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OBESITY HYPOVENTILATION SYNDROME

OPTIMIZING PATIENT IDENTIFICATION AND LONG-TERM THERAPY

PhD thesis

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List of Abbreviations

AHI - Apnea-Hypopnea Index

BMI - Body Mass Index

BIPAP - Bilevel Positive Airway Pressure

CC - Closing Capacity

COVID-19 - Coronavirus Disease 2019

CPAP - Continuous Positive Airway Pressure

EELV - End Expiratory Lung Volume

EFL - Expiratory Flow Limitation

EPAP - Expiratory positive airway pressure

ERV - Expiratory Reserve Volume

FEV1 - Forced Expiratory Volume in 1 second

FRC - Functional Residual Capacity

FVC - Forced Vital Capacity

GLP - Glucagon-Like Peptide

HMV - Home Mechanical Ventilation

HCO_3^- - Bicarbonate

ICD - International Classification of Diseases

ICU - Intensive Care Unit

IPAP - Inspiratory Positive Airway Pressure

IV - Invasive Ventilation

LOS - Length of Stay

LOV - Length of Invasive Ventilation

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NEP - Negative Expiratory Pressure

NIV - Noninvasive Ventilation

NMD - Neuromuscular Disorder

NREM - Non-Rapid Eye Movement

OHS - Obesity Hypoventilation Syndrome

OSA - Obstructive Sleep Apnea

P - Pressure

$paCO_2$ - Arterial Carbon Dioxide Tension

$ptcCO_2$ - Transcutaneous Carbon Dioxide Tension

REM - Rapid Eye Movement

Rrs - Resistance of the Respiratory System

SRBD - Sleep Related Breathing Disorder

tEFL - Tidal Expiratory Flow Limitation

V - Volume

V’ - Flow

WHO - World Health Organization

WOB - Work of Breathing

Xrs - Reactance of the Respiratory System

Zrs - Impedance of the Respiratory System

$\Delta V/\Delta Q$ - Ventilation Perfusion Ratio

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1. INTRODUCTION

1.1 Historical background

The symptoms of the so called ‘Pickwickian syndrome’ were first described by Charles Dickens in the novel called *Posthumous Papers of the Pickwick Club* (1837) (Figure 1). The character of *Joe the Fat Boy* is obese and suffers from serious daytime sleepiness. This insightful description is the first historic characterization of the medical condition currently referred to as obesity hypoventilation syndrome (OHS). Since then, the societal and health care relevance of the syndrome is undeniable, as today OHS is the leading indication for long-term respiratory support worldwide (1).

Figure 1 *- „… - and on the box sat a fat and red-faced boy, in a state of somnolency, whom no speculative observer could have regarded for an instant without setting down as…” – obesity hypoventilation syndrome: a plastic description by Dickens.*
The Posthumous Papers of the Pickwick Club – Charles Dickens (1837)
’Joe The Fat Boy’ - Harry Furniss – Pen-and-ink drawing from The Charles Dickens Library Edition (1910)

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OHS is the leading indication for long-term ventilator support in several European countries, including Hungary (2, 3). Despite this, little is known about the exact prevalence of OHS in European countries. Using the analogy of a previous calculation by Balachandran et al. we can assume the number of patients (4). As the prevalence of extreme obesity (body mass index [BMI] ≥ 40 kg˙m^{-2}) in Hungary reached 3,3% and 2,6% among women and men respectively (5), circa 28.000 Hungarian OHS patients can be presumed. This is a surprising number, as the current prevalence of patients receiving long-term respiratory support today in Hungary is estimated to be around 400 (unpublished data). However, the growing practice of home mechanical ventilation (HMV) in Hungary and the fact that OHS is the most common indication for treatment, it is reasonable to assume that a large fraction of patients are still untreated (2).

1.2 Definition

OHS is defined by the combination obesity (BMI ≥ 30 kg˙m^{-2}), sleep related breathing disorder and hypercapnia in the absence of an alternative neuromuscular, mechanical or metabolic explanation of alveolar hypoventilation (Table 1) (1, 6). Increased arterial carbon dioxide tension ($paCO_2$) can appear as hypercapnia during the day ($paCO_2 \geq 45$ mmHg), or as clinically relevant worsening of carbon dioxide elimination during sleep (change in transcutaneous carbon dioxide [$\Delta ptcCO_2$] ≥ 10 mmHg)(7). It is important to note that daytime hypercapnia is preceded by sleep-related hypoventilation, and diurnal hypercapnia represents an already advanced condition. Increased daytime bicarbonate (HCO_3^- > 27 mmol˙L^{-1}) despite normal pH is associated with hypercapnia during sleep (nocturnal only hypoventilation) and may be used as a surrogate marker for nighttime hypercapnia when screening patients with OHS symptoms.

