor reactivity). The standard quantification for the diagnosis of sleep-related breathing disorders is the apnea/hypopnea index (AHI), which measures the proportion of apneic/hypopneic events during polysomnography. Despite the impaired prognosis associated with periodic breathing, there are many aspects regarding periodic breathing that are of great research interest. For instance, automated detection and early diagnosis are of clinical relevance. The time constant of adaptation and the processes behind the genesis of periodic breathing also remain to be elucidated.

To shed light on some of the processes behind periodic breathing a variety of experiments were performed. The study was divided in different experimental settings in which among others, polysomnography and physical activity were monitored. Some settings were laboratory controlled or group design study in which healthy men exposed to high altitude or patients suffering from different pathologies were followed. The other experimental settings occurred during the over-winter period on-site at the Concordia Antarctic Station (3200 m; ~3800 m equivalent) in which the

winterover team lived and worked continuously for 12-14 months confined to the research base. Because of its chronic hypobaric hypoxia, Concordia provides an unique environment for the study of periodic breathing.

We observed in our experiments that despite a partial restoration of oxygen saturation (SpO_2), there was no evidence of change in periodic breathing through a 13 month period of exposure to high altitude [chapter 1]. Over time, periodic breathing does not seem to show a clear trend, with participants having both episodes of increasing and decreasing periodic breathing levels. A significant correlation was found between the length of the period of periodic breathing and the AHI. AHI was also positively correlated with both mean exercise time and the coefficient of variation in mean night pulsed oxygen saturations. Data indicate that exercise (i.e. physical activity) *per se* affects night SpO_2 concentrations and AHI index acutely, after as little as two bouts of moderate intensity cycle exercise [chapter 2]. We also developed the estimated amplitude modulation index (eAMI), which could be used for both detecting and quantifying periodic breathing, adding valuable information beyond the number of events per sleeping hour as described by the AHI [chapter 3]. Finally, we modelled a novel approach for describing the interaction between both the peripheral and the central chemoreceptors [chapter 4]. We suggest that chemoreceptors modulate their input by adjusting the gain of the neural pathway that transports respiratory signals, i.e. acting as a multiplicative interaction. Notwithstanding the conceptual simplicity of the model, we show that it can easily reproduce the observed behaviour of the respiratory system at both stable and unstable, i.e. periodic breathing conditions.

A MAR Y JADE.

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ACRONYMS AND SYMBOLS

AHI	Apnea/hypopnea index
AM	Amplitude modulation
AMS	Acute mountain sickness
ANOVA	Parametric repeated measures analysis of variance
CAI	Central apnea/hypopnea index
CHF	Congestive heart failure
CON	Control group
CPAP	Continuous Positive Airway Pressure
CPG	Central pattern generator
CSA	Central sleep apnea/hypopnea
CVLM	Caudal ventrolateral medulla
DRG	Dorsal respiratory group
eAMI	Estimated amplitude modulation index
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Chin surface electromyography
EOG	Electrooculography
ESA	European Space Agency
EX	Exercise group
HAPE	High altitude pulmonary oedema
HVA	Hypoxic ventilatory acclimatization
ICC	Intra-class correlations
LSS	Lake Louise Score
LVMI	Lung volume modulating index
NTS	Nucleus tractus solitarius
OSA	Obstructive sleep apnea
PB	Periodic breathing
pFRG	Parafacial respiratory group
pre-BOTC	Pre-Bötzinger complex
PRG	Pontine respiratory group
PSG	Polysomnography
RPE	Perceived exertion
RTN	Retrotrapezoid nucleus
RVLM	Rostral ventrolateral medulla

SDB	Sleep-disordered breathing
SIDS	Sudden infant death syndrome
SND	Sympathetic nerve discharge
VAS	Visual analogue scale
VPSA	Vacuum pressure swing adsorption
VRC	Ventral respiratory column
WASO	Wake after sleep onset
BMI	Body-max index
CO_2	Carbon Dioxide
F	Welch's F-ratio
H+	Hydron
H_{lung}	Drive into Pco2
hPa	Hectpascals
Kg	Kilograms
m	Meters
n	Sample size
O_2	Oxygen
p	Significance
P_{aCO2}	Arterial carbon dioxide partial pressure
P_{ACO2}	Alveolar carbon dioxide partial pressure
P_{CO2}	Carbon Dioxide partial pressures
P_{O2}	Oxygen partial pressures
r	Correlation
SaO_2	Oxygen Saturation
SpO_2	Pulse oxygen saturation
V_0	Ventilation
V_{chem}	Central and peripheral chemoreflex drives
ηp^2	ANOVA effect size

Cover photo: ESA/IPEV/PNRA–B. Healey.

Chapter 1 - Introduction

I. THE IMPORTANCE OF PERIODIC BREATHIG

The most common types of sleep-disordered breathing (SDB) are obstructive sleep apnea/hypopnea (OSA), followed by central sleep apnea/hypopnea (CSA) and periodic breathing. Periodic breathing is characterized by instability in the respiratory pattern that exhibits an oscillatory behaviour with periods of hyperventilation followed by apneas or hypopneas. Periodic breathing may be observed in a variety of situations including damage to respiratory centers[3], acute exposure to high altitude[3-7] and in patients suffering from chronic heart failure[8-11]. The prevalence of undiagnosed SDB, a condition of repeated episodes of apnea and hypopnea during sleep, is high among adults[12]. Several studies have demonstrated a direct link between periodic breathing and mortality[13-15]. Giving the impaired prognosis associated with periodic breathing, it is of utter importance not only to better detect periodic breathing but to also understand its genesis. Indeed there are still many aspects regarding periodic breathing as a phenomenon that remain a research question. Giving an answer to some of them was the purpose of this work.

Three aspects of periodic breathing will be addressed in this work. For that, we will follow a multidisciplinary approach:

1. The observation of Periodic breathing at high altitude
    a. As pointed out by Bloch et al[6], very few studies regarding periodic breathing and adaptation to hypobaric hypoxia have been performed, and there seems to be some controversy about the results. While it is widely accepted that an increase in altitude is correlated with an increase in the occurrence of periodic breathing[6,16], the magnitude, the time course and the altitude of occurrence differ markedly between studies. There are some conflicting results on the persistence of periodic breathing over successive nights. The real time of adaptation to high altitude regarding periodic breathing remains elusive. Using the unique long-term exposition to hypoxia at the Antarctic base Concordia, we were the first to be able to report changes in breathing stability after 13 months.
    b. The question whether exercise (i.e. physical activity) *per se* may affect nocturnal periodic breathing during hypoxia has never been explored. Giving that high altitude expeditions are characterised by strenuous physical demands, this question is of interest. It is accepted that exercise enhances chemoreactivity [as reviewed in [17]]. Considering that altered chemoreactivity is involved in the control of respiration during exercise and that it may also be a critical factor in the development of periodic breathing, exercise during

hypoxia may, therefore, impact the genesis of nocturnal periodic breathing. Two experiments were conducted at similar altitudes to address this question: a 10-day group-design hypoxia confinement study to observe acute effects, and a 13-month hypoxia confinement study to observe long-term effects of hypoxia on sleep-breathing disturbances.

2. Quantification and detection of periodic breathing

When one observes periodic breathing, the resemblance with amplitude modulated signals is the first thing that comes to mind. Still, the gold standard for its quantification is counting the number of events per hour. We tried to develop methods based on our engineering knowledge to understand better and quantify the process behind periodic breathing. Giving the impaired prognosis associated with periodic breathing, early and accurate diagnosis of periodic breathing is of major importance.

3. Modelling of periodic breathing

The application of mathematical models to quantify the behaviour of the respiratory system has led to major advances in the understanding of the control of ventilation. In the present study, we set out to explore the possibility of a model in which chemoreceptors interact with each other by modifying the gain of the neural pathways that transport the respiratory signals. We also analysed the implications this model has in explaining periodic breathing. The scope of this work was not to discuss if the interactions exist but rather accepting them[18] and develop the mathematical framework. The similitude between the oscillations observed in periodic breathing (see figure 1-4) and those found in unstable human-made feedback control systems has led to the idea that periodic breathing might indeed be caused by instability in the regulation of breathing[19]. We will explore the behaviour of our model in such condition.

II. RESPIRATION AND PERIODIC BREATHING

A. *The respiratory system*

The term Respiration includes two major processes: *external respiration* or the absorption of O_2 and removal of CO_2 from the body; and *internal respiration* or the utilisation of O_2 and production of CO_2 by cells, together with the exchanges of gas between the cells and their fluid medium. Respiration is divided into four categories: pulmonary ventilation; diffusion of O_2 and CO_2 between alveoli and tissues; transport of O_2 and CO_2 in body fluids to and from cells; and the regulation of respiration. The respiratory system consists of a gas-exchanging organ (the lungs) and a "pump" that ventilates them. This pump is formed by the chest wall; the respiratory muscles and cells that regulate the levels of O_2 and CO_2 in the blood by activating these muscles; nerves that connect the brain to the muscles; and several air conducts. At rest, a normal human

breathes around 12 to 15 times a minute. This breathed air mixes with the gas in the alveoli. Gases diffuse from the alveoli to the blood in the pulmonary capillaries, and vice versa, across the alveolocapillary membrane, made up of the pulmonary epithelium and their fused basement membranes.

The amount of air that moves into the lungs with each inspiration or out with each expiration is what we know as *tidal volume*. The volume expelled by an active expiratory effort after passive expiration is the *expiratory reserve volume*, and the air left after a maximal

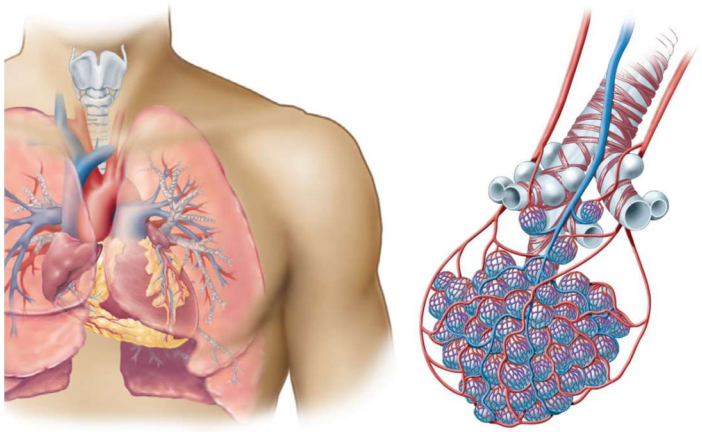

Figure 1-1. The lungs and the capillary

expiratory effort is the *residual volume*. The *respiratory dead space* of the airways is the conducting area occupied by gas that does not exchange with blood in the pulmonary vessels. The amount of air inspired and expired per minute, namely pulmonary ventilation or respiratory minute volume, is in average 6 to 8 litres of air per minute.

B. *The regulation of respiration*

One could be tempted to think that given the complexity of the human body, the respiratory system is rather simple when compared to others. However, despite its apparent simplicity, the control of breathing involves a rather complex regulatory system. There are different neural mechanisms involved in the regulation of respiration, one responsible for the automatic control, and other voluntary control. The latter system is located in the cerebral cortex and sends impulses to the respiratory motor neurones via the corticospinal tracts. The automatic system is driven by neuronal groups located in the brainstem forming what is called a central pattern generator (CPG). These circuits produce rhythmic patterns that stimulate the necessary motor neurones to control both the muscles that regulate inhalation and exhalation and the muscles that regulate air flow. CPG networks can generate rhythmic output without receiving rhythmic input[20]. Impulses from these cells activate motor neurones in the cervical and thoracic spinal cord innervating inspiratory muscles. The diaphragm is activated via the phrenic nerves by those in the cervical cord; the external intercostal muscles are activated by those in the thoracic spinal cord. However, the impulses also reach the innervation of the internal intercostal muscles

and other expiratory muscles. The main components of the CPG responsible for automatic respiration are located in the medulla. Rhythmic respiration is initiated by a small group of synaptically coupled pacemaker cells in the pre-Bötzinger complex (pre-BOTC) on both sides of the medulla between the nucleus ambiguous and the lateral reticular nucleus. Also, dorsal and ventral groups of respiratory neurones are present in the medulla. However, lesions of these

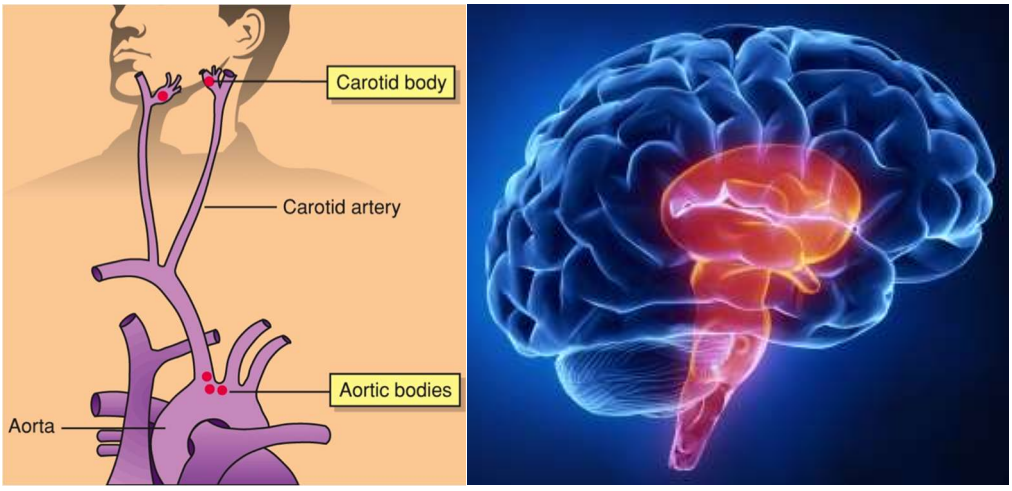

Figure 1-2 The chemoreceptors locations.
Traditionally chemoreceptors have been divided into two groups, peripheral and central ones. The glomus cells of the carotid body constitute the major peripheral chemoreceptors and are located at the bifurcations of the internal and external arteries. Unlike with peripheral chemoreceptors, the absolute location of central chemoreceptors is still under debate, with difren regions over the medula.

neurones do not abolish respiratory activity, and they apparently project to the pre-Bötzinger pacemaker neurones.

Mammals require continuous regulation of O_2 and CO_2 levels to survive; for that, they have developed a robust chemoreceptor system. Chemoreceptors are by definition in charge of transducing blood chemical signals (i.e. gas blood concentrations and the acidity or alkalinity of blood, or blood pH) into neural signals. Arterial plasma usually has a pH of 7.4, and venous pH is just slightly lower. A decrease in the pH below 7.4 is known as acidosis, while an increase above 7.4 as alkalosis. *Respiratory acidosis* occurs with any rise in arterial P_{CO2} (above 40 mm Hg) due to decreased ventilation. The pH change observed at any increase in P_{CO2} during respiratory acidosis depends on the buffering capacity of the blood. Any short-term decrease in ventilation that lowers P_{CO2} below what is needed for proper CO_2 exchange (i.e., below 35 mm Hg) results in *respiratory alkalosis.* On top of the chemoreceptors, other afferents can provide non-chemical controls that may affect breathing in other particular situations.

Traditionally chemoreceptors have been divided into two groups, peripheral and central ones. The glomus cells of the carotid body constitute the major peripheral chemoreceptors and are located at the bifurcations of the internal and external arteries. They are the main arterial O_2 sensors but also react to arterial CO_2 and pH[21]. Unlike with peripheral chemoreceptors, the absolute location of central chemoreceptors is still under debate. As noted by Wong-Riley et al., there are currently three major schools regarding candidates for central chemoreceptors[22].

Guyenet et al. propose neurones in the retrotrapezoid nucleus (RTN)[23], while neurones from the medullary raphe have been suggested by Hodges et al[24]. Finally, a decentralised scheme with multiple chemoreceptors sites has also been proposed[25]. Although central chemoreceptors are mainly sensitive to H^+ around their local environment in the medulla[26], they are often represented as directly reacting on CO_2 partial pressure (P_{CO2}). A simplification because H^+ depends on P_{CO2}. This generalisation can be misleading since CO_2 can pass through the blood-brain barrier while H^+ ions do not, meaning possible differences between central and arterial H^+. For many years, the prevailing view was that CO_2/H^+ sensitivity occurred entirely at the central chemoreceptors. There is now enough evidence to confirm that central chemoreceptors contribute about two-thirds of the ventilatory response to CO_2/H^+ while the carotid chemoreceptors contribute about one-third[27]. Recent evidence supports the interdependence between central medullary chemoreceptors and input from several sources including possibly peripheral chemoreceptors. Studies show that CO_2 response from central chemoreceptors located in the retrotrapezoid nucleus seem to be influenced by several synaptic inputs, with the carotid chemoreceptors being one among them[28]. This interaction between different ventilatory control neurones has led to highly controversial interpretations about the nature of this interconnection. At the moment there seems to be enough evidence to support an additive, a hyperadditive, a hypoadditive or even a hybrid effect on ventilation resulting from carotid-central chemoreceptor interactions[29-31]. A possible mechanism for the interaction of both chemoreceptors might be the mutual modification of discharges in autonomic nervous system nerves (both parasympathetic and sympathetic) in charge of supplying the receptors. Chemoreflexes have an important role in the regulation of the sympathetic activity, but respiration and blood pressure can also inhibit the response to chemoreflex activation[32]. Indeed an increase in sympathetic activation is often observed in populations prone to higher amounts of sleep disordered breathing[33]. For instance, sympathetic activation has been found in sojourn at high altitude, obese subjects[34,35] and in patients with heart failure[36]. Also, several studies have identified abnormally high sympathetic activity in obstructive sleep apnea (OSA) patients[37]. Additionally, the observation that Continuous Positive Airway Pressure (CPAP) treatment in both OSA[37] and congestive heart failure (CHF) patients exhibiting periodic breathing[38] decreased the overall sympathetic activity seems to further support a relationship between augmented apneas and sympathetic activation. In animal models, there is also enough accumulated evidence for direct connections between respiratory and cardiovascular sympathetic neurones in the brainstem [39]. Guyenet et al. also found in animal models that activation of the respiratory neurones can activate sympathetic neurones[40]. A possible mechanism to explain how both central and peripheral chemoreceptors can increase sympathetic nerve discharge (SND) is by activating rostral ventrolateral medulla (RVLM) sympathoexcitatory neurones, predominantly mediated by the activation of C1 and other sympathoexcitatory neurones of the RVLM[41].

Interaction of the carotid bodies and the central chemoreceptors can take place in at least three regions [as reviewed in [22,27]] 1) the nucleus tractus solitarius (NTS), where the first synapse for carotid afferents share location with CO_2/H^+ chemoreceptor neurones[42]. 2) A chemosensitive/integrating region between the parafacial respiratory group (pFRG) and the retrotrapezoid nucleus (RTN); this is supported by studies indicating that peripheral chemoreceptors inputs together with many other ventilatory related reflexes join in this area. The pFRG/RTN is characterised by chemosensitive glutamatergic neurones that can be modulated by both changes in the peripheral chemoreceptors and from central (hypothalamic) neurones[28,43]. 3) the nucleus tractus solitarius (NTS), in turn, projects to three brain stem respiratory groups: the pontine respiratory group (PRG), the dorsal respiratory group (DRG) and the ventral respiratory column (VRC)[22]. Nuding et al. found that stimulation of both central and peripheral chemoreceptors increased activity of VRC, raphe, and PRG respiratory neurones[44].

The application of mathematical models to quantify the behaviour of the respiratory system has led to major advances in the understanding of the control of ventilation. Improved research techniques in identifying underlying contributors to ventilatory patterns may result in individual clinical assessment of ventilatory control and tailored treatment when appropriate[45]. The most extended model for the interaction of chemoreceptors is what has been called the Oxford model[46], in which ventilation is the sum of three components; the central and the peripheral chemoreflex drives and a ventilatory drive that depends on state[2]. This model, which has been used in numerous mathematical approaches, features linear relations between ventilation and CO_2 partial pressures. Finally, a constant drive dependent on the state often named basal ventilation completes the model.

The most extended model for the interaction of chemoreceptors is what has been called the Oxford model, in which ventilation is the sum of three components; central and peripheral chemoreflex drives and a ventilatory drive that depends on subject's state[2]. This model, depicted in Figure 1-3, features linear relations between ventilation and CO_2, and a negative feedback loop

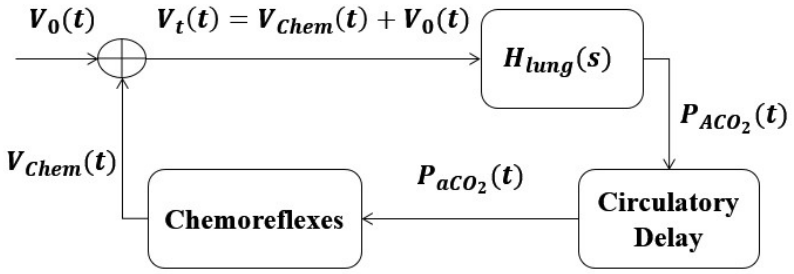

Figure 1-3 The "classical" chemoreceptor model[2]
Ventilation $V_t(t)$ is the sum of two components; central and peripheral chemoreflex drives $V_{Chem}(t)$ and a ventilatory drive that depends on state $V_0(t)$. This model features linear relations between drive and CO_2 partial pressure. $V_{Chem}(t)$ and $V_0(t)$ constitute the excitatory signals that stimulate the motor neurones producing breathing movements. These are translated in the lungs $H_{lung}(s)$ into changes in partial pressures outside the lungs or P_{ACO2}. Chemoreceptors adapt the drive to new demands based on partial pressures around the chemoreceptors $P_{aCO2}(t)$. An analog model could be assumed for cerebral partial pressure $P_{bCO2}(t)$ instead of $P_{aCO2}(t)$ assuming different circulatory delays

controlled by the chemoreceptors that maintains the right levels of arterial partial pressures $P_{aCO2}(t)$. An similar model could be assumed for cerebral partial pressure $P_{bCO2}(t)$ instead of $P_{aCO2}(t)$ assuming different circulatory delays. $H_{lung}(s)$, is the transfer function of the lungs defining the response of the alveolar CO_2 partial pressure $P_{ACO2}(t)$ to the drive ($V_t(t)$, the neurological signals) trough the mechanical movement of the lungs. The negative feedback loop is implied in the functioning of the lungs. An increase in the drive $V_t(t)$ means more minute ventilation which causes CO_2 to decrease. $V_t(t)$ represents the total drive, including the peripheral chemoreceptor drive $V_p(t)$, the central chemoreceptor drive $V_c(t)$, and it is supposed to have a 3rd component, $V_0(t)$, that depends on the state and it is often consider as constant, therefore C. This model will be further discussed in Chapter V.

C. *Hypoxia*

Although the composition of air stays the same, the total barometric pressure falls with increasing altitude. At 3000 m above sea level, for instance, alveolar P_{O2} is reduced to about 60 mm Hg. As one continues ascension, alveolar P_{O2} declines less rapidly, and the alveolar P_{CO2} falls to a certain degree because of hyperventilation. This fall in arterial P_{CO2} produces respiratory alkalosis. Hypoxia is the deficiency of O_2 at the tissue level. Hypoxia produces many changes at the cell level and has a strong impact on the functioning of the brain. Severe hypoxia can cause a fast loss of consciousness and ultimately death. Mild hypoxia can cause among other symptoms impaired judgment, drowsiness, excitement, disorientation, anorexia, nausea, vomiting, and migraines. Hypoxic hypoxia is then by definition a condition of reduced arterial $P_{O2.}$ It is experienced in sojourns at high altitude and in a variety of diseases.

Continued exposure to hypoxia induces a series of compensatory mechanisms in the human body acclimatisation that improve its ability to tolerate persistently lower environmental partial pressures of O_2 [as reviewed in [47]]. Most of the improvements occur in the first two days[48], although depending on the altitude and inter-individual differences in ventilatory response, it can take up to several weeks[49]. In non-acclimatized subjects, mental symptoms such as irritability appear at about 3700 m. At 5500 m, the hypoxic symptoms are severe; and at altitudes above 6100 m, consciousness is usually lost.

A major aspect of the ventilatory acclimatisation to hypoxia is the gradual elevation of minute ventilation despite increase in arterial O_2 and concomitant fall in arterial CO_2[48,50]. Hyperventilation at hypoxia produces respiratory alkalosis shifting the oxygen-hemoglobin dissociation curve to the left. At the same time, there is an increase in red blood cells, which decreases O_2 affinity for haemoglobin making more O_2 available to the tissues. The initial ventilatory response to increased altitude is therefore relatively small because alkalosis tends to counteract the stimulating effect of hypoxia. However, ventilation steadily increases over the next

four days. After that, the ventilatory response begins to decline slowly, but it takes years of residence at higher altitudes for it to fall to the initial level.

In the short term, between the first 8 to 24 hours when first arriving at high altitude, individuals may develop transient "mountain sickness" that might last up to 8 days[51]. Headache, irritability, insomnia, breathlessness, and nausea and vomiting are some of the symptoms associated with mountain sickness. Individuals who do not develop mountain sickness have a diuresis at high altitude, and urine volume is decreased among people who develop the condition. More severe conditions associated with mountain illness are high-altitude cerebral oedema and high-altitude pulmonary oedema. In high-altitude cerebral oedema, the capillary leakage in mountain sickness progresses to brain swelling, causing ataxia, disorientation, and in some cases coma and death. High-altitude pulmonary oedema is a patchy oedema of the lungs that is related

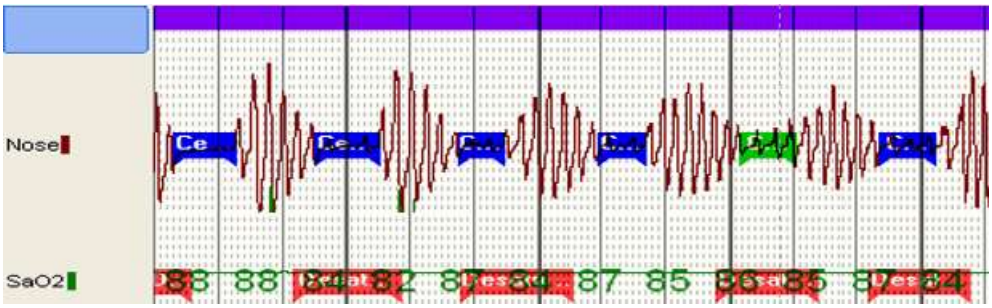

Figure 1-4 Screenshot of a respiratory signal exhibiting periodic breathing
Airflow (nose) in arbitrary units. Oxygen saturation (SaO_2) in percentage. In dark over the nose signal, each of the respiratory events. Each vertical line represents 15 seconds.

to the marked pulmonary hypertension that develops at high altitude. All forms of high-altitude illness are cured by descending to lower altitude and by treatment with acetazolamide[52].

During sleep, subjects at high altitude might also experience an unstable respiration pattern known as periodic breathing.

D. *Periodic breathing*

In Figure 1-4 an example of respiratory signals recorded during periodic breathing is depicted. Voluntary hyperventilation easily demonstrates the interaction of the chemical mechanisms regulating respiration: when a normal individual hyperventilates for 2 to 3 min, then stops and permits respiration to continue without exerting any voluntary control over it, a period of apnea occurs[53]. This is followed by a few shallow breaths and then by another period of apnea, followed again by a few breaths. This phenomenon is called periodic breathing or often known as Cheyne–Stokes respiration. It is easier to observe periodic breathing during sleep, the reason being that respiration is then no vonluntarially controlled. If the P_{CO2} falls during the waking state, other stimuli can maintain respiration, but during sleep, these stimuli are decreased, and a drop in P_{CO2} can cause apnea[53]. As mentioned before, changes in breathing patterns can be observed in sojourns at high altitude. Periodic breathing is common at a height above 2.500 meters in healthy subjects[6,54,55]. While the quantity of periodic breathing may be reduced with continued hypoxia exposure[52,56], more recent evidence supports its persistence over time[6].

Periodic breathing might also be symptomatic of different diseases. It is, for instance, most commonly seen in patients with congestive heart failure and uraemia, but it also occurs in patients with brain disease. Periodic breathing might even be observed during sleep in some healthy individuals at sea level. Some of the patients with Cheyne–Stokes respiration have increased sensitivity to CO_2. The increased response is apparently due to disruption of neural pathways that normally inhibit respiration. In these individuals, CO_2 causes relative hyperventilation, lowering the arterial P_{CO2}. During the resultant apnea, the arterial P_{CO2} again rises to normal, but the respiratory mechanism again overresponds to CO_2. Breathing ceases, and the cycle repeats. Although the mechanisms underlying periodic breathing at high altitude are not clearly elucidated[47], it is widely accepted that acclimatisation to hypoxia enhances chemoreceptor reactivity, which constitutes a critical factor inducing periodic breathing[7,19,57]. Also, when individuals with a slower circulation hyperventilate, they lower the P_{CO2} of the blood in their lungs, but it takes longer than normal for the blood with a low P_{CO2} to reach the brain. During this time, the P_{CO2} in the pulmonary capillary blood continues to be lowered, and when this blood reaches the brain, the low P_{CO2} inhibits the respiratory area, producing apnea. In other words, the respiratory control system oscillates because the delay in the negative feedback loop from lungs to the brain is abnormally long. Patients with cardiac disease also exhibit this prolongation of the lung-to-brain circulation time, what might cause periodic breathing.

Although there are still some controversial results regarding the influence of periodic breathing on sleep quality[16,54,58-60], it is widely accepted that periodic breathing is associated with increased arousal indices that can impair sleep quality[61]. Poor sleep at high altitude often leads people to feel somnolent and fatigued during the following day, reducing their productivity and increasing the probability of error as described by West et al[49,62].

III. STRUCTURE OF THE CURRENT MANUSCRIPT

We have divided this work into four chapters. Each of them does not represent only an original manuscript, but also a different approach to periodic breathing. The first two chapters include mostly the clinical and observational work related with human physiology, while the last two are the ones related to more engineering methods applied to a better understanding and observation of periodic breathing. The first chapter is what we used to call “the descriptive paper” in which we report the results obtained after 13 months of monitoring sleep-related periodic breathing in the Antarctic Concordia Station. The second chapter is a joint study that was designed to build on the largely observational results from Concordia about the influence of exercise in periodic breathing at high altitude. In the third chapter, we report a method we developed to score periodic breathing automatically. We prove that the method is highly correlated with existing ones, and that it can give additional information with respect to existing methods. Finally, in the

last chapter, we developed a non-linear model (multiplicative) for the interference between peripheral and central chemoreceptors. We were able to verify that many observations regarding periodic breathing were predicted with this simple model.

Chapter 2 - Sleep-related Periodic Breathing Does Not Acclimatize to Chronic Hypobaric Hypoxia: A 1-Year Study at High Altitude in Antarctica

The persistence of periodic breathing beyond acclimatization to high altitude is still under debate. Before our experiment, there had never been a study monitoring periodic breathing at high altitude over the course of a complete year. Monitoring sleep-related periodic breathing at high altitude during extended periods of time is hard and highly demanding regarding financial and labour resources. Being able to do that during a whole year was an exceptionally rare occasion. We had the opportunity to do so within the framework of the European Space Agency's Life Science campaign at Concordia, a French/Italian Antarctic base. The station is located at an equivalent altitude of 3,800 m above sea level. The winterover team arrives during the Antarctic late summer, living there in complete isolation the whole Antarctic winter. During the 13-month campaign, nocturnal breathing patterns were recorded by portable polysomnography. To our knowledge, this is the first study to evaluate the evolution of periodic breathing due to hypobaric hypoxia at a constant high altitude and during a complete year. This study was performed on healthy population living in a day-to-day environment. During the 13-month campaign, severe sleep-related periodic breathing was observed in most of the participants. Our study extends previous findings of periodic breathing prevalence despite partial SpO_2 restoration and the absence of acute mountain sickness symptoms during a prolonged stay at constant high altitude.

A summary of these results was published in the American Journal of Respiratory and Critical Care medicine[63]. This chapter starts with the published work, i.e. a letter to the editor, and continues with an extended version.


American Journal of Respiratory and Critical Care Medicine

Sleep-related Periodic Breathing Does Not Acclimatize to Chronic Hypobaric Hypoxia: A 1-Year Study at High Altitude in Antarctica

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I. ABSTRACT

Introduction: At altitudes above 2500 m, ventilation in healthy participants commonly shows an oscillatory behaviour termed periodic breathing. Although periodic breathing has been extensively observed, there are still aspects regarding human adaptation to hypobaric hypoxia that remain unknown.

Objectives: to address the influence of altitude on sleep disordered breathing during a prolonged stay, nocturnal periodic breathing was monitored at an approximate altitude of 3800 m over the course of 12 months.

Methods: the investigation took place at the Antarctic station Concordia, in the framework of the European Space Agency's Life Science campaign. Thirteen healthy male participants were monitored using wireless polysomnography (BioRadio, Clevemed Inc.). Throughout the 12 month campaign, each of the subject were monitored eight times, at approximately six week intervals. All recordings were analysed by a professional sleep technician.

Results: Despite a partial restoration of SpO_2, the number of apneic/hypopneic events due to nocturnal periodic breathing were at clinically severe level during the whole campaign (AHI= 65.4±14.55). There was no evidence of change in periodic breathing through the 12 month period. Over time, periodic breathing does not seem to show a clear trend, with participants having both episodes of increasing and decreasing periodic breathing levels.

Conclusion: With regard to periodic breathing, we found no evidence of acclimatization during prolonged exposure to hypobaric hypoxia over the course of one year.

II. TO THE EDITOR

At altitudes above 2,500 meters, ventilation in healthy subjects commonly shows periodic breathing: an oscillatory behaviour with alternating periods of hyperventilation followed by central apneas or hypopneas[6,54,64]. While an increase in altitude is correlated with an increase in the occurrence of periodic breathing[6,16], the magnitude, the time course and the altitude of occurrence differ markedly between studies. Some studies found an increase in periodic breathing over time at different altitudes, despite an improvement of SpO_2 and they found no relationship with acute mountain sickness (AMS)[6,65]. Other studies however, found a decrease[56,66], or no changes[64] in the amount of periodic breathing over time. All of these studies were performed at different altitudes and ascending rates. Furthermore, in these studies the time spent in hypobaric hypoxia was short, from several days to up to four weeks.

We aimed to observe the occurrence of periodic breathing over a longer time period, beyond the period of adaptation[48,49]. This study was conducted within the framework of the European Space Agency's Life Science campaign at the Antarctic base Concordia, located at an equivalent altitude of 3,800 meters above sea level. Living conditions within the station are comparable to European standards of living, with the inhabitants' conducting research and maintaining the base. Due to the confinement conditions, day-night cycles at the station are imposed by daily routines rather than daylight, which is absent for 3 months during the polar winter. Participants remained at the station an average of 13 months. This study was approved by the Ethics committee of the Free University of Brussels. Some of the results of this study have been previously reported in the form of conference abstracts[67,68].

Thirteen members of the 14 all-male crew of one winter campaign participated in the experiment (n = 13; age = 39 ± 9.8; BMI = 24.2 ± 2.2; 3 smokers). None of the subjects reported a history of significant medical conditions. Upon arrival at the station, participants' acclimatization progress was monitored weekly through physical examination, pulsed oxygen saturation (SpO_2) and self-report assessment of AMS through the Lake Louise AMS questionnaire. During the campaign, nocturnal breathing patterns were recorded on eight occasions approximately every six weeks via portable polysomnography. All recordings were analysed by the same professional sleep technician following the American Academy of Sleep Medicine criteria[69]. Data from every two cycles were pooled to represent 4 major sessions mapping seasonal variations. The evolution of parameters over time was assessed by parametric repeated measures analysis of variance (ANOVA). For non-normally distributed data, non-parametric equivalent statistical tests were used (Friedman ANOVA). The stability of interindividual differences was quantified by means of intraclass correlations coefficient (ICC) and estimates were interpreted using published benchmark ranges[70].

Of the 13 participants, 11 participated until the end of the study. A summary of results can be seen in table 2-1. Symptoms of AMS were below clinical significance within the first 3 weeks upon arrival (median AMS score after 3 weeks was 1 [range, 0 to 1.5]). As a result of periodic breathing, the average number of apneic/hypopneic events per sleeping hour (AHI) during the entire campaign was above the level clinically considered as severe (AHI= 65.4 +/- 29.1). Statistically there was no effect of time on the evolution of AHI ($F(3,30)= .500$, $p= .685$, $\eta p^2= .048$) (see Figure 2-1A), but we found "substantive" stable inter-individual differences (ICC= .770) (see Figure 2-1B). In contrast, there was a significant effect of time on SpO_2 ($F(3, 33) = 4.706$, $p = .008$, $\eta p^2= .300$), characterized by a linear increase over the first 3 seasons

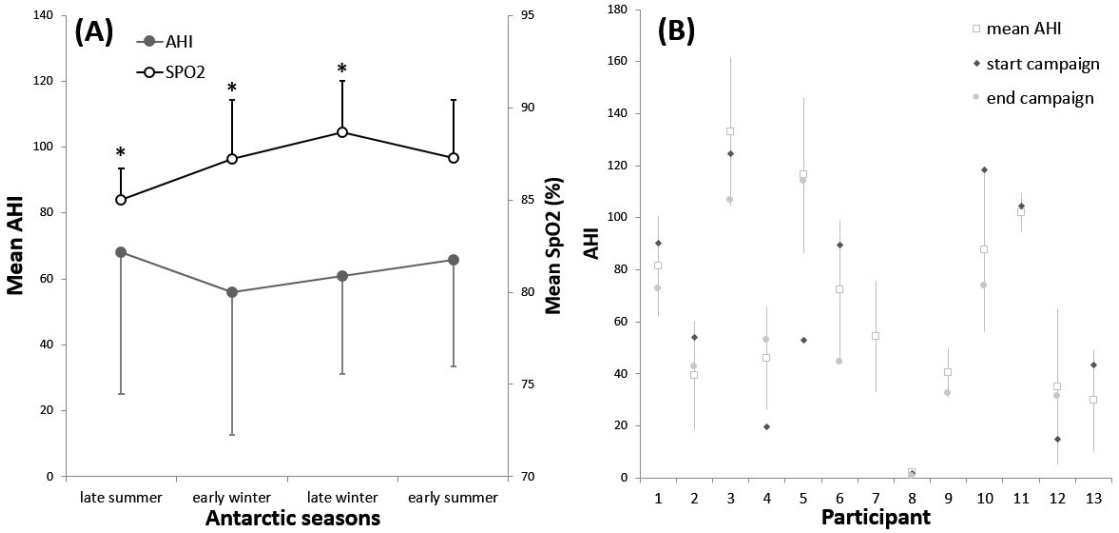

Figure 2-1 (A) Seasonal evolution of AHI averaged over the whole crew. (B) Evolution of AHI per participant.
(A) Apnea/hypopnea index and oxygen saturation by season. The points represent the means and the bars the standard deviations. (B) Apnea/hypopnea index by participant. The points represent the first, last and mean values for the entire expedition, and the bars the standard deviations.

($F(1,11) = 17.359$, $p = .002$, $\eta p^2 = .612$) (see Figure 2-1A). There was no significant correlation between AHI and SpO_2 (all p's > .25). Additionally, inter-individual differences in SpO_2 remained "moderately" stable during the winter-over period (ICC = .454). There was no significant time effect on the frequency of respiration ($\chi2(3) = .450$, $p = .930$), the length of the period of periodic breathing ($F(3,21) = .885$, $p = .465$, $\eta p^2 = .112$) or on heart rate ($\chi2(3) = 5.900$, $p = .117$). None of these parameters were correlated with participants' smoking habit, age or BMI (all p's > .1). Finally, a significant correlation was found between the length of the period of periodic breathing and the AHI during the early winter ($r = .643$, $p < .024$) and early summer ($r = .762$, $p = .010$).

Our most important finding was that during the entire 13-month campaign, for most of the participants, periodic breathing prevailed for the major part of sleeping time. Our results are consistent with previous studies reporting the prevalence of periodic breathing despite partial restoration of SpO_2 together with the absence of AMS[6,64]. Our data suggest that periodic breathing in fact does not follow any apparent trend when long term exposure is observed, with participants having both episodes of increasing and decreasing periodic breathing. Our experiment therefore contradicts the original idea that the amount of periodic breathing due to hypobaric hypoxia in sleep reduces over time[52,56,66]. Marked inter-individual differences in our results suggest the existence of responders and non-responders in terms of periodic breathing. We also observed a significant correlation between the length of the period of periodic breathing and the AHI, i.e. participants exhibiting shorter cycles of periodic breathing also had fewer apneic/hypopneic events per hour. This suggests that some physiological differences within the respiratory control loop might partially explain the existence of responders and non-responders.

Thanks to the steady confinement conditions at Concordia, we were able to observe changes in periodic breathing at a constant altitude and within an environment with more stable and less strenuous physical demands than a mountaineering expedition. It is widely accepted that periodic breathing is associated with increased arousal indices that can impair sleep quality[61].

TABLE 2-1. RESPIRATORY PATTERNS, HEART RATE AND OXYGEN SATURATION AT HIGH ALTITUDE

Season	Late summer	Early winter	Late winter	Early summer
AHI (1/h)	59.8 (25, 116.5)	56.5 (26.7, 120.4)	46.7 (18.7, 110.3)	73.3 (24.8, 99.4)
TST (h)	6.13 (4.14, 7.31)	6.87 (5.13, 7.43)	7.29 (5.39, 7.50)	6.98 (4.59, 7.32)
R_f (1/min)	18.2 (16.3, 19.7)	18.3 (16.3, 20.3)	18.3 (17.4, 20.2)	18.4 (17.5, 20.3)
PB_{length} (s)	20.3 (18.5, 22)	21.7 (19, 22.2)	21.1 (17.4, 22.3)	20.1 (17.1, 22.3)
HR (1/min)	72.6 (65.6, 79.6)	67.5 (64.5, 78.2)	68.2 (62.2, 74.2)	69.7 (62.5, 73.7)
SpO_2 (%)	85.1 (84.2, 88.3)	87.1 (85.4, 90.6)	87.9 (85.3, 90.4)	86.1 (85, 90.8)

Definition of abbreviations: AHI = apnea/hypopnea index; TST = Total sleeping time in hours; R_f = respiratory frequency in breaths per minute; PB_{length} = length of periodic breathing period in seconds; HR = heart rate in beats per minute; SpO_2 = oxygen saturation as measured by pulse oximetry. Data are represented as medians (quartiles).

Poor sleep at high altitude often leads people to feel somnolent and fatigued during the following day, reducing their productivity and increasing the probability of error[71]. This might be a major constraint in long term confinement duties in hypobaric hypoxic environments.

III. INTRODUCTION

At altitudes above 2.500 meters, ventilation in healthy subjects commonly shows an oscillatory behaviour with alternating periods of hyperventilation followed by central apneas or hypopneas[6,54,72]. Periodic breathing is associated with poor quality of sleep due to sleep fragmentation and frequent arousals. Subsequently, it decreases daytime performance and increases probability of errors in cognitive tasks[71]. Exposure to hypoxia induces a series of physiological adaptations in the body, improving the ability to tolerate the hypoxic environment. Most of the improvements occur in the first one or two days [48], although depending on the altitude and interindividual differences in ventilatory response, it can take up to several weeks[49]. Still, as pointed out by Bloch et al[6], very few studies regarding periodic breathing and adaptation to hypobaric hypoxia have been performed and there seems to be some controversy about the results. While it is widely accepted that an increase in altitude is correlated with an increase in the occurrence of periodic breathing[6,16], the magnitude, the time course and the altitude of occurrence differ markedly between studies. There are some conflicting results on the persistence of periodic breathing over successive nights. Bloch et al[6] found an increase in periodic breathing over time at different altitudes, despite an improvement on SpO_2, and they found no relation with acute mountain sickness (AMS). These results are in line with previous findings from Salvaggio et al at an altitude of 5050 m[65]. Other studies however, found a decrease[56,66], or no changes[73] in periodic breathing over time. All these studies were performed at different altitudes and ascending rates, adding a dynamic physically demanding factor. Furthermore, in these studies the time spent in hypobaric hypoxia was never more than a few weeks. All these factors may have had an influence on the results.

The goal of this study was to observe the occurrence of periodic breathing over a longer time, beyond what is considered the time of adaptation; at a constant altitude and in an environment with more constant, and less strenuous, physical demand than a mountaineering expedition. For that, the present study was carried out in the framework of the European Space Agency's Life Science campaign at Concordia, a French/Italian Antarctic base. The station is located at an equivalent altitude of 3,800 meters above sea level. During the 12 month campaign nocturnal breathing patterns were recorded by portable polysomnography. To our knowledge, this is the first study to evaluate the evolution of periodic breathing due to hypobaric hypoxia at given conditions.

IV. METHODS

A. Subject Recruitment

Thirteen members of the 14 all-male crew of one winter campaign at Concordia Station, Antarctica participated in the experiment (n = 13; age = 39 ± 9.8; BMI = 24.2 ± 2.2; 3 smokers).

Written, informed consent was obtained prior to participation in the study. The study was approved by the Ethics committee of the Free University of Brussels. None of the subjects reported a history of significant medical conditions and were fit for winterover service.

B. Setting

Concordia Station is located at an equivalent altitude of 3,800 m[74], with a mean atmospheric pressure of 645 hPa. The base allows for a confined stay during the winter, with few crew members going outside for short duration technical or scientific duties. Living conditions within the station are comparable to European standards of living, with participants operating ongoing research projects and maintaining the base. Participants arrived during the preceding Antarctic summer, and remained at the station for the Antarctic winter, on average spending 13 months at Concordia.

C. Procedure

Upon arrival at the station, participants' acclimatization progress was monitored weekly through physical examination, mood questionnaires, pulsed oxygen saturation (SpO_2) and Lake Louise questionnaires. Sleep monitoring started between 2 and 3 months after arrival, long after the symptoms of acute mountain sickness had resolved, and after the time during which acclimatization occurs[48]. During the campaign, participants performed around eight measurement cycles, approximately every six weeks. Each of the cycles comprised an embedded 4-day programme of several physiological measurements including all-night polysomnography (PSG). Participants had at least one habituation night to familiarize them with the equipment.

Data was acquired and quality-controlled by a medical doctor appointed by ESA to implement the programme, working independently to the station doctor.

D. *Material*

Participants were monitored using wireless polysomnography (BioRadio, Clevemed Inc. USA). Relative tidal volume was derived from thoracic and abdominal movements monitored by inductance plethysmography transducers placed around the participants' chest and abdomen. The electroencephalogram (EEG; 2 channels: AF3-M1, AF4-M2), electrooculogram (EOG; 1 channel), electrocardiogram (ECG; single lead) and electromyogram (EMG; 1 channel) recordings were made from surface electrodes. SpO_2 and heart rate were derived from finger pulse oximetry. During data acquisition, data was continuously downloaded to a computer using company software (BioRadio, Clevemed Inc. USA), which allowed for on-line visual inspection.

E. Data analysis

All recordings were analysed by the same professional sleep technician following the American Academy of Sleep Medicine criteria for respiratory event scoring[69]. The sleep technician was external to the study and had no aces to any information from the subjects. Discrimination between central and obstructive apneas was assessed by testing the existence of paradoxical breathing, i.e. breathing movements caused by obstruction in which the chest wall moves in reverse to the abdominal wall. Periodic breathing was qualified by the number of apneic/hypopneic events per sleeping hour (AHI) and the periodicity of each of its cycles. SpO_2, breathing frequency and heart rate were quantified in terms of the mean value during sleep. Data from every two cycles were pooled to represent 4 major seasons (cycles 1 and 2: late summer, cycles 3 and 4: early winter, cycles 5 and 6: late winter, cycles 7 and 8: early summer). Violations of normality for continuous variables were assessed by means of Kolmogorov-Smirnov tests. The evolution of parameters over time was assed by parametric repeated measures analysis of variance (ANOVA). For non-normally distributed data non-parametric equivalent statistical tests were used (Friedman ANOVA). The stability of interindividual differences was quantified by means of intra-class correlations (ICC), calculated as the proportion of between-subjects variance to the sum of the between- and within-subjects variance. ICC estimates were interpreted using published benchmark ranges[70] of *slight* (0.0-0.2), *fair* (0.2-0.4), *moderate* (0.4-0.6), *substantial* (0.6-0.8) and *almost perfect* (0.8-1.0) Statistical analysis was performed using IBM SPSS Statistics 21 (SPSS, USA).

V. RESULTS

11 of the 13 participants continued until the end of the study period. In total, over 60 measurements where performed. A summary of the results by cycle can be seen on table 2-1. Periodic breathing was present in most of the participants and during most of the sleeping time,

TABLE 2-1. RESPIRATORY PATTERNS, HEART RATE AND OXYGEN SATURATION AT HIGH ALTITUDE

Season	Late summer	Early winter	Late winter	Early summer
AHI (1/h)	59.8 (25, 116.5)	56.5 (26.7, 120.4)	46.7 (18.7, 110.3)	73.3 (24.8, 99.4)
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SpO_2 (%)	85.1 (84.2, 88.3)	87.1 (85.4, 90.6)	87.9 (85.3, 90.4)	86.1 (85, 90.8)

Definition of abbreviations: AHI = apnea/hypopnea index; TST = Total sleeping time in hours; R_f = respiratory frequency in breaths per minute; PB_{length} = length of periodic breathing period in seconds; HR = heart rate in beats per minute; SpO_2 = oxygen saturation as measured by pulse oximetry. Data are represented as medians (quartiles).

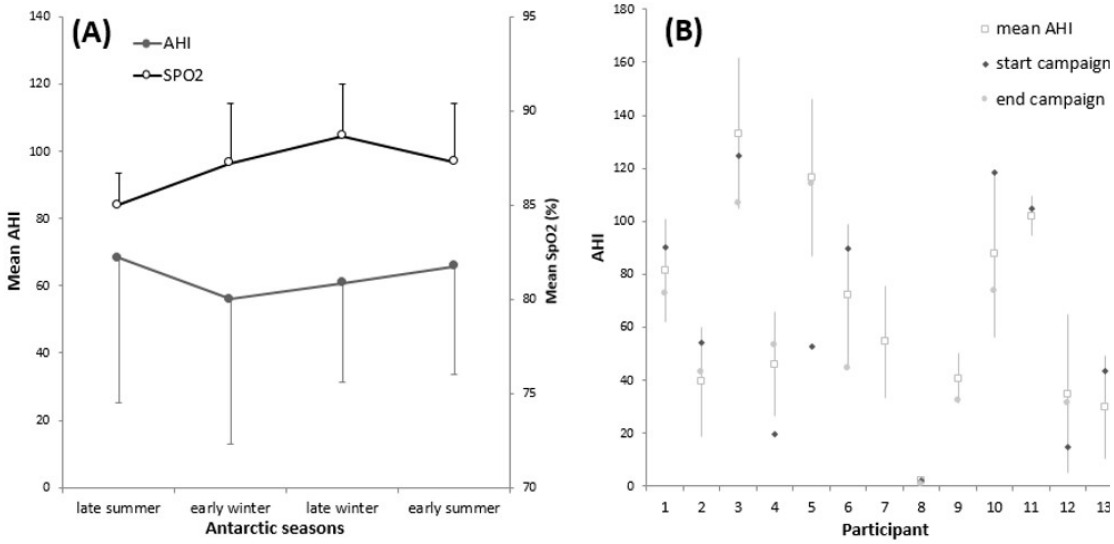

Figure 2-1 (A) Seasonal evolution of AHI averaged over the whole crew. (B) Evolution of AHI per participant.
(A) Apnea/hypopnea index and oxygen saturation by season. The points represent the means and the bars the standard deviations. (B) Apnea/hypopnea index by participant. The points represent the first, last and mean values for the entire expedition, and the bars the standard deviations.

with participants showing first events as soon as falling asleep. Due to periodic breathing, the average number of apneic/hypopneic events per sleeping hour during the whole campaign was above the level considered clinically as severe (AHI = 65.4 +/- 14.55). Figure 2-1A shows the seasonal evolution of AHI averaged over the whole crew. Statistically we found no effect of time ($F(3,30) = .500$, $p = .685$, $\eta p^2 = .048$). Figure 2-1B gives a summary of the evolution of AHI for each of the participants. We found "substantive" stable inter-individual differences in AHI over the course of the winter-over (ICC = .770). Self-report assessment of AMS by Lake Louise questionnaires show that AMS symptoms had fully resolved for all crew within 2 weeks of arrival and, at least one month before polysomnography was commenced.

In contrast to the stability of severity of periodic breathing, there was a significant main effect of time on the SpO_2 levels ($F(3, 33) = 4.706$, $p = .008$, $\eta p^2 = .300$), characterized by a linear increase of SpO_2 over time ($F(1,11) = 17.359$, $p = .002$, $\eta p^2 = .612$) (see Figure 2-1). There was no significant correlation between AHI and average SpO_2 (all p's > .25), at any time of the year during winter-over. Inter-individual differences in SpO_2 –levels remain "moderately" stable during the winter-over period (ICC= .454).

There was no significant time effect on the frequency of respiration ($\chi2(3) = .450$, $p = .930$), the periodicity of periodic breathing ($F(3,21) = .885$, $p = .465$, $\eta p^2 = .112$) or on heart rate ($\chi2(3) = 5.900$, $p = .117$). None of these parameters were correlated with subjects' physical condition, smoking habit, age or BMI (all p's > .1).

Finally, a significant negative correlation was found between the periodicity of each of the cycles of periodic breathing and the AHI during early winter ($r = -.643$, $p < .024$) and early summer ($r = -.762$, $p = .010$). That is, participants who had a fewer number of events per hours also showed consistently shorter periods of periodic breathing.

VI. DISCUSSION

The main goal of our field study was to provide new insights into the long-term effects of hypobaric hypoxia, after what is usually considered the acute phase of adaptation[48,49]. In this regard, our most important finding was that during the whole 13-month campaign, due to nocturnal periodic breathing, the average number of apneic/hypopneic events per hour was above the level clinically defined as 'severe'. This is remarkable if we take into account that these results were found in subjects that had already adapted to the hypoxic conditions: after the first two to three months of stay subjects had no symptoms of acute mountain sickness and SpO_2 levels were partially recovered. Our results are consistent with previous studies reporting the prevalence of periodic breathing despite partial restoration of SpO_2 together with the absence of symptoms of acute mountain sickness[6,64]. This is consistent with the hypothesis that acclimatization improves oxygen saturation despite the persistence of periodic breathing. To our knowledge this is the first time it has been shown that periodic breathing is still present at above clinically severe levels after one year living at high altitude.

Exposure to hypoxia induces a series of physiological changes in the body that improves the ability to tolerate the hypoxic environment. This process of adaptation responds to the steady low environmental partial pressure in O_2, to ensure sufficient O_2 is delivered to the tissues [as reviewed in [75]]. A key component of this process is the hypoxic ventilatory acclimatization (HVA), which is defined as a gradual elevation of ventilation despite a continuously increasing arterial PO_2 and concomitant fall in arterial P_{CO2}[48,50]. Although most of this process happens in the first one or two days[48], depending on the altitude, and interindividual differences in ventilatory response, it can take up to some weeks[49]. At an approximate altitude to that of Concordia, around 4000 m, Chiodi and colleagues found evidence to suggest that complete or near-complete acclimatization took between two or three weeks[48]. This period of adaptation was between four to six weeks at 5050 m[76]. Arterial PO_2 did not recover to sea-level norms. During the first controls upon arrival to the station diurnal arterial SpO_2 showed levels around 87.3 ± 3.1 and at the time of the first polysomnographic nocturnal arterial SpO_2 was at an average level of 85 ± 1.7. From this first cycle on, Arterial SpO_2 continued to increase during the following six months until it reached an average value of 90.2 ± 2.1. Thereafter, arterial saturation reaches steady-state without a total restoration to sea-level values. Our study also reinforces the idea that despite the fact that some previous experiments have reported a positive association between AMS and AHI as altitude increased[60,77], is unlikely that periodic breathing contributes to AMS, because it is associated with higher rather than lower mean sleep arterial saturation in lowland subjects at different altitudes[78]. In fact, as remarked by Burgess et al, this association is not surprising since both are due to the hypoxic stimulus, which increases with altitude[77].

There seems to be a controversy regarding the acclimatization mechanism to hypobaric hypoxia and the prevalence of periodic breathing during exposure. Previous studies have reported an increase of periodic breathing during acclimatization to hypoxia[6,65], whereas others reported decreases[56,66] or no changes[73]. However, the few previous studies that assessed the effect of high altitude on the respiratory system are difficult to compare because of different study design and settings. Marked differences in sleeping altitudes or acclimatization time probably have an impact on the results for periodic breathing. Many of the above-mentioned studies were part of mountaineer expeditions with differences in ascent rates and dynamically changing environments likely to have an impact on daily energy expenditure demands and sympathetic activation. Thanks to the steady confinement conditions of the Concordia winterover team, we were able to observe changes in PB at a constant altitude and within stable environmental conditions and energy expenditure demands. Our data suggest that PB does not decrease with time, and in fact does not follow any apparent trends when long term exposure is observed. Periodic breathing due to high altitude is then a process that might last more than several months and which might not be only affected by altitude, time of exposure or varying conditions, but perhaps also other factors. Our results extend findings from earlier hypobaric chamber studies suggesting a prevalence of periodic breathing with no clear increasing or decreasing trends [73] which is in line with previous experiments that showed the persistence of periodic breathing during ascent to high altitude: Bloch et al[6], with measurements on 34 subjects at different altitudes and, two earlier studies. One from Salvaggio et al, with five subjects exposed to hypobaric hypoxia during 28 days at 5,050 m altitude[65], and another from Zielinski et al, with nine subjects during 5 days at 3,200 m[64]. These results from short duration studies, together with our one-year experience, contradict the original idea that the amount of periodic breathing in sleep is reduced over time in hypoxia [52,56]. Marked inter-individual differences in our results suggest the existence of responders and non-responders to hypoxia, in terms of periodic breathing response, independently of measured oxygen saturation and not related to symptoms of AMS. We also showed that this relationship was independent from the subjects' physical condition, smoking habit, age or BMI.

The mechanisms behind periodic breathing are still under debate[75]. Although it is widely accepted that an increase of the chemoreceptor feedback control loop gain together with a delay in the transfer of information might cause the instability leading to periodic breathing[19,57], most likely periodic breathing during sleep at high altitude results from the interplay between multiple factors [as reviewed in [79]]. Increased control loop gain is likely due to the hypoxic ventilatory response of the peripheral chemoreceptors in reaction to low O_2 concentration in arterial blood. Acclimatization to hypoxia enhances O_2 sensitivity from the chemoreceptors located at the carotid body[80,81] and brainstem[82,83]. It also increases efferent sympathetic outflow in humans[32,84-88]. It is widely believed that long term exposure to hypobaric hypoxia partially restores arterial saturation during the first weeks, which should then reduce the sympathoexcitatory chemoreceptor drive.

Paradoxically, some studies suggest that sustained sympathoexcitation is observed during acclimatization to high altitude. For instance indirect measures of sympathetic nerve activity showed sympathoexcitation during the first weeks of acclimatization[33,89-92]. It has been also observed that sojourn at high altitude is complemented by an increase in blood pressure that might be sympathetically mediated[91,92]. In another study, Hansen et al recorded direct microneurographic measurements of muscle sympathetic nerve activity during prolonged exposure to hypobaric hypoxia[87]. They showed that sympathetic nerve activity was higher in humans well acclimatized to hypobaric hypoxia. Despite recovered blood O_2 saturation, muscle sympathetic nerve activity burst frequency was three times higher after a month at high altitude. In another study, sympathetically mediated modulation of the respiratory rhythm generator by the brain stem (pontine noradrenergic A5 and A6 groups) has already been observed in mammals[40,93]. Although not directly addressed by this study, we suggest that maintained sympathoexcitation could be a key factor on the persistence of periodic breathing in long term exposure to hypobaric hypoxia, as this could explain the controversy over increasing or decreasing levels of periodic breathing at high altitude. Since activation of the sympathetic nervous system controls many of the needed physiological adjustments to a changing environment, some other drivers of the sympathetic nervous system such as exercise may also have an impact on periodic breathing. For instance, it has been demonstrated that hypoxia potentiates exercise-induced sympathetic neural activation in newcomers[94] and in high-altitude residents[95].

We also observed a significant negative correlation between the periodicity of periodic breathing and the AHI, i.e. subjects showing shorter cycles of periodic breathing also had fewer apneic/hypopneic events per hour. This suggests that some physiological differences within the respiratory control loop might at least partially explain the existence of responders and non-responders to hypoxia. One study has observed a small but progressive decrease in the average duration of the apnea–hypopnea events with altitude[96], meaning shorter periods at higher altitudes. But in that case, altitude was also associated with higher occurrences of PB[75]. On the other hand, short lung-chemoreceptor delays are associated with higher stability of the respiratory control system[96]. Since in our experiment altitude was the same for every subject and the frequency of periodic breathing was not correlated with heart rate, we speculate that a certain lung-chemoreceptor delay 'phenotype' might at least to some extent explain the existence of responders and non-responders. However, this study was an observational study not an interventional one. Therefore, this association does not prove cause and effect between the observed correlation between the number of apneic/hypopneic events and the periodicity of periodic breathing cycle.

There were some limitations imposed by the environment, mainly due to transport restrictions that did not allow us the use of consumables such as respiratory volume calibrating bags and nasal-flow cannulas, which would have given us more information regarding the evolution of the respiratory system. But all in all, our data further demonstrate that the Concordia

ESA base is a valuable setting for the long term study of a steady exposure to hypoxia, and that our protocol was well accepted and robust enough despite the challenging logistic conditions in Antarctica. Previous investigations have observed the process of adaptation to high altitude only over several days to weeks and in changing environmental conditions, which makes our data relevant for long term (mal)adaptation. Thanks to the confined nature of the Concordia base, we were able to track changes in sleep disordered breathing due to hypobaric hypoxia at constant altitude. Our experiment was therefore performed on a normal healthy population in a day-to-day environment with no special physically demanding duties, extending previous results to a longer timeframe of exposure. This is to our knowledge the first time such a long study has been performed at constant altitude in a stable environment.

To conclude, nocturnal periodic breathing was present at a clinically severe level during the whole campaign. For most of the participants it prevailed for the major part of each sleep period during the whole winterover campaign at the Antarctic base Concordia. Therefore, periodic breathing due to exposure to hypobaric hypoxia is a process that appears to persist indefinitely, and is not related to symptoms of AMS. Despite the view that a decrease in O_2 saturation is a major driver of PB, our findings of no improvement in periodic breathing regardless of any restoration of O_2 saturation suggest some other key drivers. We hypothesize that a higher sympathetic activation could be an important causal factor on the prevalence of periodic breathing. However, since we have no direct measure of sympathetic activation, this explanation needs to be tested in future research. We also speculate that a certain lung-chemoreceptor delay 'phenotype' might partially explain the existence of responders and non-responders, and we believe it should be further investigated. Although there are still some controversial results regarding the influence of long term exposure to hypobaric hypoxia on sleep quality[16,54,60], it is widely accepted that periodic breathing decreases quality of sleep and therefore daytime performance. As described by West et al[71] at high altitude, as a result of poor sleep, people often feel somnolent and fatigued during the following day which reduces their productivity and increase the probability of error. This might be a major constraint in long term confinement duties in which hypobaric hypoxia are determinant.

Chapter 3 - Exercise during acute and long-term continuous exposure to hypoxia exacerbates sleep-related periodic breathing

With our previous study, we proved that hypoxia-induced periodic breathing persists beyond acclimatisation to high altitude. Still, there is some conflicting literature on its persistence over successive nights, with studies reporting an increase, a decrease, or even no changes in periodic breathing over time. The results described in this manuscript demonstrate a direct, positive relationship between physical activity and severity of periodic breathing under hypoxic conditions. Our data indicate that physical activity per se can negatively affect night SpO_2 concentrations and incidences of periodic breathing, as measured by the clinical gold standard AHI index. During the 13-month over-winter research campaign, nocturnal breathing patterns were recorded by portable polysomnography. Our results were compared with recorded physical activity logs during the same winter-over period in Antarctica in an attempt to account for the variability that we observed in our initial study results. When both AHI and exercise logs were compared, it demonstrated a dose-response correlation. To build on these largely observational results, a second "controlled" group design study was conducted at a research station based in Planica, Slovenia, to investigate whether exercise per se may modify periodic breathing at altitude. Within this framework, we confirmed that periodic breathing was significantly modified between the control and exercise intervention groups. The relationship between exercise i.e. physical activity and augmented periodic breathing had never been reported in the literature before and may explain (to some extent) conflicting reports on the persistence of periodic breathing over successive nights spent in hypoxia.

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SLEEP DISORDERED BREATHING

Exercise during Short-Term and Long-Term Continuous Exposure to Hypoxia Exacerbates Sleep-Related Periodic Breathing

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I. ABSTRACT

Study Objectives: exposure to hypoxia elevates chemosensitivity, which can lead to periodic breathing. Exercise impacts gas exchange, altering chemosensitivity; however, interactions between sleep, exercise and chronic hypoxic exposure have not been examined. This study investigated whether exercise exacerbates sleep-related periodic breathing in hypoxia.

Design, setting and participants: two experimental phases. Short-Term Phase: a laboratory controlled, group-design study in which N=16 active, healthy men (age: 25±3 y, height: 1.79±0.06 m, mass: 74±8 kg) were confined to a normobaric hypoxic environment (FIO_2=0.139±0.003, 4000 m) for 10-d, after random assignment to a sedentary (control, CON) or cycle-exercise group (EX). Long-Term Phase: conducted at the Concordia Antarctic Research Station (3800 m equivalent at the Equator) where N=14 men (age: 36±9 y, height: 1.77±0.09 m, mass: 75±10 kg) lived for 12-14 months, continuously confined. Participants were stratified *post-hoc* based on self-reported physical activity levels.

Measurement and Results: we quantified apnoea-hypopnea index (AHI) and physical activity variables. Short-Term Phase: Mean AHI scores were significantly elevated in the EX group compared to CON (Night1=CON: 39±51, EX: 91±59; Night10= CON: 32±32, EX: 92±48; p=0.046). Long-Term Phase: AHI was correlated to mean exercise time (R^2=0.4857; p=0.008) and the coefficient of variation in night oxyhaemoglobin saturation (SpO_2; R^2=0.3062; p=0.049).

Conclusions: data indicate that exercise (i.e. physical activity) *per se* affects night SpO_2 concentrations and AHI after a minimum of two bouts of moderate-intensity hypoxic exercise, whilst habitual physical activity in hypobaric hypoxic confinement affects breathing during sleep, up to 13+ months' duration.

II. INTRODUCTION

At altitudes above 2500 meters, ventilation in healthy individuals commonly exhibits an oscillatory behavior, with alternating periods of hyperventilation followed by central apneas or hypopneas[6] during both wake and nocturnal sleep. Whilst this quantity of periodic breathing may be reduced with continued hypoxia exposure[56], more recent evidence supports its persistence over time. Consistent with the results from previous studies, Fernandez Tellez *et al*[63] report that throughout a 13-month confinement and high altitude exposure, periodic breathing prevails for the major part of sleeping time; these data were observed in the absence of acute mountain sickness (AMS) and concomitant with partial restoration of SpO_2 levels. Indeed, periodic breathing, and its adaptation to hypoxia has been examined in the exercise literature, but with equivocal results. Namely, the magnitude, time-course and the altitude at which periodic breathing occurs, as well as its persistence over successive nights, differ greatly across studies. Some observe an increase in periodic breathing at various altitudes[6], whilst others have reported decreases[56] or indeed, no changes[73] in incidence over time. Continued exposure to hypoxia induces a series of physiological changes in the human body that improve its ability to tolerate persistently lower partial pressures of O_2 [as reviewed in [47]]. A major aspect of the ventilatory acclimatization to hypoxia is the gradual elevation of minute ventilation despite a continuously increasing arterial PO_2 and concomitant fall in arterial PCO_2[48]. Although the mechanisms underlying periodic breathing at high altitude are not clearly elucidated[47], it is widely accepted that acclimatization to hypoxia enhances chemoreceptor reactivity, which constitutes a critical factor inducing periodic breathing[57].

Aspects of the mechanisms involved in the control of respiration during exercise also remain relatively unresolved, although it is generally accepted that exercise enhances chemoreactivity [as reviewed in [17]]. Periodic breathing is exacerbated during hypoxic exercise (20 to 40% maximal aerobic power), evidenced by a breathing pattern which demonstrates a period lengthening between 11.1 to 12.0 s, determined via spectral analysis of the breath-by-breath ventilation signal, O_2 saturation, and end-tidal PCO_2[98]. High altitude expeditions are characterized by strenuous physical demands which can alter both chemo-reactivity and the control of respiration during exercise[99], which together, may translate to greater development of periodic breathing during sleep, than in response to a hypoxic stimulus alone. Furthermore, during exercise, pulmonary vasoconstriction can lead to pulmonary hypertension, whilst hypoxia is known to independently impact pulmonary circulation, such that tissue constriction becomes even more pronounced during exercise[91]. Although still contentious, it is possible that whilst performing exercise even at sea level, one can develop pulmonary oedema[100], and with the increased resistance, possibly drive higher incidences of periodic breathing[78], especially during sleep.

Thus, the purpose of the present investigation was to determine to what extent regular physical activity *per se* may affect nocturnal periodic breathing during prolonged hypoxic confinement. Two experiments were conducted at roughly equivalent altitudes: 1) a 10-day group-design normobaric hypoxic confinement study to observe the effects of moderate exercise and shorter-term hypoxic exposure, and 2) a 13-month hypobaric hypoxic confinement study to observe the longer-term effects of hypoxia and habitual physical activity on sleep-breathing disturbances.

III. METHODS

All experimental protocols and procedures were performed according to the Declaration of Helsinki. The Short-Term Phase was approved by The National Committee for Medical Ethics, Ministry of Health of the Republic of Slovenia, and the Long-Term Phase was approved by the Ethics Committee of the Free University of Brussels. Written, informed consent was obtained from each subject prior to participation in either of the two studies. All participants in both studies were native lowlanders, none of whom were exposed to high altitude environments before entry into either study.

A. Short-Term Phase: Normobaric Hypoxia Group Design Study

All participants (N=16) were near-sea level residents, and had not been exposed to altitude > 500 m during the month preceding the experiments. They were nonsmokers, and had no history of any cardiovascular or pulmonary disease. All of them were physically active on a recreational basis, and had no or very limited previous experience with cold exposure experiments. The subjects were informed in detail about the experimental procedures, and gave their written consent. The experimental protocol was approved by the National Committee for Medical Ethics at the Ministry of Health of the Republic of Slovenia and conformed to the Declaration of Helsinki. All testing was performed in the hypoxic facility at the Olympic Sport Centre Planica (Rateče, Slovenia) situated at an altitude of 940 m above sea level. The study was conducted during the northern hemisphere spring, and was part of a larger group-design study to investigate the effects of physical activity and hypoxia on various aspects of human physiology, including: metabolic adaptations[101], oxidative stress[102], and cold-induced vasodilation[103], among others. Since these investigations were performed by many other scientific teams-and fall outside the scope of the present paper- they are not discussed here.

Participants arrived at the facility for baseline data collection three nights prior to entering the hypoxic confinement condition. During the 10-day experimental period, participants were allowed to move freely between their own rooms, the common hallway and living area (~200 m^2). The normobaric hypoxic condition on the floor and in the rooms was maintained using a Vacuum

Pressure Swing Adsorption (VPSA) system (b-Cat, Tiel, The Netherlands), described in detail elsewhere [102]. The mean environmental values throughout the 10-d protocol were: F_IO_2= 0.139±0.003, P_IO_2= 88.2±0.6 mm Hg, 23.1±1.0°C, 56 ±8% relative humidity.

Peak oxygen consumption was determined using an incremental-load test on a cycle ergometer (Ergo Bike Premium, Daum electronics, Germany) to volitional exhaustion on two occasions. On one occasion, the test was conducted in normobaric normoxia, and on another occasion, in normobaric hypoxia, on both occasions using standard, validated methodology[102]. Participants were then randomly assigned to either the exercise (EX, N=8) or control (CON, N=8) group after they had completed a familiarization weekend at the facility. The EX participants were required to complete moderate intensity cycling exercise for two one-hour sessions per day (morning: 10-11:00, afternoon: 15-16:00). All exercise took place in the normobaric hypoxic laboratory. Exercise intensity was adjusted so that heart rate was maintained at 50% of their individual hypoxic peak power output. Participants in the CON group were not allowed to perform any kind of static or dynamic exercise during the course of the study.

All subjects completed two nights of full polysomnography (PSG) sleep recordings, with the first recordings taking place after they spent at least two nights in the facility, and following their familiarization weekend. The second recording was conducted on the last night of the intervention (Night 10). The PSG recordings (Nicolet One, Viasys, USA) included electroencephalography (EEG), electrooculography (EOG), chin surface electromyography (EMG), electrocardiography (ECG), nasal pressure (nasal pressure cannula), respiratory movements (chest and abdominal belts), and oxyhaemoglobin saturation (SpO_2) following protocols described elsewhere[104]. Acute mountain sickness (AMS) in participants was assessed via Lake Louise Score (LSS)[105], with the questionnaire being administered each evening at 17:00 and with the score serving as an index for both occurrence and severity of AMS.

B. *Long-Term Phase: Long-duration field-based hypobaric hypoxia study*

Thirteen members of the 14 all-male crew at the Antarctic Concordia Station participated in the experiment. The Concordia Station is a permanent international research station located on the high plateau of the Antarctic mainland at 75° 06’ S, 123° 23’ E, approximately 1100 km inland from the French coastal station Dumont d’Urville and ~1200 km inland from the Mario Zucchelli Station at Terra Nova Bay. It resides at an altitude of 3100 m above sea level, where average air pressure is 645 hPa (equivalent to an altitude of 3800 m at the Equator); thus, the base allows for long-duration, confined stay in hypobaric hypoxia. Participants arrived during the preceding Antarctic summer, and remained isolated on-site for an average of 13-months. Upon arrival at the Concordia Station, participants’ acclimatization progress was monitored weekly via physical examination, SpO_2 readings, and an assessment of AMS via Lake Louise Score[105] was obtained throughout the first 3 weeks only.

Individual physical activity sessions were recorded by the participants who logged the exercise mode, duration (min), and subjective exercise intensity via ratings of perceived exertion (RPE), scored on a 10-point visual analogue scale (VAS)[106]. The common-area gymnasium was equipped with a treadmill, a cycle ergometer, a stepping machine, and various free-weights. Subjects were assigned to the exercise group (EX) *post hoc*, if: 1) they completed regular physical activity (of any mode) for at least 24% of the days they were stationed at the base (range: 24-48%), and 2) for an average of at least 30 min duration per exercise bout. The rationale for this cut-off was that the definition loosely corresponds to international physical activity guidelines advocated for active, healthy adults, generally considered to be at minimum 30 min of physical activity, at least 4-day per week[107]. In this way, we can consider these people as being "consistently physically active"; no small feat (both psychologically and physically) when considering these individuals are confined to a small living area for an entire calendar year, with no possibility of spontaneously leaving the protected environment of the research station. The remaining subjects were designated as controls (CON).

PSG sleep data were recorded over seven testing nights measured across the entire 13-month overwinter campaign. The PSG recordings (BioRadio, Clevemed Inc., USA) included EEG, EOG, EMG, ECG, respiratory movements (chest and abdominal belts), and SpO_2 following established protocols[63]. Measurement testing times were variable throughout the year, and depended on the person's arrival to the research base. PSG testing occurred every ~6 weeks comprising of roughly eight data collection epochs over the course of 13+ months.

IV. DATA ANALYSIS

Apneas and hypopneas were defined according to international standards[108]. The Short-Term Phase incorporated nasal airflow pressure to determine respiratory restriction(s) and central apneas in addition to effort (chest, abdomen; Figure 3-1A). In the Long-Term Phase, discrimination between central and obstructive apneas was assessed by testing the existence of paradoxical breathing, i.e. breathing movements caused by obstruction in which the chest wall moves in reverse to the abdominal wall. The majority of respiratory effects were central events as a result of periodic breathing at high altitude (Figure 3-1B), previously validated using the estimated amplitude modulation index (eAMI), a mathematical tool for detection and qualification of periodic breathing[109]. On all Short-Term Phase demographic data, an independent t-test was conducted to determine potential differences between groups. On the dependent variables, a mixed-model ANOVA was conducted with one within-subjects' factor (time) and one

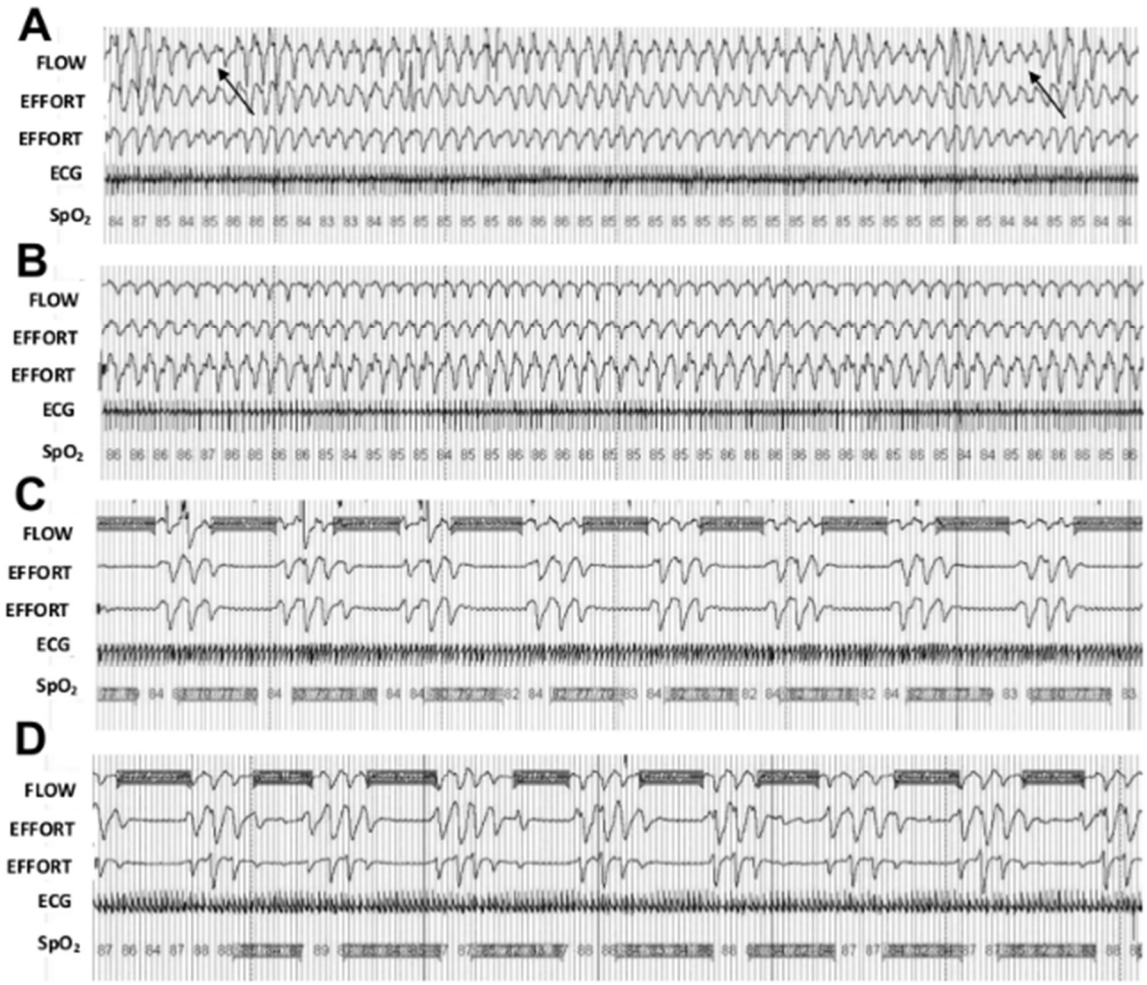

Figure 3-1 Representative nocturnal respiration and oxyhaemoglobin saturation traces from two individuals in the Short-term study

Respiratory effort was measured via piezoelectric bands at two locations (EFFORT; chest, abdomen). Capillary oxyhaemoglobin saturation (SpO_2) readings show desaturations throughout the screenshot. Nasal airflow (FLOW) was measured via nasal cannula pressure. A) CON subject, first night at simulated altitude of 4175 m. Note the arrows indicating central hypopnea (s). B) the same CON subject, night ten, C) EX subject, night one, D) the same EX subject, night ten. Highlighted areas on FLOW channel in traces C, D indicate central sleep apnoeas; highlighted sections on SpO_2 channel indicate desaturations. Time epoch of screen shots was set at 240-s to better display periodic breathing rhythmicity.

between-subjects' factor (group) to determine any differences between the Night 1 (acute, 24-h) and Night 10 (longer-term, 240-h) hypoxia exposure, and the exercise intervention.

Provided data was normally distributed and there were no significant differences by training group, significant data were pooled and paired t-tests were employed *post-hoc* (Bonferroni correction). In some cases, the Long-Term Phase data sampling epochs (1-8) have been pooled and averaged with the next consecutive testing block; therefore we report data either as one of eight testing time-points conducted throughout the 13-month campaign, or pooled by season: 1+2=late summer, 3+4=early winter, 5+6=late winter, 7+8=early summer. Total exercise data was obtained from self-reported physical activity logs which were averaged over the eight data collection epochs. Correlations to various sleep-breathing parameters (two-tailed, bivariate

correlations) were completed using a statistical package (SPSS v.17.0, Chicago, IL, USA). Data are expressed as means ± standard deviations, with 95% Confidence Intervals ('CI') for effects of interest, at $p<0.05$ level of significance.

V. RESULTS

A. Short-Term Phase

During the hypoxic confinement period, two participants withdrew from the study, one due to adaptation problems, the other due to acute appendicitis; data from these participants are excluded from further analysis. All participants assigned to the EX group were able to complete all training sessions. Physical characteristics of both EX and CON groups are described in Table 3-1. There were no differences between the Short-Term intervention groups in terms of age, aerobic fitness or anthropometry measures. After the hypoxia confinement protocol, the EX group

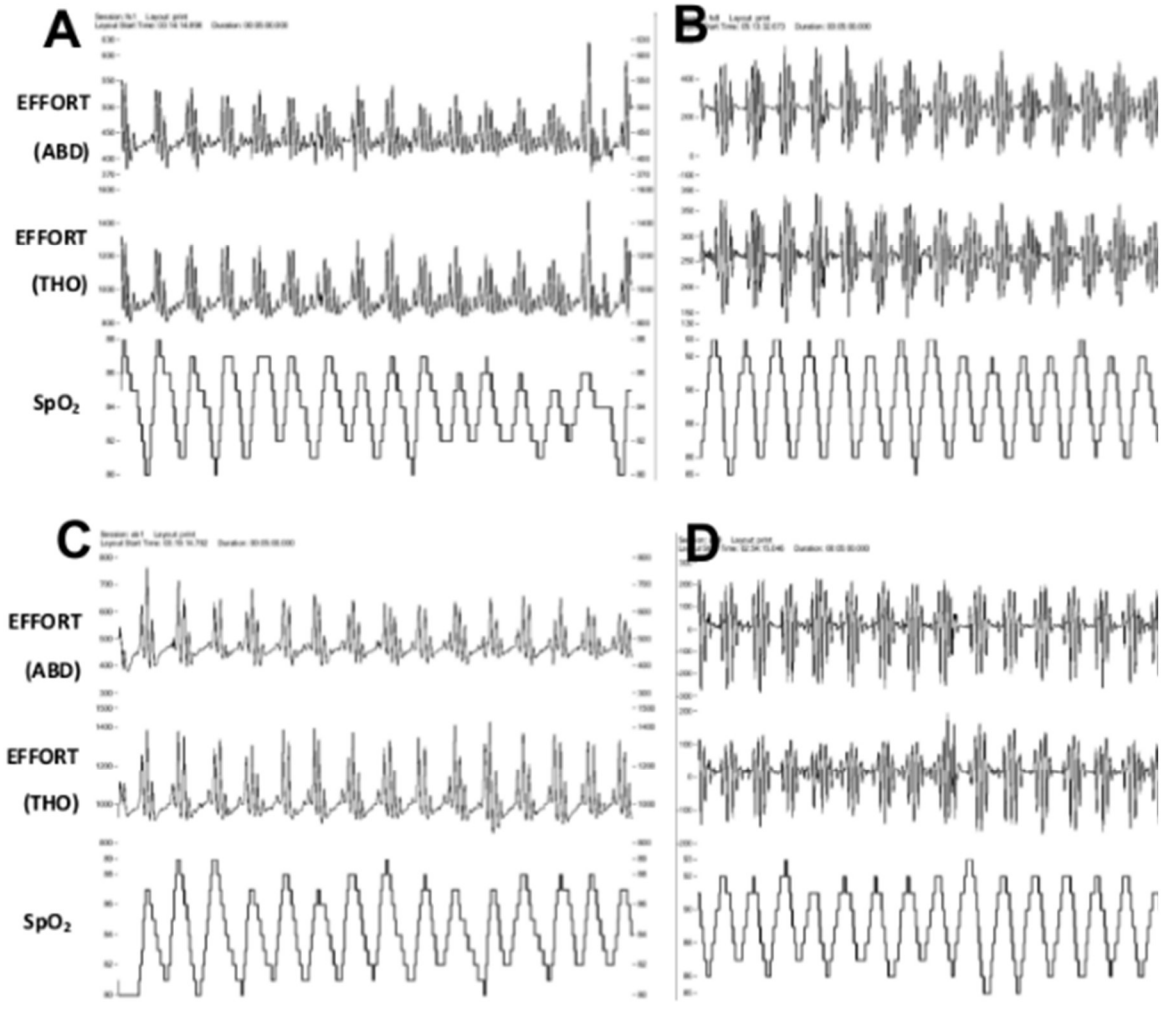

Figure 3-2 Representative nocturnal respiration and oxyhaemoglobin saturation traces from two individuals in the Long-term study

Respiratory effort was measured via piezoelectric bands at two locations (EFFORT, ABD, abdominal, THO, thoracic). Capillary oxyhaemoglobin saturation (SpO_2) readings show oscillations throughout the screenshot. A) CON subject, first epoch in Concordia B) the same CON subject, the 8th and final epoch C) EX subject, 1st epoch D) the same EX subject, 8th epoch.

had a significant increase in peak power output (EX: 260 ± 34 v 276 ± 34 W, p = 0.0001), which was not observed in the control group (CON: 244 ± 37 v 247 ± 41 W, p = 0.414). The EX group also had decreases in measured percent body fat (EX: 22.4 ± 6.2 v 21.2 ± 5.8%; p = 0.0001), whereas no change was observed in the controls (CON: 21.9 ± 4.7 v 21.3 ± 4.8%; p = 0.103). Lake Louise Scores were comparable between groups throughout the campaign; clinically significant AMS scores were noted in seven participants from both groups on Day 1 (EX = 4, CON = 3). Scores were significantly lower on Day 9 compared to Day 1 ($p < 0.05$), with an average rating (range) of 1.5 (0-6) and 1.4 (0-7) for both EX and CON groups, respectively.

Night AHI scores were significantly elevated in the EX group on Night 1 (CON: 39±51, EX: 91±59) and Night 10 (CON: 32±32, EX: 92±48; p = 0.046, Figure 3-3) compared to CON. The periodic breathing cycle was ~4 s longer after 10-d in hypoxia (p = 0.014), regardless of group. The EX group spent a greater proportion of their night at a lower given SpO_2 concentration than their CON counterparts (Figure 3-3; significant 3-way interaction (time x SpO_2 x exercise status; p = 0.013). For example, on N1 the EX spent 55% of their total sleep time at SpO_2 concentrations between 70-75%, whereas the CON spent only 29% of TST at such concentrations (95% CI: 29 to 82%; p = 0.013). Mean night SpO_2 concentrations were 5.8% higher after 10-d hypoxia exposure (95% CI: 2.9 to 6.6%; p = 0.0001), regardless of training group (Table 3-2). The overall increase in mean night SpO_2 was not significantly related to the increase in time spent in REM sleep, which also increased in both groups (Figure 3-5**,** Table 3-2, $R^2 = 0.373$, p = 0.189).

Table 3-1 PHYSICAL CHARACTERISTICS OF PARTICIPANTS IN THE SHORT-TERM PHASE STUDY CONDUCTED AT THE OLYMPIC SPORT CENTRE PLANICA, AND THE LONG-TERM PHASE STUDY CONDUCTED AT THE CONCORDIA ANTARCTIC RESEARCH STATION.

Study		*Age (y)*	*Height (cm)*	*Mass (kg)*	*Fitness ($mL \cdot kg^{-1} \cdot min^{-1}$)*	*Smoker?*
Short-Term	*Control (N=6)*	24.8 ± 3.1	177.7 ± 3.5	70.4 ± 10.0	42.2 ± 5.0	N=0
	Exercise (N=8)	25.8 ± 2.4	179.1 ± 3.1	76.6 ± 6.3	42.6 ± 6.1	N=0
	Total (N=14)	25.4 ± 2.6*****	180.6 ± 5.5	73.9 ± 8.4	42.4 ± 5.5	N=0
Long-Term	*Control (N=7)*	32.7 ± 6.3	175.1 ± 7.9	74.7 ± 10.2	No data	N=2
	Exercise (N=6)	39.0 ± 11.6	178.5 ± 9.8	75.3 ± 11.0	No data	N=1
	Total (N=13)	35.6 ± 9.3*****	176.7 ± 8.6	75.0 ± 10.9	No data	N=3

Data are mean ± standard deviations. (*) represents a significant difference between the Short-Term and Long-Term cohorts for that variable ($p<0.05$).

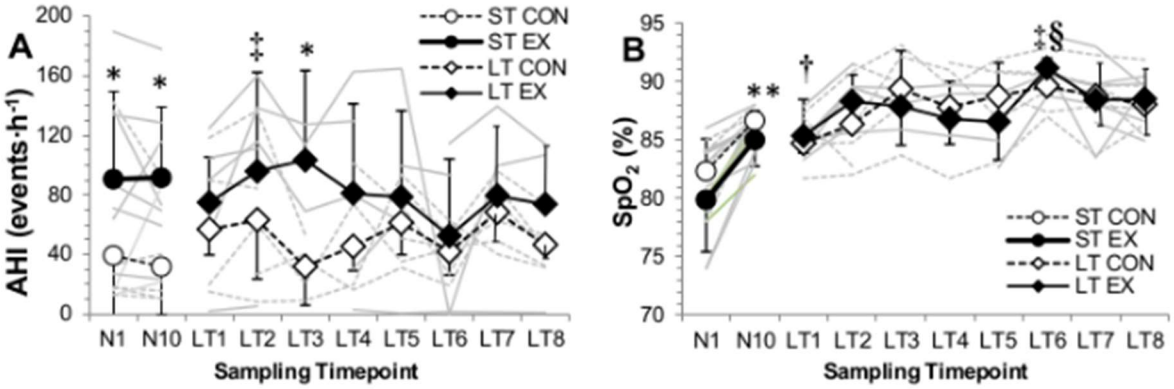

Figure 3-3 Individual data for A) Apnea-Hypopnea Index (AHI), expressed in events per hour, and B) average night pulsed-oxygen saturation (SpO2) of the Short-Term (ST) and Long-Term (LT) studies.

Mean group data with standard deviation bars are represented by black lines for the control (CON, open symbols) and exercise (EX, closed symbols) cohorts; individual responses included as grey background lines. Symbols represent (*) significant difference between training groups (**) significant difference between Short-Term night one (N1) and Short-Term night 10 (N10), (†) significantly different from all other Long-Term time-points, (‡) significantly different from Long-Term testing epoch 1 only, (§) significantly different from Long-Term Phase testing epochs 2 and 6 ($p<0.05$).

Table 3-2. NIGHT RESPIRATORY PATTERNS, TOTAL SLEEP TIME AND OXYGENATION VALUES IN HYPOXIC CONFINEMENT.

	Short-Term				**Long-Term**							
	N1		**N10**		**Late Summer**		**Early Winter**		**Late Winter**		**Early Summer**	
	CON	*EX*	*CON*	*EX*	*CON*	*EX*	*CON*	*EX*	*CON*	*EX*	*CON*	*EX*
AHI	39	90 *	32	92 *	56	83	44	75	52	70	57	76
(no/ h^{-1})	(13, 142)	(16, 190)	(10, 92)	(23, 178)	(12, 127)	(4, 142)	(14, 101)	(3, 138)	(25, 78)	(1, 114)	(36, 85)	(1, 127)
TST	5.5	5.5	5.5	5.9	6.7	5.3 *	6.9	6.3	6.1	5.7	6.8	5.5 *
(h)	(4.5, 6.9)	(3.4, 7.0)	(4.7, 6.8)	(3.3, 7.1)	(5.9, 7.6)	(4.1, 6.8)	(4.9, 8.3)	(5.2, 7.5)	(1.8, 7.9)	(1.9, 7.8)	(6.0, 8.5)	(4.2, 6.9)
REM	21	15	25 #	21 #	21	22	23	26	20	26 *	22	21
(%)	(11, 34)	(7, 25)	(20, 26)	(16, 25)	(16, 26)	(17, 27)	(19, 33)	(20, 32)	(13, 25)	(23, 31)	(17,27)	(19, 26)
PB_{length}	24	23	28 #	27 #	19	22 *	19	21	20	20	19	23 *
(s)	(22, 28)	(20, 29)	(20,40)	(22, 31)	(17,22)	(21, 24)	(17,22)	(17, 23)	(19, 21)	(16, 24)	(15, 23)	(20, 24)
SpO_2	81	78	85 #	84 #	86	87	89	87	89	89	88	88
(%)	(77, 84)	(73, 85)	(84, 86)	(81, 88)	(82, 92)	(84, 90)	(83, 92)	(85, 90)	(85, 92)	(85, 94)	(85, 92)	(86, 91)

Notes: Group data are means (min, max, ranges). AHI, apnea/hypopnea index; TST, total sleep time; REM, rapid eye movement sleep as percentage of TST; PB_{length}, length of the periodic breathing period (apnea+hyperpnea); SpO_2, mean night pulsed oxygen saturation; N1, night one measurements; N10 night ten measurements; CON, control cohort; EX, exercising cohort. The Long-Term study had eight testing time-points sampled approximately every 6 weeks, commencing with the subject`s arrival to Concordia, Antarctica. Data have been pooled into their respective seasons across the 12-month study. (*) Significantly different from CON within that sampling period, (#) significant main–effect of time difference from N1 ($p<0.05$).

Data are mean ± standard deviations. (*) represents a significant difference between the Short-Term and Long-Term cohorts for that variable ($p<0.05$).

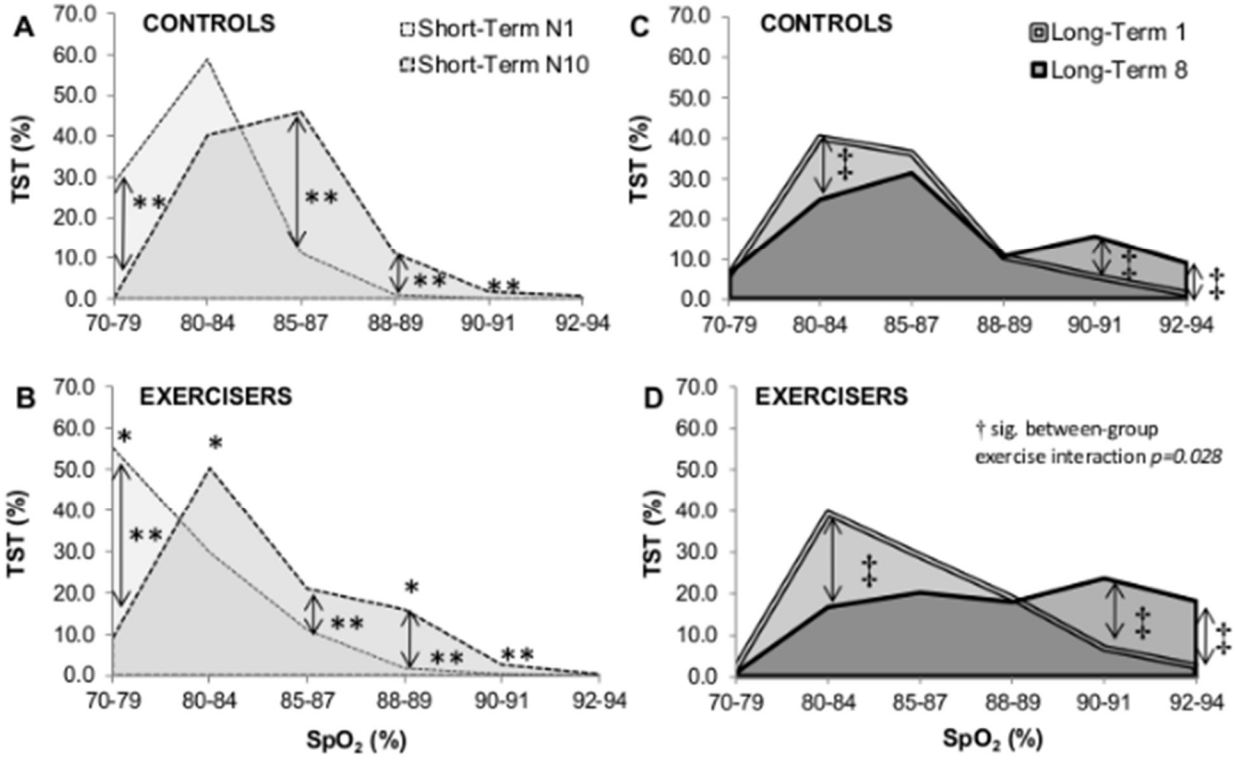

Figure 3-4 The proportion of total sleep time (TST) spent at a given SpO2 concentration for:

A) Short-Term Control (ST CON), B) Short-Term Exerciser (ST EX), C) Long-Term Control (LT CON), and D) Long-Term Exerciser (LT EX) cohorts. (*) Significantly different between training groups for that SpO_2 concentration, (**) significant difference between Short-Term night one (N1) and Short-Term night 10 (N10), (‡) significantly different from Long-Term testing epoch 1 ($p<0.05$).

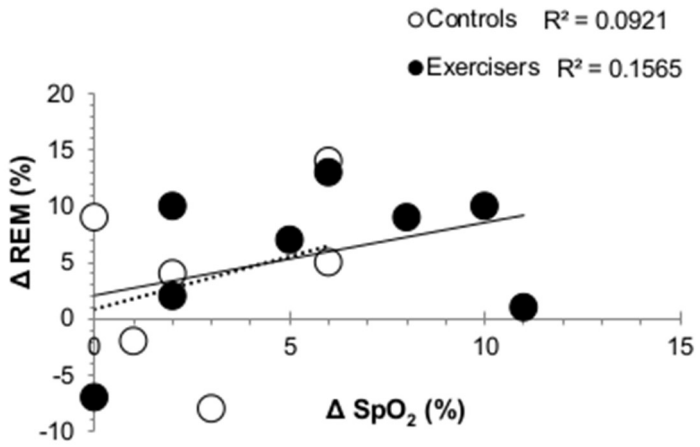

Figure 3-5 Bivariate correlations for the change in mean night SpO_2 concentrations and versus the change in proportion of total sleep time spent in REM

From Night 1 to Night 10 for exercisers (EX, closed circles) and matched controls (CON, open circles) of the Short-Term study. Linear regression equations are labeled in solid (EX) and dashed (CON) lines.

B. Long-Term Phase

Of all participants in the overwintering crew, 6/13 were assigned to the exercise group (EX), whilst 7/13 were grouped as controls (CON). Individual physical activity details are outlined in Table 3-3. AMS scores were calculated during the first 3 weeks on arrival to the Concordia Station. Symptoms of AMS did not reach clinical significance for any subject (median AMS score after 3 weeks was 1 [range, 0–1.5]).

Individuals' mean AHI was determined across the entire 13-month campaign, with the vast majority of the respiratory events happening during periodic breathing (95%). The AHI value was significantly correlated to participants' mean exercise volume per session ($R^2 = 0.4857$, $p = 0.008$, Figure 3-6A). A trend was also observed between the AHI and the total exercise load during for total stay at Concordia ($R^2=0.28$ $p=0.068$). Significant correlations between the AHI value and the mean coefficient of variation for night SpO_2 concentrations was also found ($R^2=0.3062$,

Table 3-3. INDIVIDUAL PHYSICAL ACTIVITY DETAILS FOR MEMBERS OF THE CONCORDIA ANTARCTIC OVER-WINTER CREW (N=13).

Subject Code	*Group*	*Exercise Days (count)*	*Bouts (%)*	*Mean volume/session (min)*	*RPE (scale 1-100)*
1	*CON*	8	3.5	22	64
2	*EX*	108	47.0	125.5	74
3	*EX*	67	29.1	21.7	50
4	*CON*	21	9.1	45.3	85
5	*EX*	110	47.8	60.4	69
6	*CON*	30	13.0	27	59
7	*CON*	12	5.2	20.1	68
8	*EX*	85	37.0	117.8	76
9	*EX*	102	44.3	51.8	56
10	*CON*	21	9.1	0	60
11	--	--	--	--	--
12	*CON*	1	0.4	0	65
13	*CON*	0	0	14.9	0
14	*EX*	55	23.9	176.3	79
Control (N=7)		13 ± 11*	6.7 ± 4.6*	18.2 ± 15.6*	67 ± 9
Exercise (N=6)		88 ± 22*	38.2 ± 10*	92.3 ± 52.4*	67 ± 12
Total (N=13)		48 ± 42	22.5 ± 18.0	53.7 ± 52.3	67 ± 10

Group data are means ± standard deviations. (*) represents a significant ($p<0.05$) difference between study groups for that variable. ***Exercise Days***- refer to the number of days the subject volitionally took part in physical activity for longer than 30 min, excluding their pre-scheduled maximum aerobic fitness tests, ***Bouts***- the percentage of time the subject performed volitional physical activity based on the total number of days they were stationed at Concordia research base, ***Mean volume/session***- the average amount of time in minutes of exercise volume per session , ***RPE***- Ratings of Perceived Exertion on a scale from (mean value from 1 (no exertion) to 100 (maximal exertion) of the physical activity bout.

p=0.049, Figure 3-6B). The coefficient of variation for night SpO_2 is often used as an indirect marker of breathing instability in ventilatory drive. Additionally, the periodic breathing cycle was ~2 s longer for EX than for CON during the early summer (95% CI: 1 to 5 s; p=0.006) and late summer (95% CI: 0 to 7 s; p=0.048) time epochs (Table 3-2). Total sleep time was also reduced in EX compared to in CON by between -23 to -150 min during the early summer (p=0.012) and -1 to -163 min in late summer (p=0.047).

Finally, there were significant between-subject interactions observed in mean night SpO_2 concentrations between EX and CON from the first testing epoch compared to the last epoch of the 13-month over-winter campaign (95% CI: 2.7 to 37.3%; p=0.028). There was also a 2-way interaction effect of time x SpO_2 concentration at a given percentage of total sleep time (p=0.009, Figure 3-4C, D). This relationship was not observed in the REM data, which demonstrated only one significant difference between groups, during late winter (Table 3-2), when EX spent ~ 33% greater proportion of the time in REM than did CON (95% CI: 1.9 to 12.0% absolute increase in REM as proportion of total sleep time; p=0.013).

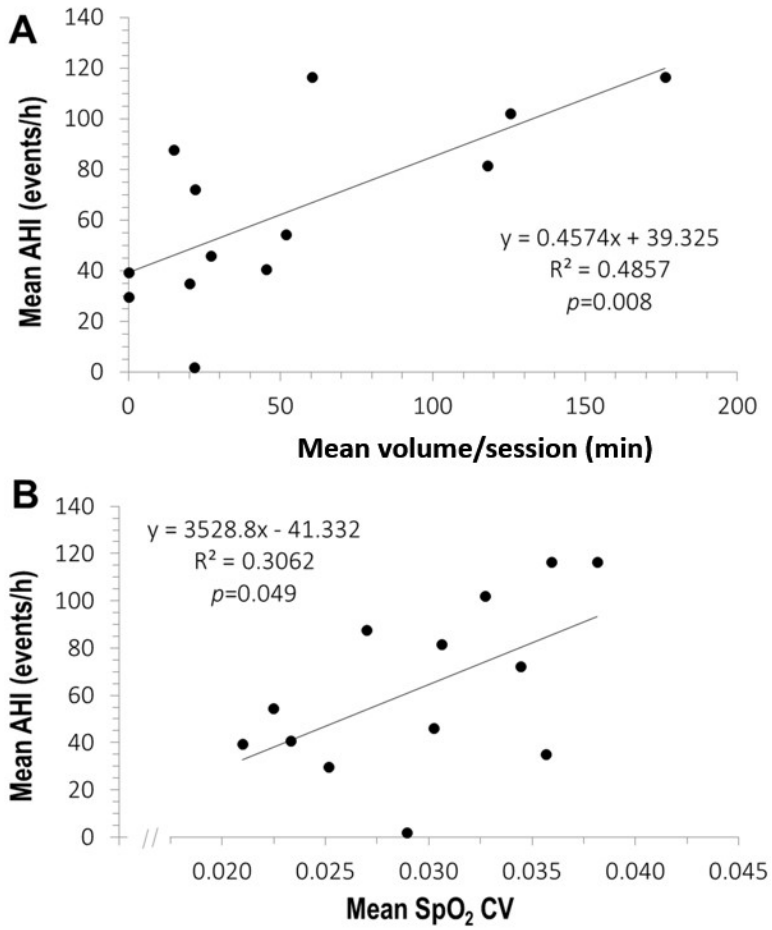

Figure 3-6 Bivariate correlations

In A) apnea-hypopnea index (AHI) and average exercise time (min) in the Long-Term Concordia participants ($p<0.05$), and between B) AHI and the mean coefficient of variation for pulsed-oxygen saturation (Mean SpO_2 CV; an indirect measure of altered ventilatory drive) in the Concordia over-winter participants.

VI. DISCUSSION

The principal finding of this joint, international investigation is that a direct, positive correlation exists between physical activity duration and severity of periodic breathing in long-term hypobaric hypoxia. Our data indicate that physical activity *per se* increases the incidence of periodic breathing, measured via clinical gold standard AHI scores and period length of the breathing disruption. We observed augmented AHI-exercise relationships in both hypobaric and normobaric hypoxic environments, regardless of habituation.

Previous studies have reported an increase in the amount of periodic breathing during acclimatization to hypoxia[6], whereas others have reported decreases[56], or no change[73]. In awake, healthy humans, periodic breathing severity is associated with physical exertion under acute, hypoxic exposure[98]. The influence of long-term hypoxic exposure on nocturnal sleep and breathing remains a concern when the exposure is inevitable (military scenarios, research expeditions, future planetary habitats), especially considering that prolonged exposure negatively affects brain function, performance, cognition and subjective alertness following poor sleep during high altitude sojourns[62]. Sleep-related periodic breathing may be influenced by regular physical activity via:

1) Chemoreceptor sensitivity- Several lines of evidence suggest that chemoreceptors play an important role in acclimatization to hypoxia[18]. It has been observed in anesthetized goats that adaptive processes within peripheral chemoreceptors are of sufficient magnitude to explain ventilatory acclimatization to hypoxia[110] and generally, that carotid bodies are needed to induce full acclimatization[111]. Peripheral mechanisms may also contribute to the initial enhanced exercise-hyperpnoea observed upon exposure to hypoxia[112]. The underlying mechanisms proposed so far include metabolic acidosis, especially during heavy exercise[113], and hyperkalemia [as reviewed in [114]]. Although a role for carotid bodies in exercise-induced hyperventilation is plausible[115], some animal models are not fully consistent with this mechanism[116]. More recent evidence suggests that central and peripheral chemoreceptors are not functionally separate, but that central stimulation modifies the reactivity of peripheral chemoreceptors [as reviewed in [18]]. Thus, exercise-related central chemoreactivity may also impact nocturnal periodic breathing. During heavy exercise, the respiratory drive is affected by chemosensors located within the working muscles[117,118] and, according to Subudhi et al [119] during dynamic leg exercise, hypoxia-induced increases in peripheral chemoreceptor activation leads to marked reductions in $PaCO_2$ and concomitant reductions in cerebral blood flow and cerebral oxygenation. Exercise-evoked sympathetic activation also induces small, but significant increases in chemoreceptor discharges that can persist up to 6 d after exercise is completed[120]. The Long-Term study's significant correlations between habitual exercisers' activity time and increased AHI are consistent with this theory.

2) Alterations to cerebral and pulmonary structure and function. Rupp et al[121] found that prolonged moderate-intensity hypoxic exercise can accentuate the effects of hypoxia, increasing total brain volume (by up to ~2%). During hypoxia, mild exercise induces cerebral vasodilation, increases cerebral blood flow, and augments cerebral oxygenation, suggesting that the exaggerated hyperpnoeas, which arise during high-intensity exercise, coincide with decreased overall cerebral blood flow. These findings are consistent with work demonstrating attenuation of middle cerebral artery flow velocity and cerebral oxygenation during hypoxic exercise after acclimation to intermittent or continuous hypoxia, resulting in augmented exercise hyperpnoea [for review, see reference [17]]. More recent research confirms that the ventilatory responses to exercise in hypoxia are augmented such that periodic breathing is positively related to both cardiac output and the ventilatory response to CO_2[98]. Whether pulmonary oedema develops during exercise at sea level remains unresolved. Several studies have identified that pulmonary oedema can follow exercise training [as reviewed in [100]]. This systematic review of the subject found that ~50% of all studies scrutinized reported evidence of exercise-induced extravascular lung fluid, whilst the remaining papers reported inconclusive results, or no changes[100]. Periodic breathing at high altitude has been hypothesised to be more frequent, and SpO_2 desaturation more severe during sleep, in subjects who develop high altitude pulmonary oedema (HAPE), and/or AMS[78] in part due to the impaired gas exchange. Clinically, pulmonary oedema is identified using radiographic imaging, which, for obvious logistic limitations, was not possible here. Although the possibility of severe pulmonary oedema remains unlikely, especially given the low LLS scores reported in both cohorts, it is possible that mild cases of pulmonary oedema did occur, especially in the Short-Term Phase in which seven participants from both groups (EX=4, CON=3) reported AMS symptoms on Day 1. The fact that there were no systematic discrepancies between groups rules out any significant correlational value of the LLS to explaining the differences in AHI and night SpO_2 concentrations.

A. Night Oxyhemoglobin Saturations

In the Short-Term Phase study, mean night oxyhaemoglobin saturations were lower in EX than CON. It appears initially counterintuitive that mean night SpO_2 should be lower in the EX than the Con group, especially on the tenth night of the Short-Term study, since during exposure to hypoxia in healthy subjects, SpO_2 during sleep is typically higher in subjects exhibiting period breathing than in those who do not [for a review see reference [47]]. On the other hand, it is also true that hypoxic exercise enhances sympathetic nerve activity and exercise-induced hypoxemia, which is consistent with the present observation of a lower SpO_2 in the EX group [as reviewed in [122]]. In summary, although other factors might have played a role, we believe that the combination of lower mean night SpO_2 in the EX group is compatible with exercise-induced exacerbation of sympathetic activation and/or hypoxemia. It is also possible that

any difference(s) in SpO_2 between EX and CON may be attributed, purely by chance, to changes in body position or a greater time spent in a given sleep stage (REM vs. NREM sleep). As there were no systematic between-group interactions in REM within the 10-d protocol, this thesis remains unlikely. Since this relationship was not reflected in the Long-Term study, it suggests that in this condition the ventilatory control of periodic breathing may have reached a constant threshold, maintained for the duration of their hypoxic exposure[63], especially since increased SpO_2 due to hypoxic acclimation (over many months) was not influenced by the presence or absence of exercise habits..

B. Effect of Season

The present study observed evidence that seasonal sleep effects exist in the Antarctica EX cohort, at least regarding total sleep time and the length of periodic breathing response. Comments on possible mechanisms are further discussed in Collet et al[123], who reported higher sleep fragmentation and night energy expenditures in summer than in winter at two Antarctic research stations. They propose a circadian de-synchronization effect, induced by melatonin secretion delays from constant light exposure in summer months as a plausible explanation for the sleep fragmentation observed. Nevertheless, it should be noted that the literature is divergent on this aspect, with others reporting longer wake after sleep onset (WASO) and more sleep fragmentation in winter compared to summer months[124]. The present study lends additional evidence to the fact that total sleep time is reduced in summer, but only in habitual exercisers.

C. Normobaric versus Hypobaric Hypoxic Exposures

A final point worth mentioning is the possible difference(s) between hypobaric and normobaric hypoxic stressors, and whether the testing environment could have impacted breathing and ventilatory drive parameters independent of exposure duration between investigations. On the one hand, Richard et al[125] concluded that 6 h of hypoxic exposure was sufficient to lower peripheral and central CO_2 thresholds, but they did not find evidence that it induced any other cardiorespiratory or AMS differences between hypobaric and normobaric hypoxic exposures. This is in line with Mounier et al[126] who argue that up-to-date studies have not provided strong enough evidence to support the theory that (patho)-physiologic responses may differ between chronic hypobaric and normobaric hypoxia. Furthermore, a recent consensus for working in hypoxia published by the "Medical Commission of the Union Internationale des Associations d'Alpinisme"[127] concludes that the physiologic differences between normobaric and hypobaric hypoxia are too insignificant for clinical relevance. On the other hand, Millet et al[128] have pointed out several works supporting the notion that hypobaric hypoxia is a more severe environmental stressor which can induce dissimilar responses to normobaric hypoxia, and thus, diverse physiological adaptations as well. Considering the nature of our stated aims and

hypotheses, we do not believe there to be significant differences in the physiological outcomes observed in either cohort of the Short- or Long-term studies in the present investigation.

D. Study Considerations

1) Study Design - Baseline fitness and personality characteristics could have influenced one's adherence to performing regular physical activity in Concordia, Antarctica, which may also have affected the distribution and characteristics of the two groups unbeknownst to the researchers. We acknowledge that a fully repeated-measures cross-over design would have been ideal to tease-out the physiological mechanisms driving our observations in both studies. Due to the extreme nature of testing environments, multi-national project scheduling, budget considerations, and other factors, this was not feasible.

Indeed baseline fitness could have also played a role in the Short-Term study. We only know from the selection of the participants that "All of them were physically active on a recreational basis". So the question that remains is if there could have been during the confinement a training and detraining effects on the participants that could have influenced the results. Indeed doing two hours of physical activity for ten days could have visible training results, not just for VO2 peak scores, or % body fat, but also with circulating hormones, lactate threshold, etc. Same applies for detraining, and probably trained participants would show some detrain effects in 10 days. The question remains how much of a decrease could someone expect in for instance muscle and aerobic function in 10 days if any. Having said that, it should also be noted that marked and significant differences between both EX and CON groups were already observed as from night 1, and therefore it seems that a training and detraining effect would be quite improbable already as from night 1. Nevertheless, the possibility of influence due to Baseline fitness remains.

2) Exercise Stratifications - Indeed, 30 min of physical activity at least 4-day per week is inherently a different physical stimulus than 2-h of structured, moderate-intensity cycling per day, which is why the two studies were not directly compared to each other, statistically speaking. Of note, individuals were stationed at Concordia for a variety of reasons, none of which involved acting primarily as research subjects (e.g. cooks, mechanics, and medical personnel). Thus, subjects were not *a priori* divided into exercise intervention groups in the Long-Term study. Although the dose-response relationship between exercise and AHI in the Long-Term study is apparent in Figure 3-6, both mentioned Study Design and Exercise Stratifications, together with other environmental (e.g. cold, light) and psychological (e.g. intense isolation) variables present in the Long-Term study could explain why differences between EX and CON groups were only significant in 2 of the periods (Figure 3-4). Therefore, the primary goal of the Short-Term study was not to duplicate (or replicate) results observed from Concordia, but to limit possible between-group differences and the number of co-factors from Antarctica. We therefore feel confident in

any differences between experiments, i.e. the binary distribution of EX versus CON in the Short-Term study, versus the self-paced, externally-valid individual variations in the Long-Term study.

3) Hypoxic Sleep Studies - We do not know what the AHI and mean night oxyhaemoglobin saturations were for either group prior to hypoxic exposure. AHI values vary markedly when individuals ascend to high altitude; however, Concordia subjects were not allowed to be stationed at the base until they passed a rigorous physical examination. Night recordings in all cases were screened before data analysis by a certified sleep professional to ensure there were no systematic obstructive apneas, no periodic limb movements, or any other discernable pathophysiological reason why a subject could not be included in the present investigation. Night recordings from the Long-Term study did not include nasal air pressure, thus respiratory events were characterized by identifying paradoxical breathing patterns, a gross measure of obstruction which may under-estimate certain respiratory events or hypopneas during sleep. The issue of whether the AHI is mainly due to OSA or CSA is crucial, thus we further investigated whether respiratory events during the Long-Term study where due to high altitude-induced periodic breathing using a validated mathematical model (eAMI[109]), confirming it is unlikely other respiratory events would have influenced these results. Indeed, the pattern of periodic breathing at high altitude is very characteristic and can be easily discernable from the effort band traces depicted in Figure 3-1 herein.

VII. CONCLUSIONS

Mean apnoea-hypopnea index scores were positively correlated to both mean exercise time and the coefficient of variation in mean night pulsed oxygen saturations in those who lived and worked in hypobaric hypoxia for up to one year in duration. This relationship was confirmed in a Short-Term study in which AHI indexes were significantly elevated in an exercise group compared to matched controls.

Chapter 4 - eAMI: a qualitative quantification of periodic breathing based on the amplitude of the oscillations

We realised during our experiments that monitoring periodic breathing at high altitude was not only complex but also resource intensive. Indeed, scoring periodic breathing by determining the AHI, the gold standard, was also labour-intensive and required the simultaneous recording of airflow and oxygen saturation.

In this chapter, we propose an automated, simple and novel methodology for the detection and qualification of periodic breathing. We show that, regarding quantification and temporal resolution, the proposed estimated amplitude modulation index (eAMI) can assess the strength of periodic breathing and underlying loop gain at any given time. Loop gain can be considered in respiration as the sensitivity of the negative feedback loop that controls respiration[129]. Regarding detection, our technique shows a 0.95 ($p<0.001$) correlation with the clinical standard, i.e. the AHI, on a dataset where high levels of periodic breathing is present.

The impaired prognosis associated with periodic breathing makes its automated detection and early diagnosis of clinical relevance. We have made substantial efforts in discussing from a clinical point of view the benefits of an early diagnosis of periodic breathing and how the proposed method can help both clinical and research environments. The proposed method was further tested in many PSG records that were acquired at sea level in a controlled clinical environment and fully compliant with the international guidelines of the American Academy of Sleep Medicine (AASM, 2012; ICSD, 2014)[108].

The following chapter is a revised version of what was published as an original manuscript in the journal SLEEP[109].

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QUANTIFICATION OF PERIODIC BREATHING BASED ON THE AMPLITUDE OF OSCILLATIONS

eAMI: A Qualitative Quantification of Periodic Breathing Based on Amplitude of Oscillations

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I. ABSTRACT

Study Objectives: periodic breathing is a sleep-disordered breathing characterised by instability in the respiratory pattern that exhibits an oscillatory behaviour. Periodic breathing is associated with increased mortality and it is observed in a variety of situations, such as acute hypoxia, chronic heart failure and damage to respiratory centres. The standard quantification for the diagnosis of sleep-related breathing disorders is the apnea/hypopnea index (AHI), which measures the proportion of apneic/hypopneic events during polysomnography. Determining the AHI is labor-intensive and requires the simultaneous recording of airflow and oxygen saturation. In this paper, we propose an automated, simple and novel methodology for the detection and qualification of periodic breathing: the estimated amplitude modulation index (eAMI).

Patients or Participants: Antarctic Cohort (3800 meters): 13 healthy individuals. Sleep Clinic Cohort: 39 different patients suffering from diverse sleep-related pathologies.

Measurements and Results: when tested in a population with high levels of periodic breathing (Antarctic Cohort), eAMI was closely correlated with AHI ($r=0.95$, $p<0.001$). When tested in the clinical setting, the proposed method was able to detect portions of the signal in which subclinical periodic breathing was validated by an expert ($n= 93$; accuracy = 0.85). Average eAMI was also correlated with the loop gain for the combined clinical and Antarctica cohorts ($r=0.58$, $p<0.001$).

Conclusions: regarding quantification and temporal resolution, the eAMI can estimate the strength of periodic breathing and the underlying loop gain at any given time within a record. The impaired prognosis associated with periodic breathing makes its automated detection and early diagnosis of clinical relevance.

Keywords: periodic breathing, quantification, Cheyne–Stokes respiration, loop gain, modulating index.

II. INTRODUCTION

The most common types of sleep-disordered breathing are obstructive sleep apnea/hypopnea (OSA), followed by central sleep apnea/hypopnea (CSA) and periodic breathing. An obstructive sleep hypopnea is an event characterised by a transient reduction in breathing during sleep while an apnea is a complete cessation, caused by a partial or complete obstruction of the upper airway during sleep. Central sleep apnea/hypopnea is an absence or reduction of breathing and respiratory effort in the absence of any obstruction of the upper airway. Finally, periodic breathing is characterised by instability in the respiratory pattern that exhibits an oscillatory behaviour with periods of hyperventilation followed by apneas or hypopneas. Periodic breathing may be observed in a variety of situations including damage to respiratory centers[3], acute exposure to high altitude[3-7] and in patients suffering from chronic heart failure[8-11]. In the latter, recurrent episodes of central and obstructive events are known to coexist due to feedback gains in addition to upper airway instability[130,131]. Although frequently treated differently and considered as pathophysiologically unrelated events, there is growing evidence to suggest that in some patients with heart failure, both obstructive and central respiratory events might be part of a spectrum of periodic breathing[130,131].

The standard measure for the diagnosis of periodic breathing is the apnea/hypopnea index (AHI): the total number of apneas and hypopneas per hour of sleep. Determining the AHI is labor-intensive and requires the simultaneous recording of airflow and oxygen saturation; thoracic and abdominal movements can be used to help distinguish central from obstructive events. Automated methods are available to determine the AHI, but due to the complexity and range of different respiratory events, computer-assisted manual scoring is yet the clinical standard. Despite being a valuable clinical tool with proven prognostic value[132], when it comes to periodic breathing, the AHI provides no qualitative information regarding the amplitude of the oscillations in the

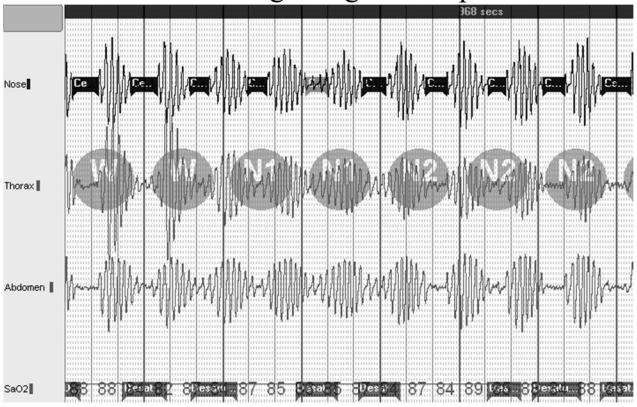

Figure 4-1 Screenshot of the standard sleep-disordered breathing scoring using a proprietary software

A portion of night record scored by a sleep expert. Airflow (nose) in arbitrary units. Thoraco-abdominal motion (thorax and abdomen) in arbitrary units. Oxygen saturation (SaO2) in percentage. In dark over the nose signal, each of the respiratory events. Each vertical line represents 15 seconds.

respiratory signal, their distribution or periodicity. Figure 4-1, displays a portion of a night record in which periodic breathing is present; it is being characterised by the number of apneic/hypopneic events instead of being analysed as a phenomenon in which the amplitude of the respiratory signal is being modulated. Literature regarding alternative tools for the quantification of periodic breathing is scarce. Of the 32 papers mentioning quantification of periodic breathing in Thomson Reuters's "Web of Science" database, only 11 applied or suggested a measure other than AHI[133-143]. In 6 of the 11 papers, an indirect measure quantifying the grade of instability of the chemoreceptor feedback loop is used[134,135,137-139,141]. In the remaining five articles, Small et al[136] estimate the fractal dimension of the respiratory flow, and both, Millar et al[140] and Pinna et al[8,133,144] use a modulating index. The former is based on the relationship between lower and higher frequency components of the respiratory signal, and the latter on a measure of the changes in the amplitude of the instant tidal volume during periodic breathing. Both methodologies do require a previous phase in which the existence of periodic breathing is validated to be later quantified by an index.

Our aim was to develop a straightforward and robust method to both detect the presence of periodic breathing and to quantify the amplitude of the oscillations in the breathing pattern at any given time. We wanted the method to be able to be applied to flow or thoracoabdominal motion signals from a variety of different devices and be independent of calibration of the instrument used. As such it was to be widely applicable beyond methodological considerations of hardware; without the need for initial validation of the existence of periodic breathing or its characterization. In this paper, we describe development and validation of an index, which we term estimated amplitude modulating index (eAMI) that addresses this aim.

III. METHODOLOGY

The behaviour of the respiratory signal during periodic breathing resembles an amplitude-modulated signal (See figure 4-2). Therefore, by comparing the amplitudes of the modulation and that of the respiratory signal (flow or thoracoabdominal motion), periodic breathing can be characterised, the key component being the characterization of the amplitude of the modulating signal. We propose a new quantification based on the amplitude of the oscillation exhibited during periodic breathing. This new index was applied to two different datasets. The first one was a large polysomnography dataset acquired at the Antarctic base Concordia. Because of the prevailing chronic hypobaric hypoxia, due to the corrected altitude of approximately 3800 meters, Concordia provides a unique environment for the study of periodic breathing[4-7,78]. The second dataset was acquired at sea level in a controlled clinical environment following the international guidelines of the American Academy of Sleep Medicine (AASM, 2012[108]; ICSD, 2014[145]).

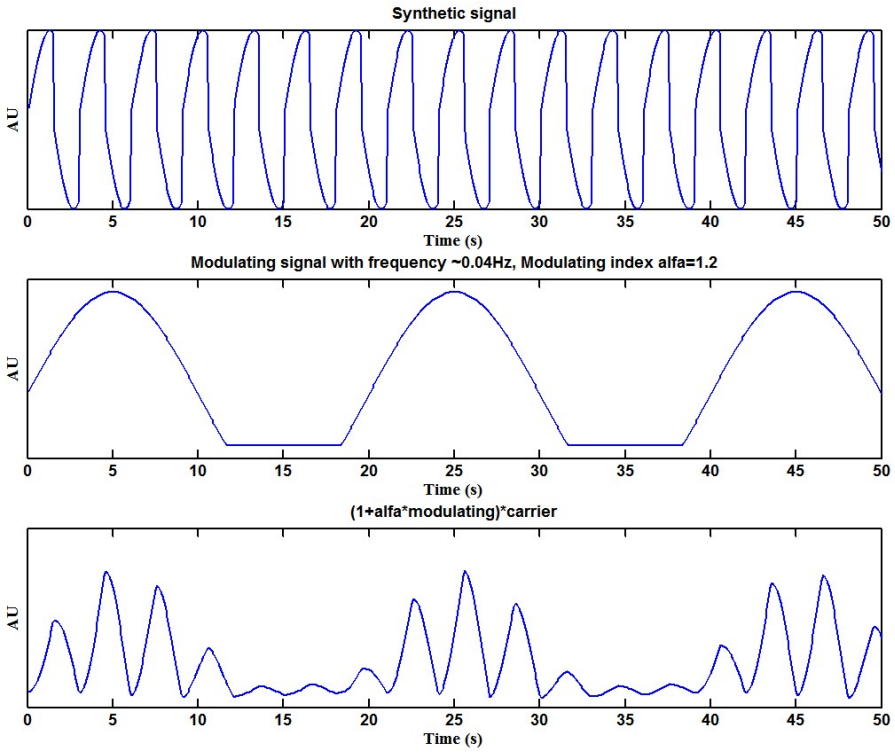

Figure 4-2 Amplitude modulation signal

An example of a modulating signal. The first 2 graphs are the carrier and the modulating signal, respectively. The last graph illustrates the resulting modulated signal. The resemblance with a respiratory signal exhibiting periodic breathing is apparent.

A. Development of the index.

1. Prefiltering and envelope extraction

Let the digital respiratory signal be RS[n]. Since it is assumed that in adults the bandwidth of quiet breathing ranges between 0.125 Hz and 0.4 Hz[146], the respiratory signal is band-pass filtered between 0.125-0.4 Hz. This first filtering reduces the amount of noise due to non-respiratory events (mechanical movement due to heart beat, electrical interferences, …). After band-pass

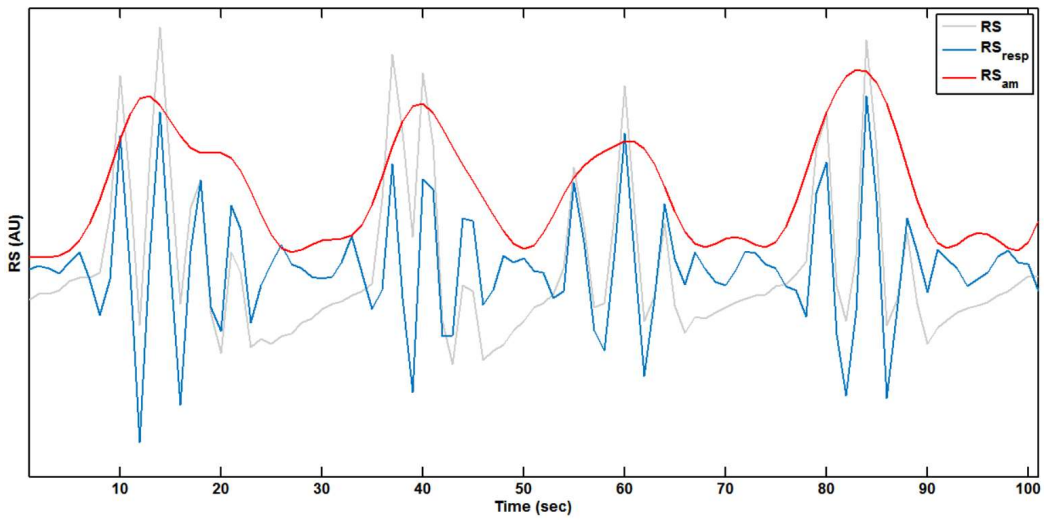

Figure 4-3 RS signals illustrating (1) and (2).

RS is a respiratory signal exhibiting periodic breathing, RS_{resp} is the respiratory signal band-pass filtered at respiratory frequencies and RS_{am} is its envelope.

filtering, the signal is downsampled to 1 Hz, finally yielding $RS_{resp}[n]$. We characterise the modulating wave exhibited during periodic breathing, $RS_{am}[n]$, by using a standard AM demodulation scheme[1], i.e. by low-pass filtering the absolute value of $RS_{resp}[n]$. Since it is assumed periodic breathing is only observed at frequencies below 0.125 Hz, the cutoff frequency of this low-pass filter is 0.125 Hz[10,15,19,47,57,96,147-151]. Filter characteristics are listed in Table 4-1,

TABLE 4-1 FILTER CHARACTERISTICS

FILTER	FP	TYPE	ORDER
Band-pass	[0.125 – 0.4] Hz	Butterworth	12
Low-pass	0.125 Hz	Butterworth	6

The band-pass filters is used for preprocessing RS[n]. Envelope extraction is done by using a standard AM demodulation scheme[1] with the low-pass filter. Fp are the pass frequencies.

and Figure 4-3 illustrates the different signals.

Butterworth filters were used[152-160] since they do not present ripples at their pass-band. An infinite impulse response (IIR) filter was selected over a finite impulse response filter (FIR) because of the improved stopband to passband cutoff and to avoid distortions added by the windowing. Furthermore, a Butterworth filter was selected over Chebyshev and Bessel filters as the small magnitude in the passband was prioritised over a rapid rate of attenuation from the passband to the stopband. Zero-phase between outputs from the different digital filters was achieved by using infinite impulse response forward-backward filtering[161]. Although literature seems to be entirely inconsistent with the order of the filters used to isolate respiratory bands, we decided to use the highest order found in the literature of 6 for the low-pass and a 12 for the band-pass[152-160]. It should be remarked here that doing an analysis on different approaches to pre-process physiological signals based on various filter types is out of the scope of this work.

2. Index computation

$RS_{resp}[n]$ and $RS_{am}[n]$ can be characterised by the amplitude of the sine wave that would exhibit the same energy E[n]

$$E_{\gamma}[n] = \frac{1}{N}\sum_{k=-N/2}^{N/2}\left|RS_{\gamma}[n+k] - \overline{RS_{\gamma}[n]}\right|^2 \qquad (1)$$

where $\overline{RS_{\gamma}[n]}$ is the moving average of $RS_{\gamma}[n]$

$$\overline{RS_{\gamma}[n]} = \frac{1}{N}\sum_{k=-N/2}^{N/2} RS_{\gamma}[n+k] \qquad (2)$$

Where the subscript γ is either "resp" or "am", depending on the considered signal. The influence of N will be further developed in the results section. To compute both the energies from $RS_{resp}[n]$ and $RS_{am}[n]$ we first remove the mean of the signals as in equation (1). The reason for that is that

in the absence of PB, the envelope $RS_{am}[n]$ is a signal with mean greater than zero. Knowing that the square root of the energy of a sinusoidal wave is proportional to its amplitude, we can define an estimated amplitude signal $eA_{\gamma}[n]$ for a given respiratory signal $RS_{\gamma}[n]$ during an interval N as

$$eA_{\gamma}[n] = \sqrt{E_{\gamma}[n]}\,, \qquad (3)$$

where the subscript γ is either "resp" or "am", depending on the signal to which it is applied. Then, $eA_{am}[n]$ and $eA_{resp}[n]$ will denote the estimated amplitudes of both the modulating and the respiratory signals computed over a moving window of length N. We finally propose a modulating index, the estimated amplitude modulating index (eAMI) as

$$eAMI[n] = 1 - \log\left(eA_{resp}[n] / eA_{am}[n]\right) = 1 - 0.5\log\left(E_{resp}[n] / E_{am}[n]\right). \qquad (4)$$

It must be noted that comparing either the energies ($E_{resp}[n]$ and $E_{am}[n]$) or the equivalent amplitudes ($eA_{am}[n]$ and $eA_{resp}[n]$) is fundamentally the same approach, as it only implies a change in the scale. The eAMI takes values around one when both equivalent amplitudes are the same, i.e. around apneas, and takes negatives values in the absence of periodic breathing. Figure 4-4 depicts several examples of eAMI calculations.

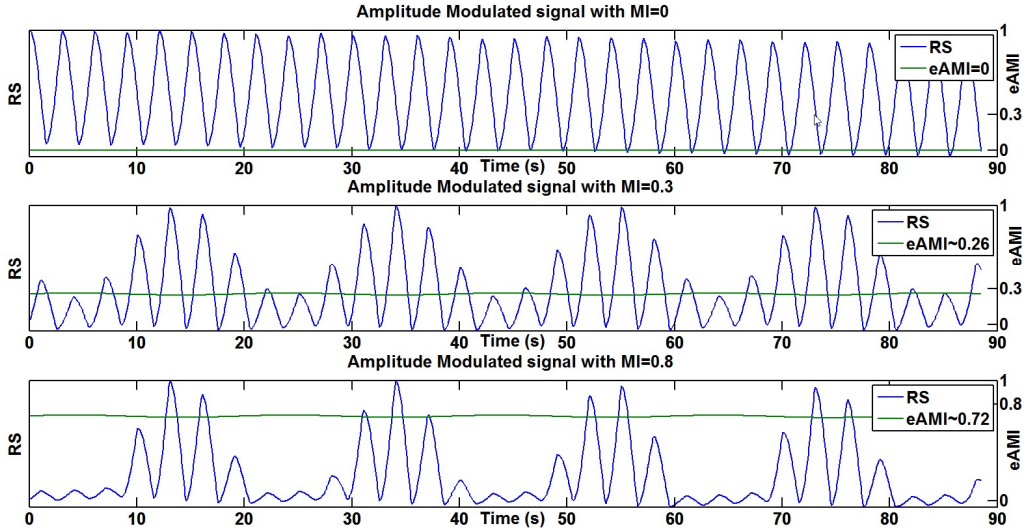

Figure 4-4 eAMI for three different amplitude modulated signals.

First graph: eAMI in the absence of modulation gives values of 0. When the modulation index is 0.3, eAMI takes the value 0.26. Finally, for a modulating index of 0.8, eAMI takes 0.72.

3. Illustration of the computation of the index

Figure 4-5 illustrates a possible scheme for the calculation of eAMI[n]. The method was implemented in Matlab.

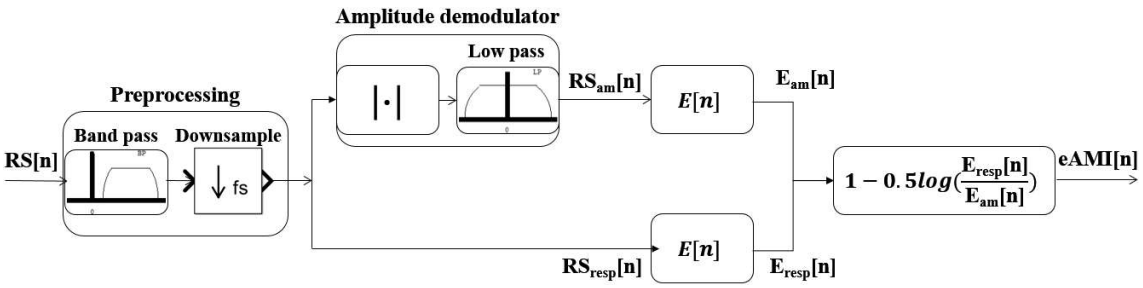

Figure 4-5 Scheme proposed for computing eAMI

4. Detection of periodic breathing and loop gain estimation

As eAMI[n] is a signal that qualifies periodic breathing regarding the amplitude of the oscillations of the respiratory signal, we can use it to both quantify and detect periodic breathing. We consider the possible existence of a periodic breathing event if eAMI[n] remains above a certain clinical threshold θ_C during at least a specified duration, L (expressed in samples). The condition of a minimum length aims at removing artefacts. The value of L is discussed in the next section. Since the gold standard AHI quantifies the number of apneic/hypopneic events per hour during one night record, to be able to compare both the AHI and the eAMI, we defined the clinical periodic breathing index (cPBI) as the ratio of the sum of the length of the events longer than L during which eAMI[n] is above θ_C and the total recording time. θ_C is computed to maximise the correlation between cPBI and the AHI. This measure is analogous to the frequently used fraction of time spent during periodic breathing but estimated from the eAMI. By definition, values of eAMI between 0 and θ_C can be then considered as "subclinical oscillation" or periodic breathing that does not reach international guidelines for respiratory events (AASM, 2012)[108].

Finally, given that the amplitude of the oscillations during periodic breathing is thought to vary with the loop gain of the respiratory control, we tested whether the eAMI was a good estimator of the instability of the respiratory system. For that, the average loop gain for each of the files was calculated as proposed by Sands et al[139] and then compared against the average eAMI for each of the files.

5. Artefact management

The energy from artefacts and spiky respiratory events such as sighs might spread through both the modulating and the respiratory frequency bands. This can cause the eAMI at some point to take values above zero despite the absence of periodic breathing. Short time false positives are rejected by requiring a minimal time during which the eAMI has to remain above the threshold θ_C. For simplicity, we will set L=2N, i.e. require an event to be at least twice as long as the length of the window used to compute the signal energy. Longer duration artefacts related to signal loss

or subject movements, or successive sighs during a period could still cause false positives. Although it is recommended to remove artefacts from the signal (AASM, 2012[108]; ICSD, 2014[145]), we kept them in our study, to further support our claim of simplicity of the method regarding requirements for pre-processing.

B. Validation of the Index

1. Datasets

Antarctica cohort: To validate the proposed methodology, we performed an analysis on polysomnography recordings in which periodic breathing without additional comorbidities was expected. For this, a dataset of polysomnography recordings (around 518 hours of data) was taken at the Antarctic base Concordia. Because of its location (at an approximate equivalent altitude of 3800m), Concordia provides a unique environment for the study of periodic breathing due to high altitude in otherwise healthy individuals[63]. Participants arrived during the previous Antarctic summer, and remained at the Concordia Station for the Antarctic winter, on average spending 13 months at altitude. Thirteen members of the 14 all-male crew of one winter campaign participated in the experiment (age = 39 ± 9.8 yrs.; BMI = 24.2 ± 2.2; 3 smokers). None of the subjects reported a history of significant medical conditions. Thoraco-abdominal motion was monitored by inductance plethysmography with transducers placed on the participants' chest and abdomen. We recorded the electroencephalograms, electrooculograms, electrocardiogram and electromyograms from surface electrodes. Oxygen saturation and heart rate were also derived from an oximeter. Data collection was programmed throughout the entire overwintering campaign with a periodicity of six weeks. Each of the subjects had on average seven scheduled repeated measures during the campaign, including one habituation night at the beginning of their campaign. From the total 91 recorded measures, 74 files including habituations nights were finally acquired and used in this study. The remaining 17 measures were not successful due to device failure or malfunction of the respiratory inductance plethysmography bands (n = 8) and because occasionally, some of the participants declined a scheduled measure (n = 9). A sleep expert analysed all recordings following the AASM (2012) criteria for respiratory event scoring[108]. Hypopnea was defined as a reduction in thoracoabdominal motion compared to the preceding two minutes baseline of > 50%, and apnea was defined as a reduction of > 90%. Only events lasting for at least 10 s and accompanied by an oxygen desaturation of > 3% were taken into account[108]. Due to the lack of nasal airflow signal, discrimination between central and obstructive apneas was done by testing for the occurrence of paradoxical breathing: breathing movements caused by an obstruction in which the rib cage moves in on inspiration and out on expiration, in reverse of the abdomen. Periodic breathing was present at a clinically significant level in most of the recordings (AHI=65.4±14.55).

TABLE 4-2 PSG CHARACTERISTICS

COHORT	AHI	OSA	CAI	MIX	TST H	SpO_2 %
Antarctic (n=74)	58.6 (36.7, 93.4)	4.8 (0.4, 22.4)	26.5 (24.7, 64.9)	0 (0, 0.8)	6.4 (5.2, 7.2)	88 (85.3, 89.9)
Clinical (n=39)	17 (0.7, 49.0)	2 (0, 24)	0.2 (0, 8.9)	0 (0, 0.6)	6.4 (5.1, 7)	94.3 (92, 95.6)

Definition of abbreviations: AHI = apnea/hypopnea index; CAI = central apnea/hypopnea index; OSA = obstructive apnea/hypopnea index; MIX = mixed apnea/hypopnea index; SpO2=oxygen saturation as measured by pulse oximetry; TST = total sleeping time.
Data are represented as medians (quartiles).

Clinical cohort: to validate the proposed method with signals that were acquired in a clinical setting, a set of 39 polysomnographic recordings from 2 different clinical environments was used. The dataset was used to test both the proposed method's ability to detect periodic breathing at subclinical levels, i.e. in records where no CSA events were identified by the sleep expert, and also at clinical levels in records with very high indices of CSA and/or CSA events. For this, a dataset of polysomnography recordings from 39 different patients suffering from various sleep-related pathologies was used. Signals were collected in controlled clinical environments in accredited sleep laboratories in both Brussels (~ 60 m altitude) and Ljubljana (~ 300 m altitude). Full polysomnography recordings included nasal airflow, thoraco-abdominal motion, electroencephalograms, electrooculograms, electrocardiogram, electromyograms, leg movements and oxygen saturation. A certified expert somnologist analysed all records following international guidelines[108]. Detailed PSG characteristics for both cohorts are reported in Table 4-2.

2. Validation protocols

Optimum θ_C threshold: to estimate a candidate value for θ_C, we made use of the fact that high levels of periodic breathing were expected in the Antarctic cohort. Indeed, once the dataset was scored, the sleep expert corroborated that high AHI levels were mainly due to periodic breathing. To estimate the optimum θ_C, we divided our complete set of 74 high altitude recordings in 10000 randomised groups of 30. We used one of the randomised groups to find an optimum θ_C, i.e., we chose θ_C to maximise the correlation between the AHI and the resulting cPBI. We computed the correlation between the AHI and the resulting cPBI for each of the 10000 randomised groups. The variance of the correlation among the 10000 groups gave an idea of the sensitivity of θ_C as a function of particular signals. This optimum θ_C was then tested against the second cohort.

Detecting events missed by clinicians (subclinical periodic breathing): to test if the proposed method was able to unmask undetected apparent episode of periodic breathing, for each of the files from the clinical cohort a pruned signal including only periods in which the sleep expert did not score any events was obtained. All events with values of eAMI above 0 and lasting for at least L were pre-selected. Each of these events was visually inspected by an expert and classified into two different groups:

- Non-PB events or false positives and periodic breathing events with erratic or more complex variations of the respiratory signal, and
- periodic breathing events with variations of the respiratory signal above 50%.

It is important to note that this criterion to classify periodic breathing events was established solely on the amplitude of the oscillation of the respiratory signal without taking into account any of the other requirements suggested by the AASM guidelines for measuring sleep-related breathing disorders in adults[108]. A ROC curve was calculated to illustrate the performance of a binary classifier system discriminating between subclinical periodic breathing and false positives for different thresholds θ.

Implications of the source of the respiratory signal used for computing eAMI: To further demonstrate our claim that the eAMI works independently of the type of source signals, where possible, eAMI was calculated from both the nasal air flow and thoracoabdominal motion signals and the results compared.

Statistics: correlations were computed using two-tailed, bivariate correlations (SPSSv 17.0, Chicago, IL, USA) at $p<0.05$ level of significance. Data are expressed as means ± standard deviations, with 95% Confidence Intervals ('CI') for effects of interest.

IV. RESULTS

A. Characterising periodic breathing by the amplitude of the oscillation of the respiratory signal

In Figure 4-6, we show the behaviour of the eAMI on a portion of a respiratory signal where periodic breathing was present. This figure illustrates both the temporal resolution and the descriptive value of the proposed method. The eAMI signal qualifies periodic breathing regarding

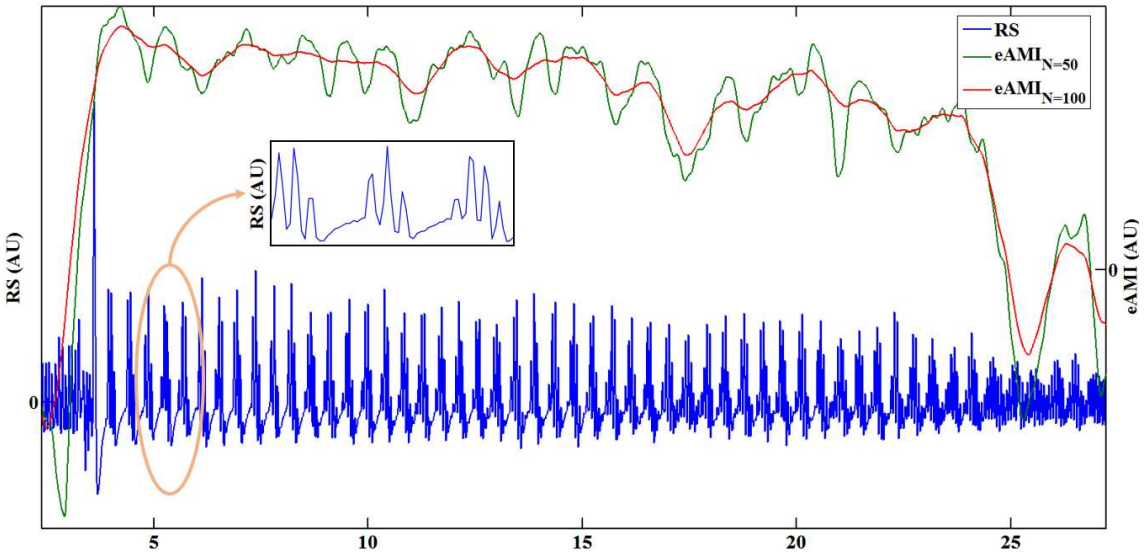

Figure 4-6 Fragment of respiration with different levels of PB and the value of eAMI for the given period.
In deep blue, the respiratory signal LV. In red and green eAMI as defined in (5) for N=100 and N=50 respectively. In both we did not use any lower threshold θ'.

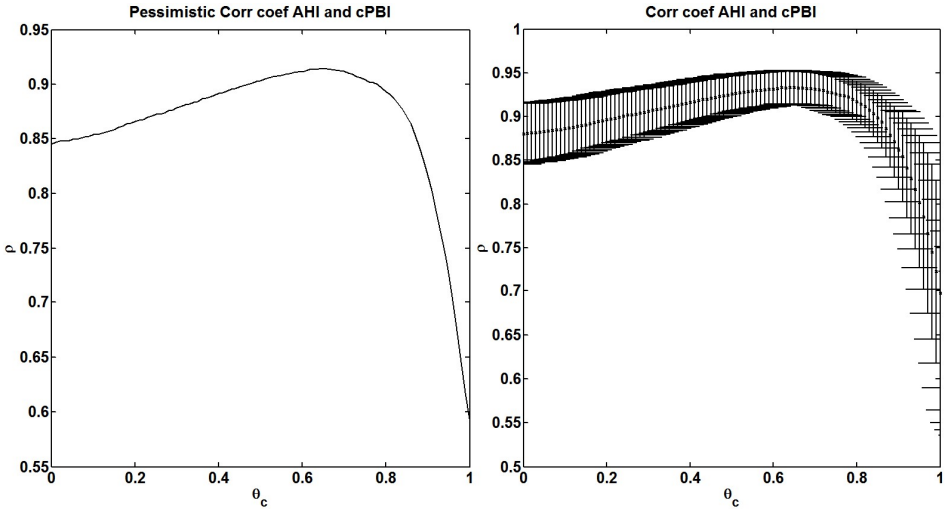

Figure 4-7 Average correlation coefficient between AHI from a dataset scored by a professional sleep expert and proposed cPBI.
The dataset was divided in 10000 randomized groups of 30 nights. For each of the group the correlation between the AHI gold standard and the proposed method was calculated and averaged for different values of θ_C. Right, the average correlation factor (ρ) with the standard deviation (sd). Left, a detail view of the pessimistic correlation (ρ-sd) as a function of θ_C.

the amplitude of the oscillation of the respiratory signal, which changes over time. For an expert, it was easy to observe oscillations on the respiratory signal with positive values of eAMI, whereas with negative values of eAMI, oscillations were not relevant enough or discernable. The eAMI apneic threshold, i.e. the value of eAMI for which apneas start to be observed by an expert, was approximately 0.9.

The effect of the length N of the window can also be observed in Figure 4-6 and is further discussed in section B.

In non-preprocessed signals, we noted that the eAMI could produce false positives in the presence of some long-duration artefacts or the presence of an accumulation of sighs during a period longer than L. While single events were rejected by the previously mentioned minimum event length requirement, an accumulation of them during a period could induce a higher eAMI

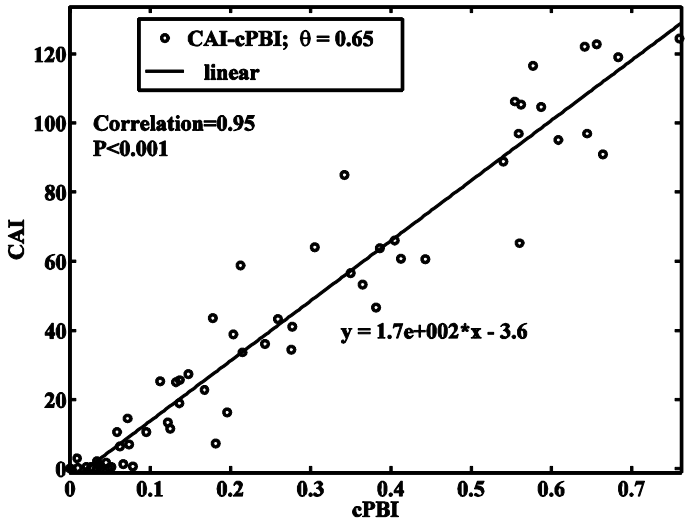

Figure 4-8 Correlation between eAMI and central apnea/hypopnea index (CAI).
Plot shows that shows for each of the records both the scored CAI and the cPBI.

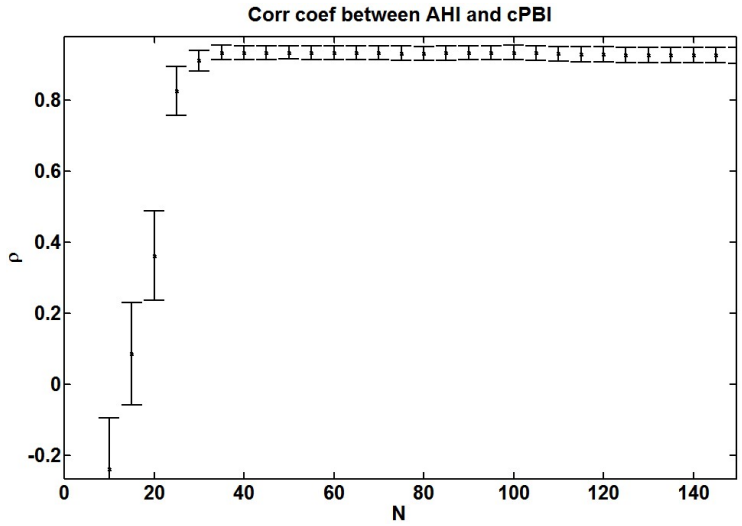

Figure 4-9 Average correlation coefficient between AHI from a dataset scored by a sleep expert and proposed cPBI as a function of N
The dataset was divided in 10000 randomized groups of 30 nights. For each of the group the correlation between the AHI gold standard and the proposed method was calculated for different values of N. The results for the 10000 groups was averaged together.

meeting the minimum length requirement thus leading to a false positive.

B. Optimum θ_C and periodic breathing detection performance

Results for the obtained average correlations between the AHI and the cPBI for a varying θ_C are depicted in Figure 4-7. We found θ_C=0.65 to be the optimal value, achieving a maximal mean correlation coefficient of 0.89 ±0.01 8 ($p<0.01$) between the cPBI and the AHI. We can also observe that the correlation between the cPBI and the AHI does not depend on the combination of signals used, as the variance of that correlation is smaller than <2%. When using this threshold, the correlation between the central apneic events (CAI) and the cPBI for the whole dataset was r=0.95 ($p<0.001$). A scatter plot of the data is shown in Figure 4-8. In Figure 4-9, we can observe the obtained average correlations between the AHI and the cPBI in the Antarctica cohort for a varying N and fixed θ_C=0.65. For N > 40 (which corresponds to 40s), the average correlation between the AHI and the cPBI remains practically constant.

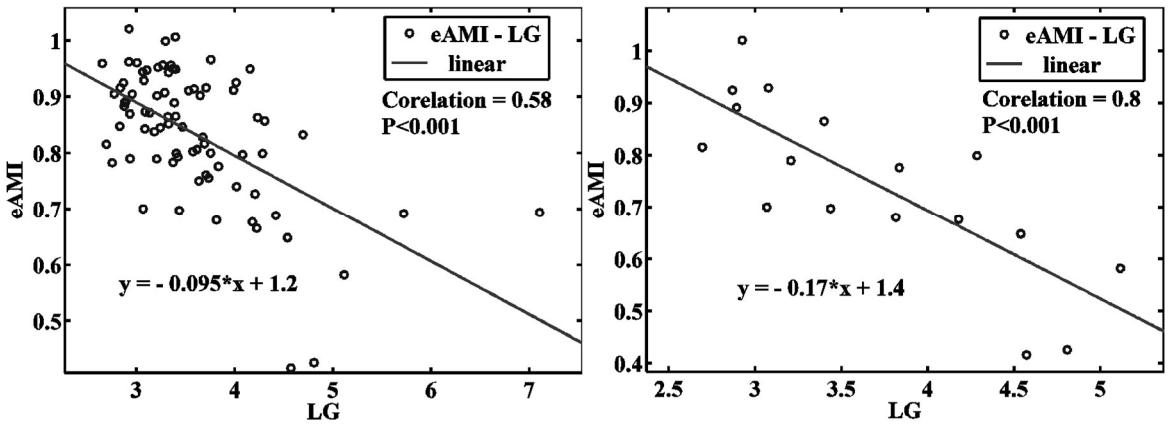

Figure 4-10 Correlation between eAMI and loop gain (LG).
On the left, plot shows that shows for each of the records both the average LG and eAMI. On the right, only for the Clinical Cohort.

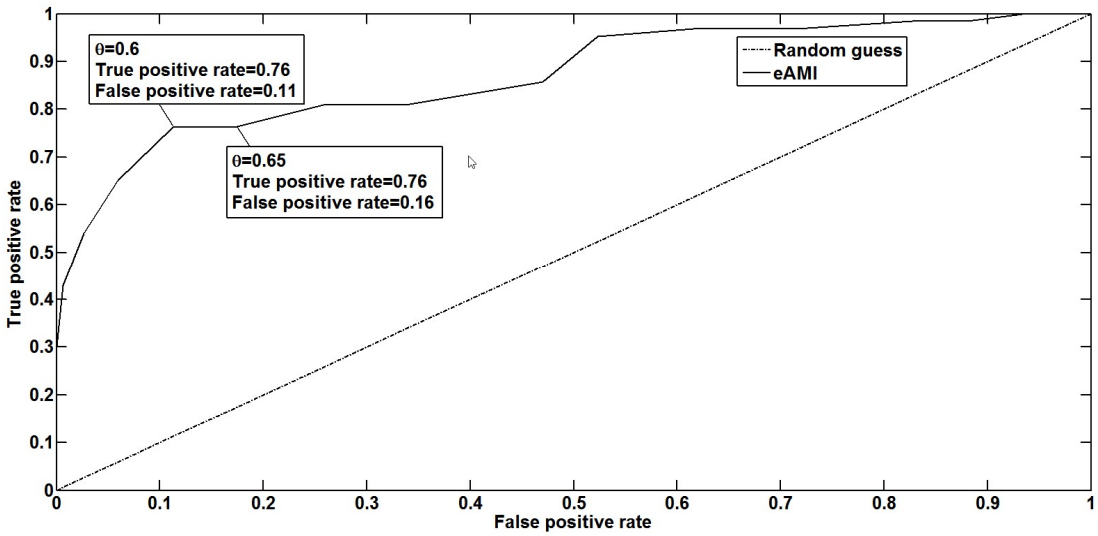

Figure 4-11 ROC curve
ROC curve for the detection of subclinical periodic breathing using eAMI. Area under the curve is 0.97

Using the same optimum θ_C=0.65, the correlation between the AHI and the cPBI in the clinical cohort was r=0.89 (p<0.001). When using this threshold, the correlation between the CAI and cPBI for the whole clinical dataset was r=0.79 (p<0.001).

C. eAMI as a predictor of the loop gain

The correlation between the average eAMI and the loop gain for the combined clinical and Antarctica cohorts was r=0.58 (p<0.001). If only using the clinical cohort, the correlation was r=0.8 (p<0.001) when using the nasal airflow signal for the computation of eAMI or r=0.76 (p<0.001) when using the thoracoabdominal motion instead. A scatter plot of the data is shown in Figure 4-10.

D. Detecting events missed by clinicians (subclinical periodic breathing)

In the clinical cohort, when using the nasal airflow signal, eAMI identified 253 events as periodic breathing that were not scored by the expert; 242 when using thoracoabdominal signal. Missing events were due to thoracoabdominal motion signal corruption. Events were visually classified by the sleep expert using the previously mentioned classification. Of these, 37 were periodic breathing events with erratic or more complex variations of the respiratory signal and 151 were periodic breathing events with fluctuations of the respiratory signal above 50%. In the remaining 65 events (false positives), different types of respiratory instabilities such as a succession of sighs were observed in a short period. In the Antarctic data, the number of non-scored periodic breathing events which still exhibited an eAMI above 0 were numerous. From the approximately 518 hours of data analysed, a portion of 90 hours had subclinical periodic breathing, i.e. with an eAMI above θ_C. These were events in which the amplitude of the oscillation of the respiratory signal was still above 50%, but was not considered as periodic breathing by the

expert. From the ROC curve, figure 4-11, it seems that values around θ_C are the best compromise also for the detection of subclinical periodic breathing

V. DISCUSSION

The primary goal of our study was to provide a new tool for the early diagnosis of nocturnal periodic breathing. It should be clearly stated that the eAMI is not a substitute for the clinical gold standard AHI but a new way to look at periodic breathing. The prevalence of undiagnosed sleep-disordered breathing (SDB), a condition of repeated episodes of apnea and hypopnea during sleep, is high among adults[12]. Several studies have demonstrated a direct link between SDB and mortality[13,14]. SDB is likely to be a risk factor for hypertension, which might result in increased cardiovascular morbidity in the general population[162,163]. SDB has also been associated with impaired daytime performance in children[164], while drowsiness due to SDB might be the cause of many accidents[165,166]. Periodic breathing may be observed in a variety of situations including damage to respiratory centers[3], acute exposure to high altitude[3-7] and in patients suffering from chronic heart failure[8-11]. Prognosis of heart failure is uniformly poor when treatment of the underlying problem is not initiated as soon as possible; half of the patients with a diagnosis of heart failure will die within four years, and in patients with severe heart failure the rate of mortality is >50%[167]. As pointed out by Gilmartin et al[168], although central apneas and severe periodic breathing, including Cheyne-Stokes respiration, are readily recognisable, more subtle forms of periodic breathing are much harder to characterise. Understanding the mechanisms behind periodic breathing and developing the necessary screening tools might help to improve early diagnosis and treatment of underlying diseases, including chronic heart failure cases in which period breathing is present.

In this paper, we propose an automated, simple and novel methodology to detect and quantify periodic breathing, a form of SDB, based on the estimated amplitudes of the respiratory signal and its envelope (eAMI). Regarding quantification and description, we have shown that the eAMI is a continuous signal that qualifies periodic breathing relating to the amplitude of the oscillation of the respiratory signal. This treats the periodic breathing event as a single process describing its evolution through time instead of treating periodic breathing as an accumulation of single central events, as in the current clinical gold standard AHI. Furthermore, the average value of the eAMI was also correlated with the loop gain of the record (combined cohorts $r=0.58$ $p<0.001$; clinical cohort $r=0.8$ $p<0.001$). This descriptive capability might help us to unravel further how this phenomenon evolves over time assessing how loop gain changes with sleep state or under the effects of different interventions. Since an increased loop gain in the respiratory control feedback loop has been proposed as a possible explanation for periodic breathing[57,134,169], a quantifying tool

that is correlated with loop gain might facilitate our understanding of the processes involved in its development and may help monitor certain patient categories in clinical settings.

Regarding clinical periodic breathing detection, we have proposed a candidate value for the clinical threshold θ_C by maximising the correlation between the fraction of time spent above this threshold (cPBI) with the AHI scored by the sleep expert. Although the AHI and the eAMI are two completely different approaches to quantify periodic breathing, this method allowed us to estimate the threshold in the level of oscillation as measured by the eAMI that clinicians would consider as central events. We found an optimal value for the clinical threshold θ_C around 0.65. When using this threshold in the Antarctica cohort, the correlation between the cPBI and AHI was $r=0.89$ ($p<0.01$) and between the cPBI and CAI was $r=0.95$ ($p<0.001$). The reason for this is that in this cohort the majority of the events were indeed central. This clinical threshold θ_C was further tested in the clinical cohort, showing, in that case, a higher correlation with the AHI ($r=0.89$, $p<0.001$) than with the CAI ($r=0.79$, $p<0.001$). These results might at first glance appear contradictory. The explanation, however, is that in the clinical dataset there were three recordings from patients showing severe cyclic OSA (AHI 39.64, 92.87 and 97.35), in which the proposed method detected a high periodicity resembling that of periodic breathing. Although this could be considered a limitation of the method, it should be noted that in these three patients, before the block of air flow one could easily observe the consecutive crescendo and decrescendo cycles characteristic from periodic breathing. This raises the question whether it is appropriate to treat the patients as exclusively exhibiting classical OSA, or whether other abnormalities, including CSA, might have contributed to their breathing patterns. This notion has recently been considered by several research groups, such as Tkacova and colleagues[130,170], who concluded that in some patients with heart failure, OSA and CSA are part of a spectrum of periodic breathing that can shift over time. In another study by Hoffman and Schulman on the appearance of CSA after treatment of OSA, the authors indicate that there is evidence that many laboratories diagnose patients shown to have mixed apneas with OSA, treating these events as if they were obstructive, when in fact, they pathophysiologically may be closer related to CSA[131]. The authors suggest that by eliminating the contributing obstructive component after CPAP, therapy could expose central hypopneas and centrally originating mixed apneas that were classified as obstructive from the initial PSG. Therefore, eAMI detects periodic breathing without discriminating between CSA and OSA. This does not mean that eAMI can be a substitute for the clinical gold standard AHI, but a new source of evidence. Once periodic breathing has been identified, the estimated loop gain by the eAMI, or its periodicity, might open a new window of information. For instance, short cycles of periodic breathing are believed to be caused by peripheral chemoreceptors, while longer ones would have a more central origin. This will be further discussed in chapter 5.

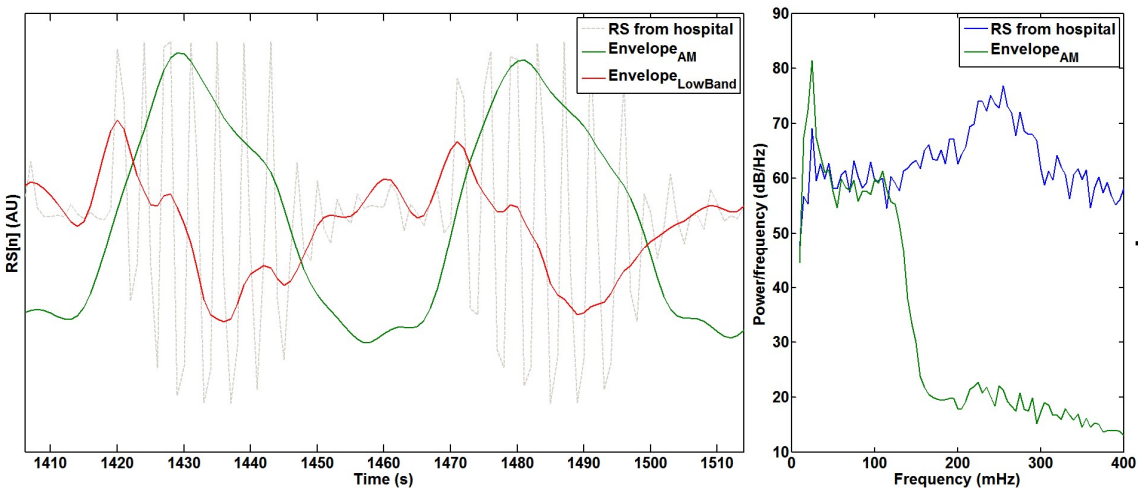

Figure 4-12 A respiratory signal that has been high-pass filtered by the device manufacturer.
This is an example of a respiratory signal, in which due to some pre-processing of the signal, the component at lower-frequencies is much smaller than the one recovered using a standard amplitude demodulator.

Regarding subclinical periodic breathing, we have also validated the usefulness of the proposed algorithm in both detecting and in quantifying periodic breathing events that were not scored at first by the sleep expert. Therefore, not only can we assert that the proposed method can detect periodic breathing at clinical levels and estimate the AHI, but it appears that it may also help in detecting and quantifying periodic breathing at subclinical levels. This can be particularly useful in cases in which the sleep expert has to reject episodes of apparent periodic breathing in which the duration of the central event was not long enough to be considered an apnea or a hypopnea by current scoring rules. Given the impaired prognosis associated with periodic breathing, such ability to detect both clinical and subclinical levels holds promise as a valuable tool for early diagnosis. Modulating indices of the respiratory signal or the relationship between lower and higher frequency components of the respiratory signal for detecting or qualifying periodic breathing have already been explored by other authors, e.g., Millar et al[140], Pinna et al[8,133,144] and Macey et al[142]. We have shown that the eAMI has some additional benefits, mainly in that it can be used to both detect and quantify periodic breathing, but also regarding simplicity. Finally, of all algorithms in the publications above, only that of Pinna et al[8,133,144] and the eAMI compute the envelope of the signal instead of using the low-frequency component. This might be an issue when comparing results from different respiratory signals (nasal airflow and thoracoabdominal motion), the same respiratory signals but different sensors (e.g. thoracoabdominal motion measured by inductance plethysmography or strain gauges), or finally, even the same sensors but different device manufacturers. This is for instance apparent in figure 4-12. In the case of this signal, when we received it from the hospital as it was recorded by the device, we could see that the component at the lower frequencies (the peak around 10 mHz) was indeed much smaller than the one recovered from the envelope. To show that the proposed method could be computed in different respiratory signals, we used different ones in each of the datasets, and when possible,

compared the results. The method by Pinna et al[8,133,144] is perhaps the one that shows the most similarities with eAMI. However, the former method also requires a preliminary phase in which the existence of periodic breathing has to be validated before quantifying it. The reason is that, by definition, the lung volume modulating index (LVMI) proposed by Pinna et al[8,133,144] is the normalised difference between the maximum and the minimum values of the instantaneous tidal volume at each of the periods of periodic breathing. Therefore, LVMI cannot be computed in the absence of these periods. Finally, we have shown that it is possible to obtain similar results with a much simpler envelope recovering technique: an AM demodulator. This also avoids the need for a preliminary phase in which the existence of periodic breathing has to be validated.

The eAMI is a very simple tool for detection and quantification of periodic breathing. It can reduce costs and thus resources needed to screen periodic breathing, and it is a good candidate for automated monitoring devices. The eAMI is inexpensive regarding computing resources: routines for the method were programmed in Matlab and the analysis of an entire 518 hours of dataset takes around 20 seconds using a commercial laptop running an Intel Core i7 (2627M@2.7GHz) with 8GB of RAM. The eAMI quantifies periodic breathing as a single event, where the amplitude of the oscillations of the respiratory signal is the evolving variable. This measure, beyond simply giving a quantitative measure as the AHI, offers qualitative information about periodic breathing and the loop gain associated. The use of the eAMI could thus help achieve a better understanding and an earlier diagnosis of periodic breathing in both clinical and research environments.

Chapter 5 - Modelling central and peripheral chemoreceptors hyperadditive interaction: implications for the occurrence of periodic breathing

In this chapter, we model the interaction between both peripheral and central chemoreceptors involved in respiration.

The classical interaction between chemoreceptors is the additive model. In that model, peripheral and central chemoreceptors do not interact in any significant way. Their contribution to the overall respiratory drive is modelled as additive. Currently, there seems to be evidence enough to support additive, hyperadditive, hypoadditive or hybrid effects on ventilation resulting from carotid-central chemoreceptor interactions (see the cross-talk discussion around the theme[29-31]). In this work, we develop a multiplicative alternative to model chemoreceptors interactions. Accepting that chemoreceptors modulate their input through either potentiation or blockade by adjusting the gain of the neural pathway that transports centrally driven respiratory signals, we propose a new mathematical framework in which the iteration is modelled as multiplicative. We ultimately show that this model predicts some of the observations related to periodic breathing and gives a plausible explanation to others.

This chapter is the conclusion of 4 years studying sleep-related periodic breathing at high altitude during prolonged stay. During this time, there were two key observations in periodic breathing hard to explain using an oscillation of increasing amplitude in additive models: the sudden sigh-driven occurrence of periodic breathing and the ability of either central or peripheral chemoreceptors to induce by themselves central apneas and periodic breathing without the intermediation of the other.

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Modelling central and peripheral chemoreceptors hyperadditive interaction: implications for the occurrence of periodic breathing.

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I. ABSTRACT

Rationale:

The interconnection between different ventilatory control neurones has led to controversial interpretations about the nature of their interdependence. There is enough evidence to support an additive, hyperadditive and hypoadditive effects on ventilation resulting from carotid-central chemoreceptor interactions[29-31].

Methods:

We propose a model to describe the interaction between peripheral and central chemoreceptors. In our model, chemoreceptors interact by modifying the gain of the neural pathway that transports the respiratory signals (hyperadditive interaction). The present paper includes modelling and simulations.

Results:

The analytical solution of the equations shows several experimental observations: 1) for a given pair of chemosensitivity and delay there is a particular amplitude of the perturbation that causes oscillations; 2) the frequency at which the system oscillates depends on the delay of the loop; 3) an increase in the drive is followed by a longer lasting oscillation.

Conclusions:

Despite conceptual simplicity of the model, it can reproduce the respiratory drive at stable and unstable conditions such as periodic breathing. The model also explains the sudden sigh-driven occurrence of periodic breathing, an event hard to explain using an oscillation of increasing amplitude in additive models.

II. INTRODUCTION

The control of breathing involves a rather complex system of neurones that regulate blood levels of O_2 and CO_2. Chemoreceptors are in charge of transducing the gaseous and pH signals from the blood into neural signals. Traditionally, chemoreceptors have been divided into two categories: peripheral and central chemoreceptors. The glomus cells of the carotid body constitute the primary peripheral chemoreceptors and are located at the bifurcations of the carotid arteries. They are the main arterial O_2 sensors but also react to CO_2 and pH levels in arterial blood[21]. The location of central chemoreceptors is more widespread in the medulla [as reviewed in [171]]. For many years, the prevailing view has been that CO_2/H^+ sensitivity occurred entirely via central chemoreceptors. There is now enough evidence to confirm that central chemoreceptors contribute for about two-thirds of the ventilatory response to CO_2/H^+ concentration changes, while the carotid chemoreceptors provide for the remaining third[27].

The most common model for the interaction of chemoreceptors is what has been called the Oxford model, in which ventilation is the sum of three components; central and peripheral chemoreflex drives and a ventilatory drive that depends on subject's state[2]. This model, depicted in Figure 5-1, features linear relations between ventilation and CO_2, and a feedback loop controlled by the chemoreceptors that maintain the right levels of arterial partial pressures $P_{aCO2}(t)$. A similar model could be assumed for cerebral partial pressure $P_{bCO2}(t)$ instead of $P_{aCO2}(t)$ considering different circulatory delays. $H_{lung}(s)$, is the transfer function of the lungs defining the response of the alveolar CO_2 partial pressure $P_{ACO2}(t)$ to the drive ($V_t(t)$, the neurological signals) through the mechanical movement of the lungs. An increase in the drive $V_t(t)$ means more minute ventilation which causes CO_2 to decrease. $V_t(t)$ represents the entire drive that reaches the lungs. It includes the entire chemoreceptor drive, $V_{chem}(t)=V_p(t)+V_c(t)$, where $V_p(t)$ is the peripheral chemoreceptor drive and $V_c(t)$ is the central chemoreceptor drive. They constitute the excitatory signals that stimulate the motor neurones producing breathing movements. It also has another component, $V_0(t)$, that depends on the state and it is often considered as constant. We then have

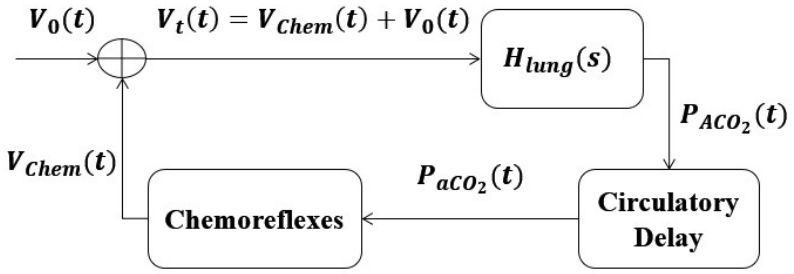

Figure 5-1 The "classical" chemoreceptor model
Ventilation $V_t(t)$ is the sum of two components; central and peripheral chemoreflex drives $V_{Chem}(t)$ and a ventilatory drive that depends on state $V_0(t)$. This model features linear relations between drive and CO_2 partial pressure. $V_{Chem}(t)$ and $V_0(t)$ constitute the excitatory signals that stimulate the motor neurones producing breathing movements. These are translated in the lungs $H_{lung}(s)$ into changes in partial pressures outside the lungs or P_{ACO2}. Chemoreceptors adapt the drive to new demands based on partial pressures around the chemoreceptors $P_{aCO2}(t)$. An similar model could be assumed for cerebral partial pressure $P_{bCO2}(t)$ instead of $P_{aCO2}(t)$ assuming different circulatory delays

$$V_t(t) = V_p(t) + V_c(t) + V_0(t) \quad (1)$$

Where $V(t)_{chem} = V_c(t) + V_p(t)$ and $V_0(t)$ is a ventilatory drive that depends on state. The equations that define the drive levels can be approximated in steady state by

$$V_p(t) = \begin{cases} G_p\left(P_{aCO_2}(t) - a_p\right) & if\ P_{aCO_2} > a_p \\ 0 & if\ P_{aCO_2} < a_p \end{cases}, \text{ and}$$
$$V_c(t) = \begin{cases} G_c\left(P_{bCO_2}(t) - a_c\right) & if\ P_{bCO_2} > a_c \\ 0 & if\ P_{bCO_2} < a_c \end{cases}, \quad (2)$$

where drives V_p and V_c are in liters per second [Ls^{-1}], G_p and G_c are expressed in litres per second and per millimetres of mercury [$Ls^{-1}mmHg^{-1}$] and define both the linear relationships between drives and partial pressures of CO_2 (arterial and cerebral partial pressures, expressed in millimetres of mercury [mmHg]). a_p and a_c are the peripheral and central apneic thresholds[172], or the minimum level of CO_2 below which breathing ceases and also expressed in millimetres of mercury [mmHg]. Units of the different components are shown in Table 5-1.

TABLE 5-1 UNITS OF THE DIFFERENT COMPONENTS OF THE MODEL

	V	G	P_{CO2}	a
Units	Ls^{-1}	$Ls^{-1}mmHg^{-1}$	mmHg	mmHg

V are the drives in liters per second; G, the gains in liters per second per millimeter of mercury; P_{CO2} the partial pressures in millimeter of mercury and finally, a, the apneic threshold also in millimeter of mercury.

One of the first works featuring this additive interaction was Grodins model for the chemical control of breathing[173]. Grodins model incorporated dynamic behaviours represented in linear second-order differential equations describing the dynamics of different tissues. Partial pressure of CO_2 (P_{CO2}) and partial pressures of O_2 (P_{O2}) around the locations of the chemoreceptors are the feedback signals used to adapt ventilation. Many later models have been developed using Grodins equations and the assumption that central and peripheral chemoreceptors do not interact with each other[96,172,174]. Nevertheless, recent evidence supports the interdependence between central medullary chemoreceptors and input from several sources including probable peripheral chemoreceptors. Studies show that CO_2 response from central chemoreceptors located in the retrotrapezoid nucleus (RTN) seem to be influenced by several synaptic inputs, with the carotid chemoreceptors being one among them[28]. This interconnection between different ventilatory control neurones has led to highly controversial interpretations about its nature. Currently, there seems to be evidence enough to support additive, hyperadditive, hypoadditive or hybrid effects on ventilation resulting from carotid-central chemoreceptor interactions (see the cross-talk discussion around the theme[29-31]).

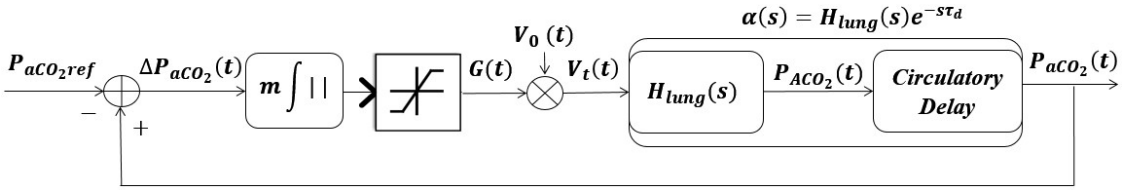

Figure 5-2 Proposed model.
In the proposed model, chemoreceptors adapt the gain G(t) (multiplicative interaction) of the neural pathway that transport the central drive $V_0(t)$ instead of adding drive to the signals coming from the central pattern generator. We assume in our model that positive gains are not possible. The drive is then $V_t(t)=V_0(t)G(t)$. Chemoreceptors sense partial pressures $P_{aCO2}(t)$, and compare them with a reference (or homeostatic) partial pressure $P_{aCO2ref}$. Depending on the difference between the actual and the reference value, chemoreceptors modify the gain of the neural pathway. This process behaves as an integrative process. m, represents the magnitude in which chemoreceptors can modify the gain of the circuit (chemoreactivity). $H_{lung}(s)$, is the transfer function of the lungs that turns drive $V_t(t)$ in alveolar partial CO_2 pressures [mmHg]. $\alpha(s)$ is the transfer function between drive and the arterial partial pressures. We have also defined $\Delta P_{aCO2}(t)= P_{aCO2}(t)-P_{aCO2ref}$.

In the present study, we set out to explore the possibility of a model in which chemoreceptors interact with each other by modifying the gain of the neural pathway that transports the respiratory signals, modelling hyperadditive interaction as a multiplication between both. We also analysed the implications this model has in explaining periodic breathing, characterised by instability in the respiratory pattern that exhibits an oscillatory behaviour with periods of hyperventilation followed by apneas or hypopneas[145].

III. METHODS

The proposed model is depicted in Figure 5-2. In the present work, we will consider a model in which only peripheral chemoreceptors are reactive in order to simplify its study. G(t) modifies the gain of the neural pathways modulating the motor neurones that control the respiratory muscles. Although chemoreceptors can sense P_{CO2} and P_{O2} in the arterial blood, in our simplified model, we will only contemplate the possibility of P_{CO2} sensing, i.e. P_{aCO2}. The limitations of doing so for the model will be further discussed. The output of the combination of respiratory drive $V_0(t)$ and the gain of the controller is the entire drive $V_t(t)$. The controller behaves as an integrative process in which the gain at any given time depends on the integral of the difference between the reference (homeostatic) partial pressure $P_{aCO2ref}$ and the partial pressure at the chemoreceptors. This integrative process models the way in which neurones adapt the excitability of a neural pathway by potentiation or blockade. When potentiation is applied, ventilation increases. When the stimulus is withdrawn, or blockade is used, ventilation decreases similarly. This adjustment runs until the difference between actual (P_{aCO2}) and reference ($P_{aCO2ref}$) partial CO_2 pressure is zero, indicating that the steady state level of ventilation is achieved. This process therefore naturally incorporates a certain inertia which also corresponds to the observed phenomenon "short-term potentiation"[175,176]. The rest of the components of the model are discussed hereunder.

A. Model Equations

Considering a respiratory system with two components, $\alpha(s) = H_{lung}(s)e^{-s\tau d}$ (the lungs transfer function and the circulatory delay) on the one hand and the respiratory drive controller on the other hand. The equation for the lungs transfer function can be derived from Grodins' model and can be simplified as a first order system

$$H_{lung}(s) = \frac{P_{ACO_2}}{V_t} = \frac{-G_l}{\tau_l s + 1} \tag{3}$$

where G_l is the lung gain and τ_l the lung delay[177].

It should be remarked that the negative static gain for $H_{lung}(s)$ in (3) implies that, as mentioned above, an increase in the drive $V_t(t)$ means more minute ventilation which causes partial CO_2 pressure to decrease.

The controller regulates the air flow to the lungs and hence the ratio at which CO_2 is being removed to maintain the necessary levels of partial CO_2. The controller adapts the gain G(t) depending on the levels of partial CO_2 pressure around the chemoreceptors P_{aCO2}. This adaptation occurs by modifying the gain in the feedback loop so that for a given drive $V_0(t)$, $P_{aCO2}(t)$ is kept at $P_{aCO2ref}$. The system is therefore ruled by:

$$P_{aCO2}(t) = [V_0(t)G(t)] * \alpha(t) = V_t(t) * \alpha(t) \tag{4}$$

where $*$ is the convolution, and $P_{aCO2}(t)$ is the arterial CO_2 partial pressure.

The control of the gain is ruled by the integrative process

$$G(t) = \begin{cases} m\int_{-\infty}^{t} \Delta P_{aCO2}(\tau)\,d\tau & if \quad \left[m\int_{-\infty}^{t} \Delta P_{aCO2}(\tau)\,d\tau\right] < 0 \\ 0 & if \quad \left[m\int_{-\infty}^{t} \Delta P_{aCO2}(\tau)\,d\tau\right] \geq 0 \end{cases}; \tag{5}$$

where $\Delta P_{aCO2}(t) = P_{aCO2}(t) - P_{aCO2ref}$. As it is physically impossible for $P_{aCO2}(t)$ to become negative, G(t) may not become positive thus leading to (7). m represents the magnitude in which chemoreceptors can modify the gain of the circuit. We will further analyze the behavior of the system for different values of m. $P_{aCO2ref}$ is the homeostatic value of $P_{aCO2}(t)$ and is taken equal to 40 mmHg[177]. The system is in steady-state when $P_{aCO2}(t)$ stops evolving and one then has

$$P_{aCO2}(t) = P_{aCO2ref}. \tag{6}$$

B. Model simulation

The model was implemented using Simulink in Matlab. The model was used to simulate experimental night breathing trials of 60 min. Each trial started with simulated resting human breathing during sleep. After 5 min, a sudden increase of 20% in $V_0(t)$ is introduced, such as

V_0(t=5min)=1.2V_0(t=0). To observe the influence of m and τ_d, two sets of simulation runs were performed for varying values of m and τ_d. The influence of the parameter on the duration of periodic breathing, the proportion of time spent in periodic breathing and the duty ratio were calculated using the eAMI method described in Chapter 4[109].

IV. RESULTS

A. Model response to a step

The response of the model to a step in the drive is further developed in Appendix A.1 to A.3. A sudden change on the drive is modeled as a perturbation $\Delta V = l$ at time t=0, i.e. $V_0(t) = V_c + lu(t)$ where u(t) is the Heaviside step function. It turns out that such a simple solicitation on the drive is equivalent to an additive step on the output of the integrator G(t) as shown in Appendix A, thus making linear analysis of the system possible. The output of the system, ΔP_{aCO2}(t), for is then given by (see appendix A)

$$\begin{aligned}\Delta P_{aCO2}(s) &= -\frac{lP_{aCO2ref}}{\alpha(s=0)V_c}\cdot\frac{\alpha(s)}{s - m(V_c + l)\alpha(s)} \\ &= \frac{lP_{aCO2ref}}{V_c}\cdot\frac{e^{(-s\tau_d)}}{\tau_l s^2 + s + m(V_c + l)G_l e^{(-s\tau_d)}}\end{aligned} . \quad (7)$$

This expression is used in the analysis below.

B. Estimation of the frequency of periodic breathing oscillations

Oscillations will occur whenever (7) has poles in the right hand half plane. In order to pursue the analysis, we consider the values of m(V_c+l)G_l, τ_d and τ_l for which poles are located on the imaginary axis. In that case, the poles are characterized by s=jω and satisfy (see developments in Appendix A.4)

$$0 = -\tau_l w^2 \cos(w\tau_d) - w\sin(w\tau_d) - m(V_c + l)G_l \text{ , and} \quad (8)$$

$$0 = -\tau_l w^2 \sin(w\tau_d) + w\cos(w\tau_d) . \quad (9)$$

Equation (9) gives ω, the frequency of periodic breathing for a given pair of delays τ_d and τ_l. Equation (8) gives the value of m(V_c+l)G_l for which the poles are located on the imaginary axis. For the sequel, we consider the smallest possible value of m(V_c+l)G_l for which a solution to (10) and (11) exists, i.e., whenever there are no other poles to the right of the imaginary axis. For instance in the case of τ_l=3.84 s and τ_d=12 s, we obtain ω=0.1003 rad s^{-1} or f=0.016 Hz. If for instance, if we consider τ_l=3.8s and τ_d=5s we get the a frequency of f=0.03Hz. Using values of V_c+l and G_l for a healthy subject (see Appendix B), we get m =0.0316 that will later be denoted m_0.

On can conclude that in first approximation, the frequency at which the system oscillates depends on the delays of the feedback loop.

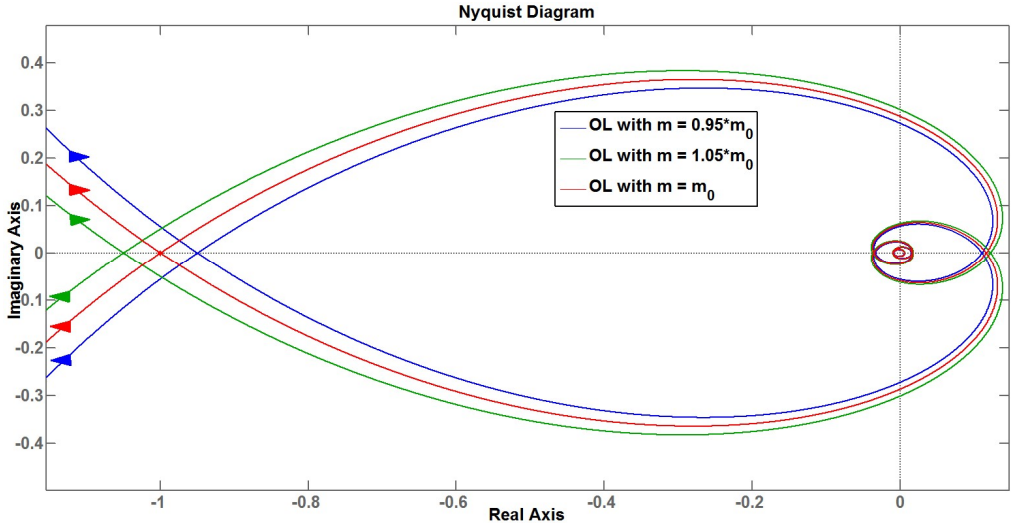

Figure 5-3 Nyquist diagram of the open loop (10) defining stability of the system for a given τ_d, τ_l, ω_0, and $(Vc+l)G_l$ and 3 difrent m

C. Model stability analysis

Finally, stability of the system can be studied applying Nyquist criterion on the open-loop[178]

$$\mathrm{OL(s)} = \frac{m}{s}(V_c + l)\alpha(s) = \frac{m}{s}(V_c + l)H_{lung}(\mathrm{s})e^{(-s\tau_d)} = -\frac{m}{s}(V_c + l)\frac{G_l}{\tau_l s + 1}e^{(-s\tau_d)} \quad (10)$$

Figure 5-3 depicts the Nyquist plot of the open loop for different values of m. One can conclude that for a given pair of chemosensitivity and delays, there is a particular amplitude of the open-loop gain and hence the perturbation l above which the system diverges. For perturbations below that threshold, the system does not diverge. Conversely, decreasing the drive can bring the system back to stability.

D. Model simulation

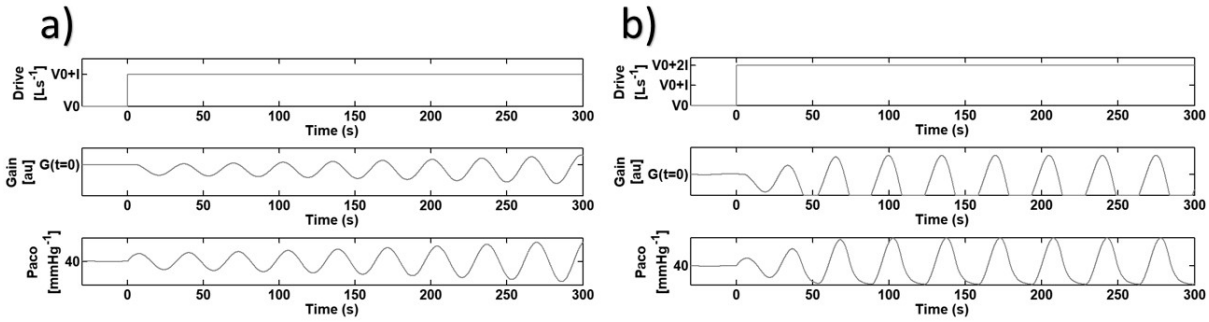

Figure 5-4 Response to sudden perturbation inducing periodic breathing
a) Response to a sudden increase in the drive. The system exhibits a diverging oscillation leading to saturation b) Response to a sudden increase in the drive twice the magnitude from a). The system exhibits a diverging oscillation with saturation occurring earlier.

We will illustrate the predictions of the model using Matlab Simulink, i.e. implementing the positivity constraint on the gain, and for the detection of the presence of periodic breathing and its frequency we will use the eAMI method described in Chapter 4[109]. Figure 5-4 depicts the response of the model to a sudden increase in the drive with m 15% above m_0. This illustrates that

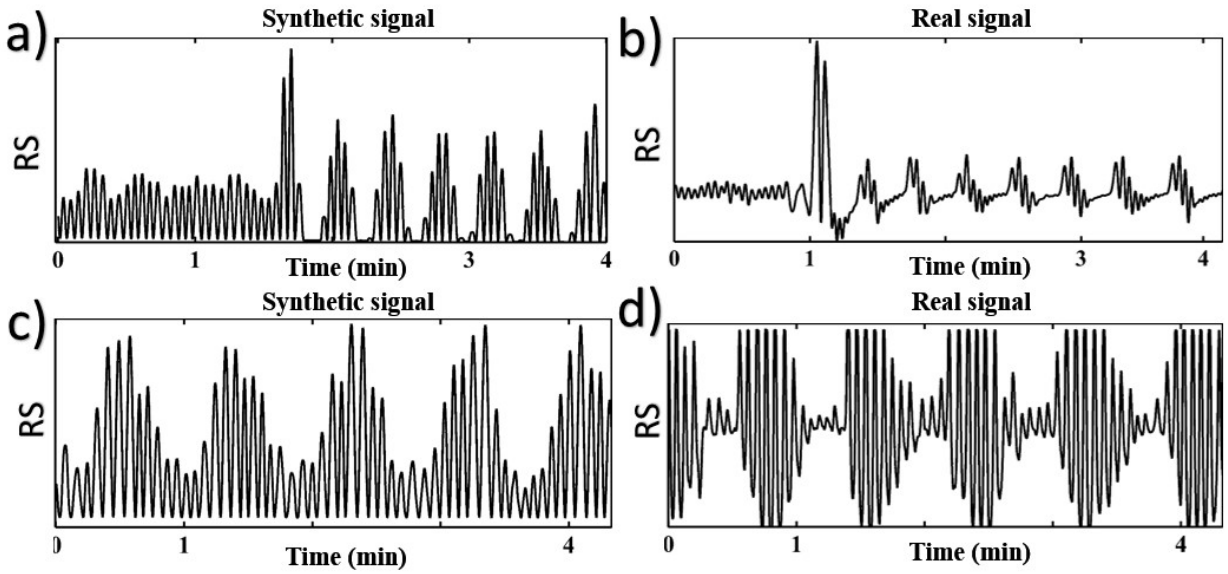

Figure 5-5 Synthetic periodic breathing compared with real Periodic Breathing.
a) Simulation of high altitude periodic breathing (τ_d=4.5 s); a respiratory signal where a sudden sigh triggers periodic breathing b) A portion of a real respiratory signal where a sudden sigh triggers periodic breathing. c) Simulation of periodic breathing at sea level (τ_d=12 s). d) A portion of a real respiratory signal taken at an altitude of 60 m exhibiting periodic breathing.

higher $m(V_c+l)G_l$ lead to a more severe divergence. The fact that the divergence is limited is due to the non-negativity constraint imposed on G(t).

C. Realistic Simulations

To simulate the movement of the lungs RS(t), the signal driving the muscle of the lungs is first simulated. The movement of the lungs is then obtained by integrating that signal. The signal driving the muscle of the lungs is obtained by multiplying G(t) with a sinusoidal signal having a frequency equal to the mean respiration frequency[146]. Natural variations of the respiration frequency are modelled as random variations on the frequency of the sinusoid. Those random frequency variations are modelled as Gaussian with a standard deviation of 0.03Hz[146]. Similarly, random variations on the amplitude are modelled as Gaussian with a standard deviation of 20%[146].

Figure 5-5 illustrates these more realistic simulations (synthetic signals) and similar real respiratory signals. Figure 5-5a shows an instance where the model starts to oscillate suddenly due to an isolated sigh in the signal modelled as a short duration pulse on $V_0(t)$ with 3 time the nominal amplitude of $V_0(t)$[179]. This is a phenomenon that can be observed in real periodic

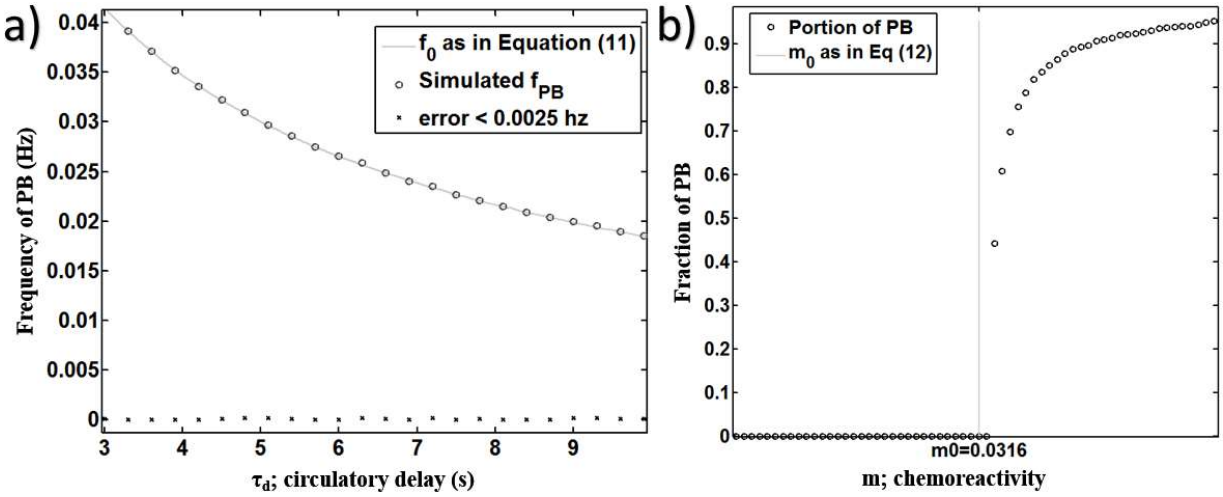

Figure 5-6 Results from model simulation.
a) Frequency of periodic breathing as a function of circulatory delay for a fixed chemoreactivity of m=1.05 m_0; b) Fraction of periodic breathing as a function of chemoreactivity m for a fixed circulatory delay of τ_d =5s.

breathing as illustrated in figure 5-5b. Fig 5-5c illustrates periodic breathing occurring for a larger loop delay (12s) corresponding to a situation at sea-level leading to a periodic breathing period of 60s as would be observed in heart-failure patients as seen in Fig 5-5d. This has to be compared to Fig 5-5a for which the loop delay was of 4.5s corresponding to a situation a high altitude. This also illustrates that the oscillation frequency depends on the delay of the loop as discussed above. Finally Figure 5-6 illustrate the effect of the reactivity and the delay on the output signal. As predicted by the Equations (8) and (9), Figure 5-6a shows how the frequency of oscillation depends on the delay of the loop for m=1.05*m_0. As can be seen, the oscillation frequency decreases as the delay increases.

To observe the influence of delay, τ_d, and m, simulation runs for varying τ_d, and m were performed. The duration of periodic breathing and the proportion of time spent in periodic breathing was then calculated using previously described method[109]. Fig 5-6b illustrates that for values of chemoreactivity larger than m_0, the system becomes instable and therefore periodic breathing appears. For values close to m_0 the simulation only exhibits clinical periodic breathing somewhat after the triggering event as a consequence of the increasing amplitude of the oscillation. This (and the limited duration of the simulation) causes the fraction of time spent in periodic breathing to be smaller. The larger the value of m_0, the more rapidly periodic breathing develops, and henceforth the fraction of time spent in periodic breathing gets closer to 1. This detections were done by means of the eAMI method described in Chapter 4[109].

V. DISCUSSION

A. Summary

In this paper, we model the control of respiration by assuming chemoreceptors control the gain of the system by adjusting the excitability of the neural pathways that transport respiratory signals

(multiplicative model), instead of adding a contribution to the drive (additive model). The model can explain stable respiration and reproduce periodic breathing. In the proposed model, stability is affected by:

- The chemoreactivity m, as the capacity of the chemoreceptors to modify the reactivity of the neural pathways; for a given delay, there is a threshold value of the loop gain, i.e. the combination of chemoreactivity, gain and disturbance, $m(V_c + l)G_l$, above which undamped oscillations (periodic breathing) occur. This behaviour corresponds to the most common hypothesis for the cause of instability in the chemoreceptor control feedback loop, i.e. the increased circulatory delay and loop gain[144].
- The delay in the transfer of information τ_d;

Although (7) has been used in the simulation, the saturation effect is not considered in the analysis. It is, however, clear that this threshold plays a key role in limiting the amplitude of the oscillations. When the system becomes unstable and thus starts to oscillate, the non-positive constraint on the gain prevents the gain to diverge, leading to a steady periodic breathing. This can be observed in Figure 5.6.

Finally, the theoretical analysis of the model is limited to sudden changes (step) in the drive. More complex situations have been analyzed on the basis of realistic simulations and provide similar results as what is observed in actual cases.

B. Properties of the model

One of the most remarkable properties of the model is the ability to reproduce periodic breathing once the conditions required for periodic breathing are met. Periodic breathing may have been considered as an exotic phenomenon that rarely occurs, but when the conditions are met, periodic breathing is sufficiently frequent and cannot be seen as an anomaly. As an illustration, a recent study showed that periodic breathing prevailed for the major part of the sleeping time during an entire 13-months experiment at high altitude for most of the participants[63]. Furthermore, using the model, it is possible to analyse the influence of delays and chemoreactivity, showing the direct influence of these parameters on periodic breathing occurrence and its behaviour.

Another noteworthy feature of the model is that it can reproduce the occurrence of sudden periodic breathing after a transient perturbation such as a sigh or a sudden change of the drive (real example in Figure 5-5b and simulated one in Figure 5-5a). To the best of our knowledge, this is the first model able to reproduce such behaviour.

Finally, the proposed model describes how the chemoreceptors add a drive in synchrony with the respiratory signal without complication: what they modify is the gain of the neural pathways that transport the respiratory signals.

C. Limitations of the model

In this model, we have only taken into account the influence of CO_2 on the control of respiration. Although it is known that peripheral chemoreceptors are also sensitive to O_2, in the present paper, we investigated a model based on the regulation of the gain rather than the sum of drives, which could explain respiratory control to some extent. O_2 could be modelled by having an antagonist effect on the chemoreceptors and the multiplicative effect as the one model with CO_2

D. Predictions of the model

The length of the cycles of periodic breathing is directly dependent on the delay in the transfer of information (Figure 5-6a), with longer cycles of periodic breathing occurring with longer delays. The proposed model can thus easily reproduce both periodic breathing with shorter periods, which occurs for example at high altitude; and longer-cycle forms of periodic breathing observed in patients suffering from different pathologies, e.g. chronic heart failure (CHF). It should be added here that periodic breathing at high altitude cannot easily be compared with periodic breathing in CHF patients. At high altitude, the trigger is hypoxia, and breathing can be stabilised by O_2 inhalation[56]. However, not all CHF patients are hypoxic, and in these cases, O_2 inhalation does not eliminate periodic breathing. It should be noted that in this simulation, we used P_{aCO2} as the feedback loop signal, what this model demonstrates is that a multiplicative interaction between chemoreceptors can reproduce periodic breathing; in which the length of the cycle is dependent on the delay in the loop. The time delays needed to reproduce periodic breathing at the frequency observed at high altitude are of the order of 3 to 5 seconds, whereas delays of the order of 10 to 15 seconds were needed for long cycles forms of periodic breathing. These magnitudes are very close to the average circulatory delay of 12.4 seconds calculated by Ahmed and co-workers[180]. Time delay between central and peripheral chemoreceptors have also been measured in dogs and found to be of the order of 11 seconds. Furthermore, previous studies in humans showed that the time constant for the ventilatory response of central chemoreceptors was one order of magnitude greater than the one from the carotid bodies[181]. These orders of magnitude are consistent with the idea that long-cycle forms of periodic breathing are likely due to central chemoreceptors[144,151], whereas periodic breathing at high altitude, with shorter cycles, is mainly due to peripheral chemoreceptors as supported by the evidence that carotid body denervation prevents periodic breathing in hypoxia[182]. The increased cardiac output observed at high altitude can also shorten the delay, which, together with the relation between the length of the cycles and the circulatory delay, can also explain why the length of the cycle shortens at higher altitudes.

Our model also predicts more stability with shorter delays, meaning shorter periods of periodic breathing. Such a relation has been recently observed in a dataset of polysomnography records obtained at high altitude in Antarctica[63].

Finally, the proposed model predicts with a destabilizing effect of a sudden increase ($l > 0$) in drive while a sudden decrease ($l < 0$) has a stabilizing effect, which is an effect that has been widely observed in sleep-wake transitions[183]. This destabilizing effect of the drive has also been observed during sleep at high altitude[184].

E. Mechanism

There is enough evidence to support interconnection between central chemoreceptors and sympathetic activation: central chemoreceptor stimulation induces sympathetic nerve discharge (SND) in a burst, synchronised with respiration; whereas lesion of the ventrolateral medullary surface attenuates phrenic nerve discharge and the respiratory-related oscillations SND[185]. Excitation of the rostral ventrolateral medulla (RVLM) and brain stem nuclei in the dorsomedial medulla by peripheral chemoreceptors neurones is also widely accepted[22,186]. In the model proposed by Moreira et al.[41], the excitatory effect of partial CO_2 pressures around RVLM sympathoexcitatory neurones results either from the intrinsic chemosensitivity of these cells or from the activation of the pH-sensitive interneurones located in the RTN. In their work, they attribute the respiratory modulation of SND to two processes: active inhibition by GABAergic neurones located in the caudal ventrolateral medulla (CVLM) and disfacilitation of the retrotrapezoid nucleus neurones (RTN). This localised interconnectivity between chemoreactivity and sympathetic activity also suggests that peripheral and central chemoreceptors might interact. Peripheral chemoreceptors can theoretically reach vast areas of the brain stem, which could in itself be a chemosensitivity network; and central chemoreceptors can interact with peripheral ones[22]. This has led to the assumption that interaction between both might also be of other forms beyond additive, namely hyperadditive, hypoadditive or even a hybrid model (see the cross-talk discussion around the theme[29-31]).

F. Gain control and sudden infant death syndrome

Although still debated, the sudden failure of the respiratory system in infants leading to death, called sudden infant death syndrome (SIDS), seems to be related to the development of the respiratory system during infancy[22]. Despite its obvious importance for survival, ventilatory control is immature at birth. Carotid bodies do not seem to be mature enough, which translates in a non-fully functional carotid chemoreceptor sensitivity to O_2[187], which, when challenged with hypoxia, reacts with a relatively weak ventilatory response[188]. It has been suggested that the development of the peripheral chemoreceptors is critical in the final maturation of the respiratory system[189]. Periodic breathing and failure to arouse from apneic events have also been suggested as likely causes for SIDS[190,191]. Given the epidemiology of SIDS, in which most of the deaths

occur 2-4 months after birth, we might consider that a failure occurs when the mature chemoreceptors start controlling the gain of the circuit. In the proposed model, this process of tuning the proper gain rather than adding drive might lead to a total temporary blockade of the neuronal pathways that transport the respiratory signals, which could certainly explain SIDS as a system failure in which the blockade reaches a point of no return.

VI. CONCLUSIONS

The current paper presents a model of the chemical control of breathing based on a multiplicative central-peripheral interaction. The proposed equations model chemoreceptor reactivity as the magnitude in which chemoreceptors can modify the gain of the feedback loop. This model can both reproduce short-cycle periodic breathing, which occurs in response to hypoxia, and long-cycle periodic breathing, as observed in different pathologies. In the model, the length of the cycle depends directly on the delay. The model is also able to reproduce sudden occurrences of periodic breathing caused by a perturbation such as a sigh, a phenomenon difficult to explain with previous models. The interactions between central and peripheral chemoreceptors are still debated in the current literature. However, multiplicative models in which peripheral chemoreceptors can amplify the reaction of central ones and vice versa, have been previously proposed[18]. The scope of this paper is not to further deepen the debate, but rather accept the possibility and develop the mathematical model for a better understanding of its implications. As Forster and Smith pointed out, if we assume that carotid body chemoreceptors can modulate the gain of the central chemoreceptors, we should no longer consider central and peripheral chemoreceptors as independent. In their words, “rapid modulation of the gain of the central chemoreceptors could be of particular importance in understanding ventilatory control in the face of transient stimuli such as in sleep apnea or in conditions in which carotid body chemoreceptor activity is known to be upregulated such as heart failure or chronic hypoxia”[27]. To the best of our knowledge, this is the first work to provide a mathematical model to better understand this possibility.

APPENDIX A: BEHAVIOUR OF THE SYSTEM

1. Introduction

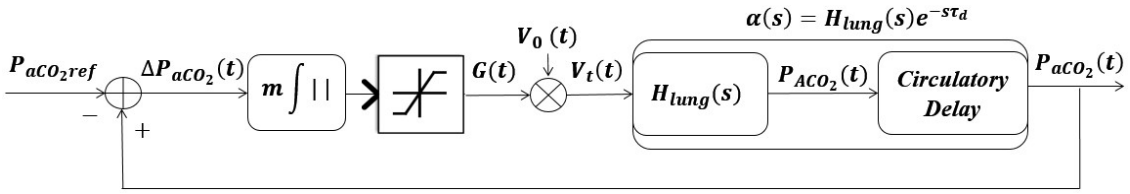

Figure 5A-1 A canonical representation of the proposed model
This is the same graphs as Figure 5-2

The system is ruled by (6), (7) copied here for convenience

$$P_{aCO2}(t) = [V_0(t)G(t)] * \alpha(t) = V_t(t) * \alpha(t) \tag{A1}$$

where $*$ is the convolution, and $P_{aCO2}(t)$ is the arterial partial CO_2 pressure. Defining $\Delta P_{aCO2}(t) = P_{aCO2}(t) - P_{aCO2ref}$, the control of the gain is ruled by (7)

$$G(t) = \begin{cases} m\int_{-\infty}^{t} \Delta P_{aCO2}(\tau)\,d\tau & if \quad \left[m\int_{-\infty}^{t} \Delta P_{aCO2}(\tau)\,d\tau\right] < 0 \\ 0 & if \quad \left[m\int_{-\infty}^{t} \Delta P_{aCO2}(\tau)\,d\tau\right] \geq 0 \end{cases}, \tag{A2}$$

where m is the chemoreceptor reactivity, a constant that tries to model the level of excitability of the chemoreceptors, or the magnitude in which they can modify the gain.

2. Behaviour of the control loop for a constant input

Assuming a constant input $V_0(t) = V_c$, the system is linear and therefore, for the open loop equation we have

$$P_{aCO2}(s) = \varepsilon(s)\frac{m}{s}V_c\alpha(s), \tag{A3}$$

in closed-loop, we have then

$$\varepsilon(s) = P_{aCO2}(s) - \frac{P_{aCO2ref}}{s}, \tag{A4}$$

then

$$P_{aCO2}(s) = \left(P_{aCO2}(s) - \frac{P_{aCO2ref}}{s}\right)\frac{m}{s}V_c\alpha(s). \tag{A5}$$

Rearranging, we have

$$P_{aCO2}(s) = -\frac{mV_c\alpha(s)}{s - mV_c\alpha(s)}\frac{P_{aCO2ref}}{s}. \tag{A6}$$

Using the final value theorem,

$$\lim_{t\to\infty} P_{aCO2}(t) = \lim_{s\to 0} sP_{aCO2}(s) = P_{aCO2ref}.$$

The output of the system, if stable, is equal to $P_{aCO2ref}$. This is of course expected as, thanks to the integrator in the loop, one has a zero static error.

3. Behaviour of the control loop for a sudden change in the drive

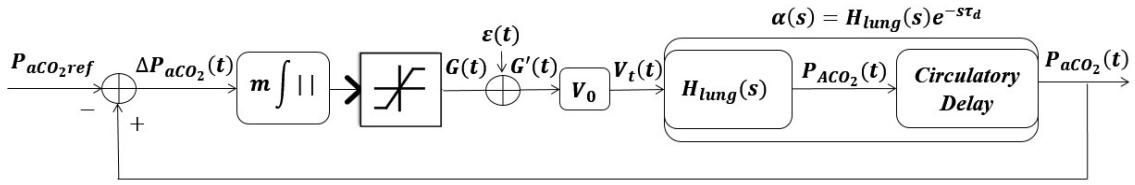

Figure 5A-2 A canonical representation of the proposed model
This is the same graphs as Figure 5A-1 but we have added the possibility of an input at G(t).

A sudden change in the drive $V_0(t) = V_c + l\ u(t)$ (figure 5A-1) is equivalent to a step on $G'(t) = G(t) + \varepsilon\ u(t)$ (figure 5A-2) where u(t) is the Heaviside step function. We now have to determine ε such that the same effect is achieved.

We consider two instances of the closed loop system (figure 5A-2), one right before the change in the drive, denoted by CL^- where the gain $V_0 = V_c$ and another right after the perturbation, denoted by CL^+, where the gain $V_0 = V_c + l$. In steady state, the only difference between the two instances CL^- and CL^+ is the value of the gain G (t), denoted respectively G^- and G^+. As thanks to the presence of the integrator there is no steady state error, we have

$$G^- = \frac{P_{aCO2ref}}{\alpha(s=0)V_c} - \varepsilon^-,$$

$$G^+ = \frac{P_{aCO2ref}}{\alpha(s=0)(V_c + l)} - \varepsilon^+, \qquad \text{(A7)}$$

To have $G^- = G^+$ one must have for t>0, $\varepsilon^+ = 0$ in order to correspond to the actual system and hence for t<0, $\varepsilon^- = -\frac{lP_{aCO2ref}}{\alpha(s=0)V_c(V_c + l)}$

So, at t=0, ε(t) makes a step

$$\varepsilon(t) = -\frac{lP_{aCO2ref}}{\alpha(s=0)V_c(V_c + l)}u(t)\ . \qquad \text{(A8)}$$

This shows that a sudden change in the multiplicative input $V_0(t)$ equals to a sudden additive change in G(t).

The transfer function between ε(t) and $\Delta P_{aCO2}(t)$ is readily obtained as

$$H(s) = \frac{\Delta P_{aCO2}(s)}{\varepsilon(s)} = \frac{(V_c + l)\alpha(s)}{1 - \frac{m}{s}(V_c + l)\alpha(s)}. \qquad \text{(A9)}$$

From here, obtaining $\Delta P_{aCO2}(t)$ due to the sudden change in the gain is immediate

$$\Delta P_{aCO2}(s) = H(s)\varepsilon(s) = -\frac{lP_{aCO2ref}}{\alpha(s=0)V_c}.\frac{\alpha(s)}{s - m(V_c + l)\alpha(s)}. \quad \text{(A10)}$$

Using the final value theorem,

$$\lim_{t\to\infty} \Delta P_{aCO2}(s) = \lim_{s\to 0} s\Delta P_{aCO2}(s) = 0$$

which shows that the static error of the system is zero, as expected due to the presence of the integrator in the loop.

4. Calculus of m_0 and ω_0

$m_0(V_c+l)G_l$ is defined as the smallest gain for which poles are on the imaginary axis. Any value of the gain above $m_0(V_c+l)G_l$ will lead to periodic breathing. We then define ω_0 as the resonant frequency of such system for a gain $m_0(V_c+l)G_l$.

The frequency response of $\Delta P_{aCO2}(s)$ is obtained by substituting s=jω in

$$\begin{aligned}\Delta P_{aCO2}(s) &= -\frac{lP_{aCO2ref}}{\alpha(s=0)V_c}.\frac{\frac{-G_l}{\tau_l s+1}e^{(-s\tau_d)}}{s - m(V_c+l)\frac{-G_l}{\tau_l s+1}e^{(-s\tau_d)}}\ ; \\ &= \frac{lP_{aCO2ref}}{V_c}.\frac{e^{(-s\tau_d)}}{\tau_l s^2 + s + m(V_c+l)G_l e^{(-s\tau_d)}}\end{aligned} \quad \text{(A11)}$$

yielding

$$\Delta P_{aCO2}(j\omega) = \frac{-lP_{aCO2ref}}{V_c}\frac{1}{-\tau_l\omega^2 e^{(j\omega\tau_d)} + j\omega e^{(j\omega\tau_d)} + m(V_c+l)G_l}\ . \quad \text{(A12)}$$

$m_0(V_c+l)G_l$ and ω_0 are defined by the poles of $\Delta P_{aCO2}(\omega)$ for a given set of parameters (G_l, V_c, τ_l, τ_d). $m_0(V_c+l)G_l$ and ω_0 thus satisfy

$$\begin{aligned}&-\tau_l\omega_0^2 e^{(j\omega_0\tau_d)} + j\omega_0 e^{(j\omega_0\tau_d)} + m_0(V_c+l)G_l = 0 \\ &-\tau_l\omega_0^2\left[\cos(\omega_0\tau_d) + j\sin(\omega_0\tau_d)\right] + j\omega_0\left[\cos(\omega_0\tau_d) + j\sin(\omega_0\tau_d)\right] = -m_0(V_c+l)G_l\end{aligned} \quad \text{(A13)}$$

Separating the real part from the imaginary part we find

$$0 = -\tau_l\omega_0^2\cos(\omega_0\tau_d) - \omega_0\sin(\omega_0\tau_d) - m_0(V_c+l)G_l \text{ , and} \quad \text{(A14)}$$

$$0 = -\tau_l\omega_0^2\sin(\omega_0\tau_d) + \omega_0\cos(\omega_0\tau_d)\ . \quad \text{(A15)}$$

Both equations have an infinite number of solutions and the solution for which m_0 is the smallest is selected.

Equation (A15) solely defines the frequency of periodic breathing for a given pair of delays. For instance in the case of τ_l=3.84 s and τ_d=12 s, the resonant frequency occurs at ω_0=0.1003 rad s^{-1} or f_0=0.016 Hz or the equivalent of transient oscillations in ventilation of a cycle duration of 62.5s. These are consistent with the oscillation periods observed in heart failure

patients[8-11]. If we now set τ_l=3.8s and τ_d=5s, we get the resonant frequency occurring at f=0.03Hz, which is equivalent to a periodicity of approximately 33s. These cycle durations are consistent with the oscillation observed in healthy subjecs exposed to high-alitidue[3-7].

Note that, for gains larger than $m_0(V_c+l)G_l$, the model becomes unstable and the threshold on the gain G(t) limits the amplitude of the oscillations, which also affect the frequency of these oscillations. The calculus here above can in that case not be used.

APPENDIX B: SIMULATION PARAMETERS

Parameter values as a starting point for the simulations, corresponding to a healthy subject

- V_{lung}=2.5L
- K_{C02}=0.0065mmHg^{-1}
- $\dot{V}_E$=0.12Ls^{-1}
- $\dot{V}_D$=0.03Ls^{-1}
- P_{ICO2}=0mmHg
- $P_{aC02ref}$=40mmHg
- $\dot{Q}$=0.1Ls^{-1}.
- τ_d =5s

Introducing these values in

$$G_l = \frac{P_{aCO2ref} - P_{ICO2}}{\dot{V}_E - \dot{V}_D + 863\dot{Q}K_{CO2}} \tag{16}$$

and in τ_l (the lung delay)

$$\tau_l = \frac{V_{lung}}{\dot{V}_E - \dot{V}_D + 863\dot{Q}K_{CO2}}, \tag{17}$$

where P_{ICO2} is the CO_2 partial pressure of inspired CO_2 [mmHg], $\dot{V}_E$ and $\dot{V}_D$ are the minute and dead spaces ventilations [Ls^{-1}], $\dot{Q}$ is the cardiac output [Ls^{-1}], K_{CO2} is the slope of dissociation curve of CO_2, and finally V_{lung} is volume of the lungs [L] yields

- τ_l=3.84s
- G_l=61.44Ls^{-1}mmHg^{-1}

We will also set the values for l and V_c such that

- V_c=0.1Ls^{-1}
- l+V_c=0.12Ls^{-1}

Chapter 6 - Conclusions and future research

This work summarises four years of study around sleep-related periodic breathing. There are many aspects regarding periodic breathing that remain research questions. In this study, we have tried to bring an answer to some of them. We could divide this work into two major blocks. In the first one we derived conclusions from the observation of periodic breathing under different conditions and in the second we tried to apply engineering methods for its better understanding.

I. THE OBSERVATION OF PERIODIC BREATHING

As pointed out by Bloch et al.[6], very few studies regarding periodic breathing and adaptation to hypobaric hypoxia have been performed, and there seems to be some controversy about the results. While it is widely accepted that an increase in altitude is correlated with an increase in the occurrence of periodic breathing[6,16], the magnitude, the time course and the altitude of occurrence differ markedly between studies. There are some conflicting results on the persistence of periodic breathing over successive nights. The real time of adaptation to high altitude regarding periodic breathing remains elusive. Using the unique long-term exposition to hypoxia at the Antarctic base Concordia, we were the first to be able to report changes in breathing stability after 13 months. Antarctica, certainly the most remote area of the world, is also an excellent example of an extreme environment: isolation, sensorial deprivation, hostile outside environment (deadly), a long-term mission with limited to no evacuation possibilities, and one of the most determining factors, hypoxia.

The main goal of our first field study was to provide new insights into the long-term effects of hypobaric hypoxia, after what is usually considered the acute phase of adaptation[48,49]. We know from the literature that high-altitude sojourns experience periodic breathing. Still, some aspects regarding periodic breathing remain unresolved or even wrongly assumed. For instance, it is often thought that periodic breathing is a transitory difficulty mountaineers have to deal with during acclimatisation. In fact, up to our knowledge no one had reported the persistence of periodic breathing beyond several weeks. Long-term isolation conditions at the Antarctic base Concordia offered us the perfect setup to observe the evolution of periodic breathing during a

whole year. Our most significant finding in this experiment was that during the entire 13-month campaign, for most of the participants, periodic breathing prevailed for the major part of sleeping time, despite partial restoration of SpO_2 together with the absence of AMS. This observation, for instance, is consistent with the hypothesis that acclimatisation improves oxygen saturation despite the persistence of periodic breathing[6,64] but contradicts the idea that a positive association between AMS and AHI might be due to a periodic breathing contribution to AMS[60,77].

Regarding the prevalence of periodic breathing and hypoxic exposure, there are some conflicting results. Some groups have reported an increase of periodic breathing during acclimatisation to hypoxia[6,65], whereas others reported decreases[56,66] or no changes[73]. However, it is challenging to compare those studies because of different designs and settings. Many of the studies mentioned above were part of mountaineer expeditions with differences in ascent rates and dynamically changing environments which could impact daily energy expenditure demands and sympathetic activation. Thanks to the steady confinement conditions at Concordia, we were able to observe changes in periodic breathing maintaining other parameters like altitude or physical demands constant. Despite those more controlled conditions, we also noted that periodic breathing did in fact not follow any apparent trend when observing long-term exposure. In fact, results showed within the same participant in different repeated measures both episodes of increasing and decreasing periodic breathing. Therefore, our experiment did not only contradict the original idea that the amount of periodic breathing due to hypobaric hypoxia in sleep reduces over time[52,56], but also suggested that perhaps it was also affected by other factors beyond altitude, time of exposure, subjects' physical condition, smoking habit, age or BMI. Our results were more in line with earlier hypobaric chamber studies reporting this lack of trend[73].

In an attempt to explain the observed variability among subjects and measures, we looked retrospectively among different cofactors for an explanation, finding a potential cofactor: mean apnoea-hypopnea index scores were positively correlated to mean exercise time. Although an unexpected result, we could identify several mechanisms to explain this interaction. As previously discussed [chapter 3, page 36], sleep-related periodic breathing may be influenced, among others, by regular physical activity via chemoreceptor sensitivity, since several lines of evidence suggest that chemoreceptors play a major role in acclimatisation to hypoxia[18]. To our surprise, the question whether exercise (i.e. physical activity) *per se* may affect nocturnal periodic breathing during hypoxia had never been explored before. Given that high altitude expeditions are characterised by strenuous physical demands, this question was for us of obvious interest. It is accepted that exercise enhances chemoreactivity and considering that altered chemoreactivity is involved in the control of respiration during exercise and that it may also be a critical factor in the development of periodic breathing, exercise during hypoxia could influence to some extent nocturnal periodic breathing. While the correlation we observed between mean apnoea-hypopnea

index scores and mean exercise time was interesting, the retrospective analysis was not enough to draw any conclusions. Therefore, a second "controlled" study was carried out to limit the number of cofactors from the Concordia Station, including possible differences between groups and other environmental (seasonal variation, light, temperature) and psychological (intense isolation from Antarctica study) variables. We carried out this clinical study in partnership with the Jozef Stefan Institute in Ljubljana, the University Clinical Centre in Ljubljana and the Swedish Aerospace Physiology Centre of the Royal Institute of Technology in Stockholm. The primary goal of this new controlled Acute Phase study was not to replicate Concordia conditions but to limit the number of possible cofactors.

The principal finding of this second investigation was that indeed mean apnoea-hypopnea index scores were also positively correlated to mean exercise, as AHI indexes were higher in the exercise group compared to the control group. Both combined results seemed to support then that exercise *per se* affected night SpO_2 concentrations and AHI index acutely in both hypobaric and normobaric hypoxic environments, regardless of habituation. However, those results should still be analysed taking into consideration several factors. For instance, one could argue that in the experiments discussed in Chapter 3, baseline fitness or self-adherence to perform a regular physical activity may also have influence results or distributed both the two groups in natural responders and not responders. Although having controlled exercise routines would have been more rigorous, the fact that individuals were not at Concordia acting primarily as research subjects made it not feasible. We should also take into account differences between both studies that could have indeed played a significant role in the results: variances in study design, exercise stratifications, environmental and psychological variables. We look forward seeing new research improving possible flaws of our setups.

I would like to finish this part, mentioning something that our study seems to show strongly: the presence of interindividual differences in the results, suggesting the existence of responders and non-responders. Furthermore, beyond some interindividual differences in the development of periodic breathing, we also saw a correlation between the length of the period of periodic breathing and the AHI, meaning that participants exhibiting shorter cycles of periodic breathing also had fewer apneic/hypopneic events per hour. The length of the period of periodic breathing could be for instance related to the speed of information within the chemoreceptor feedback loop. Higher stability of the respiratory control system and short lung-chemoreceptor delays seem to be associated[96]. Since in our experiment altitude was the same for every subject and the frequency of periodic breathing and heart rate were not correlated, we speculate that a certain lung-chemoreceptor delay 'phenotype' might at least to some extent explain the existence of responders and non-responders. This observation does not prove cause and effect between the number of apnoeic/hypopneic events and the length of the periodic breathing cycle, and therefore more

studies should be performed. Having said that, if we could find a way to discern between responders and non-responders, we could also do a better assessment of the ability of subjects to resist and perform under hypoxic conditions. The influence of long-term hypoxic exposure on nocturnal sleep and breathing remains a concern when the exposure is inevitable (military scenarios, research expeditions, future planetary habitats), especially considering that prolonged exposure negatively affects brain function, performance, cognition and subjective alertness following poor sleep during high altitude sojourns[62]. Although there are still some controversial results regarding the influence of long-term exposure to hypobaric hypoxia on sleep quality[16,54,60], it is widely accepted that periodic breathing decreases the quality of sleep and therefore daytime performance. At high altitude, people are often exposed to decreased productivity and increased probability of error as a result of poor sleep.

II. QUANTIFICATION, DETECTION AND MODELLING: THE ENGINEERING APPROACH

When observing periodic breathing from an engineer's perspective, the resemblance between the oscillatory behaviour of the respiratory signal under periodic breathing and amplitude modulated signals is striking. We tried to develop methods based on our engineering knowledge to understand better and quantify the process behind periodic breathing. It was also apparent to us that the symmetry and stability behind the modulation of the respiratory signal observed during periodic breathing looked too seamless to be explained by a succession of single respiratory events. Nowadays, in clinical environments this is still the case: by using the AHI, periodic breathing is being characterised by the number of apnoeic/hypopneic events instead of a phenomenon in which the amplitude of the respiratory signal is being modulated. The main goal of our first engineering approach was to provide a new tool for the early and easy diagnose of nocturnal periodic breathing. Therefore, we looked at the familiar concept of modulating indexes to see if more information could be obtained from the respiratory signal during periodic breathing. We came up with the eAMI, an index between an estimation of both the amplitude of the modulating and respiratory signals. The eAMI proved itself to be a very simple tool for the detection and quantification of periodic breathing. The use of the eAMI could thus help achieve a better understanding and an earlier diagnosis of periodic breathing in both clinical and research environments. This measure, beyond simply giving a quantitative measure like the AHI, offers qualitative information about periodic breathing and the associated loop gain. This descriptive capability might help us to unravel further how this phenomenon evolves over time by assessing how loop gain changes with sleep state or under the effects of different interventions. A quantifying tool that is correlated with loop gain might facilitate our understanding of the processes involved in its development and help monitor certain patient categories in clinical

settings[39, 128] as well as to contribute improving early diagnosis and treatment of underlying diseases.

To prove its validity, this new index was tested later on different real datasets. The first one was our experimental polysomnography data from the Antarctic base Concordia. The second were true clinical data from various hospital settings. In our experimental data (Concordia), our new method was not only helpful for us to easily score the severity of periodic breathing, but also help us to unmask for instance the significant correlation between the length of the period of periodic breathing and the AHI at high altitude. This observation, for example, was achieved by the ability of our new method to run tests in an automated way.

On our clinical data, the proposed method detected in some patients a strong periodicity resembling that of periodic breathing in cases in which the sleep expert only observed obstructive events. This observation raises the question whether it is appropriate to consider these patients as exclusively OSA, or whether other abnormalities might have contributed to their breathing patterns. This notion is not new and has been discussed by several research groups, such as Tkacova and colleagues[130,170], who concluded that in some patients with heart failure, OSA and CSA are part of a spectrum of periodic breathing that can shift over time. In another study by Hoffman and Schulman[131] on the appearance of CSA after treatment of OSA, the authors indicate that there is evidence that many laboratories diagnose patients shown to have mixed apneas with OSA, treating these events as if they were obstructive, when in fact, they pathophysiologically may be closer related to CSA[131]. eAMI is capable then of detecting this periodical instability beyond CSA, or OSA and once periodicity has been identified, it might help doctors providing better care beyond solutions to decrease the number of obstructive events.

Regarding subclinical periodic breathing, we have also validated the ability of the proposed algorithm in both detecting and in quantifying periodic breathing events that were not scored at first by the sleep expert. Therefore, not only can we assert that the proposed method can detect periodic breathing at clinical levels and estimate the AHI, but it appears that it may also help in detecting and quantifying periodic breathing at subclinical levels. This possibility can be particularly useful in cases in which the sleep expert has to reject episodes of apparent periodic breathing because the duration of the central event was not long enough to be considered an apnea or a hypopnea by standard scoring rules. Given the impaired prognosis associated with periodic breathing, such ability to detect both clinical and subclinical levels holds promise as a valuable tool for early diagnosis. Future research should nevertheless define which levels of subclinical periodic breathing are of clinical interest.

The eAMI is a very simple tool for detection and quantification of periodic breathing. Moreover, we believe it can reduce costs and thus resources needed to screen periodic breathing.

We could not have finished this work without finding a possible explanation for the processes involved in the genesis of periodic breathing. The similitude between the oscillations seen in periodic breathing and those found in unstable human-made feedback control systems has led to the idea that periodic breathing might indeed be caused by instability in the regulation of breathing[19]. In general, the application of mathematical models has resulted in significant advances in the understanding of the control of ventilation. In the most extended model, it is assumed that periodic breathing is originated as an instability caused by the combination of a delay in the respiratory control loop together with an increased loop gain. In this model, periodic breathing is often seen as an increasing oscillation that ultimately leads to a continued instability on the respiratory signal. In our view, this seemed to be a clear misconception. It only required a quick look at a respiratory signal in which periodic breathing was present to realise that most often periodic breathing started after a sigh, for instance. We had the impression when looking at our Antartica dataset, that this model could not fully give an answer to periodic breathing at high altitude. Another general misconception of most of the mathematical models is considering periodic breathing as a rather exotic or uncommon event. The truth is that under the necessary condition, periodic breathing becomes a relatively common phenomenon. Finally, it was hard for us to believe that in an additive model for the interaction of the chemoreceptors, periodic breathing could happen just by the modulation effect of one of them. If periodic breathing could happen due to the influence of peripheral chemoreceptors, why would peripheral chemoreceptor denervation then not necessarily cause periodic breathing to disappear. In the most extended model peripheral and central chemoreceptors did not interact, adding both independently to the drive. Our observations of the periodic breathing signal showed somehow that perhaps some non-linear interactions could be behind it. In fact, this is not a new idea. Other interactions between central and peripheral chemoreceptors are still debated in the current literature. We looked at other models, and we thought that multiplicative models in which peripheral chemoreceptors can amplify the reaction of central ones, and vice versa could, for instance, explain those observations[18]. This idea was for example suggested by Forster and Smith. According to them, we should no longer consider central and peripheral chemoreceptors as independent. Rapid modulation of the gain of the central chemoreceptors could explain ventilatory control behaviour in the face of transient stimuli such as in sleep apnea or in conditions in which carotid body chemoreceptor activity is known to be upregulated[27]. Without going too much again into detail, some observations seem to support the idea that there are areas of interconnection between both central and peripheral chemoreceptors [chapter 6, page 70]. Peripheral chemoreceptors can theoretically reach wide areas of the brain stem, which could in itself be a chemosensitivity network; and central chemoreceptors can interact with peripheral ones[22]. This, has led to the assumption that interaction between both might also be in other forms beyond additive, namely hyperadditive, hypoadditive or even a hybrid model[29-31].

It was our intention to explore the possibility of a model in which chemoreceptors interact with each other by modifying the gain of the neural pathways that transport the respiratory signals. In an attempt to model this behaviour, we presented a model of the chemical control of breathing based on a multiplicative central-peripheral interaction. Our work was completed by also proposing a set of equations that modelled chemoreceptor reactivity as the magnitude in which chemoreceptors can modify the gain of the feedback loop by either potentiation or blockade. It was beyond the scope of this study to discuss if the interactions exist[18]. Rather, we accepted them and developed the mathematical framework.

In the model that we suggested, chemoreceptors modulate the gain of the neural pathway that transports centrally drive respiratory generating signals, i.e. behaving as a gated process. Despite the conceptual simplicity of the proposed model, we showed that it could easily reproduce the observed behaviour of the respiratory system at both stable and unstable, i.e. periodic breathing, conditions. This model can also both reproduce short-cycle periodic breathing, which occurs in response to hypoxia and long-cycle periodic breathing as observed in different pathologies. In the model, the length of the cycle depends directly on the delay. The model is also able to reproduce unexpected occurrences of periodic breathing caused by a perturbation such as a sigh, a phenomenon hard to explain with previous models. One of the most remarkable properties of the model is the ability to reproduce periodic breathing in a simple manner once the conditions needed are met: a perturbation significant enough given a sufficient chemoreactivity for a given delay. As previously commented, when the conditions are met, periodic breathing is sufficiently frequent not to be seen as an exotic event.

Some predictions on our model might suport its validity. 1) The length of the cycles of periodic breathing is directly dependent on the delay in the transfer of information, with longer cycles of periodic breathing occurring with longer delays. The proposed model can therefore easily simulate both periodic breathing with shorter length of periods, which occurs for example at high altitude; and longer-cycle forms of periodic breathing observed in patients suffering from different pathologies, e.g. chronic heart failure (CHF). With this assessment, we do not want to imply that both events are pathophysiologically similar, periodic breathing at high altitude cannot easily be compared with periodic breathing in CHF patients. At high altitude, the trigger is hypoxia, and breathing can be stabilised by O_2 inhalation[56], however, not all CHF patients are hypoxic and in these cases O_2 inhalation does not eliminate periodic breathing. What this model demonstrates is that a multiplicative interaction between chemoreceptors can easily produce periodic breathing; in which the length of the cycle is dependent on the delay in the loop. The time delays needed to reproduce periodic breathing at the frequency observed at high altitude are of the order of 3 to 5 seconds, in line with peripheral chemoreceptors delay. Intervals of the order of 10 to 15 seconds were needed for long cycles forms of periodic breathing, which are

magnitudes very close to the average circulatory delay of 12.4 seconds calculated by Ahmed and co-workers[180]. These orders of magnitude are consistent with the idea that long-cycle forms of periodic breathing are likely due to central chemoreceptors[144,151], whereas periodic breathing at high altitude, with shorter cycles, is mainly due to peripheral chemoreceptors as supported by the evidence that carotid body denervation prevents periodic breathing in hypoxia[182]. Furthermore, this relation between the length of the cycles of periodic breathing and the delay in the transfer of information seems to be also supported by the observation that the length of the cycle shortens at higher altitudes as an effect of increased cardiac output depending on altitude. 2) Our model also predicts more stability with shorter delays, meaning shorter periods of periodic breathing. This prediction is also in line with or previous observation in Antarctica, where participants exhibiting shorter cycles of periodic breathing also had fewer apneic/hypopneic events per hour[63]. 3) Finally, our model predicted higher instability with sudden increases in drive compared to sudden decreases, which is an effect that has been widely observed in sleep-wake transitions[183].

To summarise, our model proposed a new conceptual interpretation of chemoreceptor reactivity, as the magnitude in which chemoreceptors can modify the gain of the neural pathway can be either potentiation or blockade. To our knowledge, this is the first work to provide the mathematical framework for such a possibility. The model can explain stable respiration and simulate periodic breathing. In the proposed model, stability depends on three factors: the chemoreactivity, as the capacity of the chemoreceptors to modify the reactivity of the neural pathways; the delay in the transfer of information; and a perturbation significant enough to trigger instability.

III. FUTURE RESEARCH

Being able to not only understand better periodic breathing but also observe it with adequate tools is of clinical importance. Periodic breathing is associated with impaired prognosis[15,38,132,192,193]. Periodic breathing may be seen in a variety of situations beyond acute exposure to high altitude[3-7], including damage to respiratory centers[3], and in patients suffering from chronic heart failure[8-11]. The latter is a case of major clinical relevance. Prognosis of heart failure is uniformly poor when the treatment of the underlying problem is not initiated as soon as possible[167]. It should be investigated in this regard if the use of early diagnosis tools for periodic breathing like eAMI can help physicians to discover earlier some of these conditions.

Periodic breathing is also associated with increased arousal indices that can impair sleep quality[61]. As a result of poor sleep, people at high altitude often feel somnolent and fatigued during the following day which reduces their productivity and increases the probability of error[49,62]. Our results suggest the existence of responders and non-responders, and we have some evidence of a

possible biomarker: the length of the period of periodic breathing. This longitudinal observation does not prove cause and effect, but given the importance of such biomarker, future research should indeed validate our findings.

Gilmartin et al[168] have already mentioned the need for screening tools of more subtle forms of periodic breathing beyond central apneas and severe periodic breathing. For instance, as previously discussed, in some patients with heart failure, OSA and CSA are part of a spectrum of periodic breathing[131]. There is evidence that many laboratories diagnose mixed-events patients with OSA and propose treatment as if these events were merely obstructive. It should be further investigated if screening tools based on the periodicity of periodic breathing like eAMI might help to improve early diagnosis and treatment of underlying diseases, including chronic heart failure cases in which period breathing is present.

Although still debated, sudden infant death syndrome seems to be related to the development of the respiratory system during infancy[22]. It has been suggested that the development of the peripheral chemoreceptors is critical in the final maturation of the respiratory system[189]. Periodic breathing and failure to arouse from apneic events have also been suggested as likely causes for SIDS[190,191]. Given the epidemiology of SIDS, early detection of periodic breathing might improve life expectation on infants. In this regard, eAMI could be further investigated. Also in our proposed model, the modulation interaction between chemoreceptors might lead to a total temporal blockade of the neuronal pathways that transport the respiratory signals, which could explain SIDS as a system failure in which the blockade reaches a point of no return. Understanding the underlying mechanisms behind SIDS might also help us to shape new tools to decrease its impact on infants.

We are setting in this work a stepping stone towards a better understanding of periodic breathing. Many questions need still to be answered. What are the mechanisms behind the relationship between periodic breathing and physical activity? What are the physiological differences within the respiratory control loop that might partially explain that the participants exhibiting shorter cycles of periodic breathing also had fewer apneic/hypopneic events per hour? To try to answer some of these questions, we have been involved in a female 10-day bed-rest study at Planica, Slovenia. The hypoxic conditions of experiment together with the combination of bed-rest and ambulatory groups will hopefully give us some new insights into the process behind periodic breathing. Can we improve the early diagnosis of periodic breathing? Are we treating properly OSA patients presenting periodic breathing? Several studies are now being outlined to investigate further the benefits of eAMI. Next year a double-blinded study will commence in Slovenia. The study objective will be to assess the prediction viability of the eAMI in severe cases of OSA. Polysomnographic data from the Clinical Hospital in Ljubljana will be

analysed by the eAMI and used to predict the outcome of upper airway surgery. The hypothesis being that in the cases in which periodic breathing is present, surgery should not have a positive outcome. The results of the study will be compared with the post-surgery evaluation of the patients. In another study with obese patients exposed to hypoxia, eAMI will be used for scoring periodic breathing and evaluate the loop gain of participants. All the results obtained from the mentioned experiments will be used to validate further the model for the iteration of the chemoreceptors proposed in the last chapter.

We believe there are many questions and new lines of investigation that arise from our work. Hopefully, if not us, some other research teams will continue from here.

Scientific output

- First author manuscripts
    - Fernandez Tellez H, Mairesse O, Macdonald-Nethercott E, Neyt X, Meeusen R, Pattyn N. "Sleep-related Periodic Breathing Does Not Acclimatize to Chronic Hypobaric Hypoxia: A 1-Year Study at High Altitude in Antarctica". *American Journal of Respiratory and Critical Care Medicine* 2014.

    - Fernandez Tellez H & Morrison S A, Neyt X, Mairesse O, Piacentini MF, Macdonald-Nethercott E, Pangerc A, Dolenc-Groselj L, Eiken O, Pattyn N, Mekjavic I B & Meeusen R. 1. "Exercise during acute and long-term continuous exposure to hypoxia exacerbates sleep-related periodic breathing". SLEEP 2016.

    - Fernandez Tellez H, Pattyn N, Mairesse O, Dolenc-Groselj L, Eiken O, Mekjavic I B, Migeotte PF, Macdonald-Nethercott E, Meeusen R, Neyt X. "eAMI: a qualitative quantification of periodic breathing based on the amplitude of the oscillations". SLEEP 2015.

    - Fernandez Tellez H, Pattyn N, Mairesse O, Meeusen R, Neyt X. "Modelling central and peripheral chemoreceptors as a gated process: implications for their interaction and for the occurrence of periodic breathing". *Medical & Biological Engineering & Computing* (submitted).

- Collaborations
    - Pattyn N, Van Puyvelde M, Fernandez Tellez H, Roelands B, Neyt X. "Sleep in Antarctica: an update on *the Big Eye"*. Sleep Medicine Reviews (submitted).

    - Collet G, Mairesse O, Cortoos A, Tellez HF, Neyt X, Peigneux P, Macdonald-Nethercott E, Ducrot YM, Pattyn N. "Altitude and seasonality impact on sleep in Antarctica.". Aerosp Med Hum Perform 2015.

    - De Pauw K, Roelands B, Marusic U, Tellez HF, Knaepen K, Meeusen R. "Brain mapping after prolonged cycling and during recovery in the heat". *Journal of Applied Physiology* 2013.

- International symposia
    - Fernandez Tellez, H, Piacentini, M.F, Mairesse O, Macdonald Nethercott E, Neyt, X, Meeusen R, Pattyn N. "Exercise at high altitude is associated with higher degree of sleep discorded breathing due to hypoxia". Annual Meeting European College of Sport Science 2014. Amsterdam.

    - Mekjavic IB, Pattyn N, Mairesse O, Cortoos A, Collet G, Fernandez HT, McDonald-Nethercott E, Morrison SA, Dolenc-Groselj L, Eiken O. "Sleep and performance during the winter months in Antarctica". Proceedings from 35th Annual International Gravitational Physiology Meeting, Waterloo, 2014.

    - Gregory Collet, Vinciane Fontenelle, Kristel Knaepen, Helio Fernandez, Bart Roelands, Guy Nagels, Romain Meeusen, Nathalie Pattyn. "Behavioural and electrophysiological assessment of sustained attention: effect of time-on-task". 53rd Annual Meeting of the Society for Psychophysiological research. October 2-6th, Firenze, 2013.

    - Fernandez H, Pattyn N, Mairesse O, Migeotte P, Cortoos A, Macdonald-Nethercott E, Neyt X, Meeusen R. "Long-term acclimatization to moderate altitude in Antarctica. 84th Annual Scientific Meeting of the Aerospace Medical Association, Chicago, IL. Aviat Space Environ Med 2013.

    - Fernandez H, Pattyn N, Mairesse O, Meeusen R, Macdonald-Nethercott E, Neyt X. "One year monitoring of nocturnal periodic breathing at the Antarctic pole". 5th World Congress on Sleep Medicine, Valencia, Spain. Sleep Med 2013.

    - Helio Fernandez, Nathalie Pattyn, Olivier Mairesse, Pierre-François Migeotte, Aisha Cortoos, Eoin McDonald-Nethercott, Xavier Neyt, Romain Meeusen. "Sleep Disordered Breathing at Antarctica". 19th IAA Humans in Space. Cologne. July 7-12th, 2013.

    - Maria Francesca Piacentini, Helio Fernandez Tellez, Nathalie Pattyn, Bart Roelands and Romain Meeusen (2013). "Feasibility of self-paced exercise regimen as a countermeasure for long-duration missions: self-monitored exercise logs of an isolated crew in Antarctica". 19th IAA Humans in Space. Cologne. July 7-12th, 2013.

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- Nathalie Pattyn, Olivier Mairesse, Aisha Cortoos, Xavier Neyt, Eoin McDonald-Nethercott, Bart Roelands, Helio Fernandez Tellez, Romain Meeusen. "Move to sleep: How physical activity enhances sleep quality in Antarctic expeditions". European College of Sports Science, Bruges, 4-8th July 2012.

- Kristel Knaepen, Helio Fernandez and Meeusen Romain. "Movement Related Potentials Related To Self-Paced Treadmill Walking". Meeting of the Society of Applied Neuroscience. Thessaloniki, May 5-8th, 2011.

- National Symposia
  - Helio Fernandez, Nathalie Pattyn, Pierre-François Migeotte, Olivier Mairesse, Aisha Cortoos, Eoin McDonald-Nethercott, Xavier Neyt, Romain Meeusen . "Quantification of Periodic Breathing: An absolute measure". Annual Symposia of the Belgian Association for Sleep Research and Sleep Medicine. Brussels, November 24th, 2012.

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