Table 1 Diagnostic criteria of Obesity Hypoventilation Syndrome (1)

- Obesity (body mass index ≥ 30 kg˙m^{-2})
- Daytime hypercapnia (arterial carbon dioxide tension ≥ 45 mmHg)
- Sleep related breathing disorder

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1.3 Diagnosis

An American Academy of Sleep Medicine Task Force defined OHS in 1999, and 25 years later the current literature continues to demonstrate some uncertainty in the definition (8). Currently, the two most comprehensive guidance on the diagnosis and management of OHS is included in the Practice Guideline by the American Thoracic Society and in a recent European Task Force statement (1, 6). As can be seen from the definition, the diagnosis of OHS is based on quite arbitrary conditions and these indeed have little evidence-based framework. Elective work-up is warranted if obesity and the possible symptoms of OHS are present.

1.3.1 Symptoms

Due to the many possible unspecific symptoms, a delay in the diagnosis of OHS is common. Sustained hypercapnia while awake ($paCO_2 \geq 45$ mmHg), or intermittent hypercapnia during sleep ($\Delta ptcCO_2 \geq 10$ mmHg) is by definition always present in OHS or, although, it is seldom the first finding in the disease.

Daytime sleepiness interrupted nighttime sleep and chronic exhaustion may all draw attention to sleep related breathing disorder (SRDB). Loud disruptive snoring, witnessed apneas, headache and neck pain are important symptoms of concomitant obstructive sleep apnea (OSA).

Secondary organ damages, as a result of chronic respiratory failure, are often extensively studied in these patients and may be the first clues to alert the clinician to finding the actual diagnosis. Symptoms of cor pulmonale, such as lower extremity oedema, nocturia, dyspnea, may alert physicians for OHS as the underlying diagnosis (9).

The exact gender distribution of OHS is still unknown. In the treated OHS population the men appear to be over-represented, however, in the acute settings women are at least equally affected (10, 11).

Increasing body weight may increase the probability of having OHS. The prevalence of OHS among obese patients with BMI of 30 - 35 $kg \cdot m^{-2}$ may be 5%, meanwhile, it may increase up to 20% with BMI ≥ 40 $kg \cdot m^{-2}$ (9).

1.3.2 Screening

Room air arterial blood gas is the gold standard for diagnosing alveolar hypoventilation. Searching for a less invasive test, many investigators evaluated whether natural consequences of hypoventilation, namely measuring hypoxaemia or elevated bicarbonate level, may be suitable tests for screening patients for OHS.

Hypoxemia may occur in OHS due to various reasons. Ventilation / perfusion ($\Delta V/\Delta Q$) mismatches, sleep related breathing abnormalities, severe alveolar hypoventilation, and cardiovascular comorbidities all can be responsible for decreasing arterial oxygen tension. The degree of hypoxaemia and desaturation, however, appears to be highly variable in this population. Although daytime hypoxaemia and nighttime desaturation are risk factors for having OHS, measuring oxygenation is unable to predict alveolar hypoventilation, and it is not recommended for screening (1).

On the other hand, elevated HCO_3^- level as the consequence of alveolar hypoventilation is a commonly used test for screening for OHS. $HCO_3^- \geq 27$ mmol˙L^{-1} may draw attention to daytime or nighttime hypoventilation, and levels < 27 mmol˙L^{-1} have a very high negative predictive value (97%), making it an effective tool to rule out hypercapnia, which makes the probability of OHS low. Therefore, using HCO_3^- to screen for OHS appears to be useful and it is suggested by the American Thoracic Society and European Respiratory Society (1, 6).

There are a variety of techniques to measure carbon dioxide besides arterial blood gas, such as capillary blood gases, venous blood gases, end-tidal carbon dioxide and $ptcCO_2$ monitoring. In chronic respiratory failure end-tidal and transcutaneous measurements of carbon dioxide are reliable and practical methods for identifying sleep hypoventilation. Both can reduce the frequency of arterial blood gas measurements. Continuous $ptcCO_2$ monitoring has more advantages, such as allowing assessment of trends in $paCO_2$ across the day or night without disrupting sleep, and it can be used during therapeutic intervention as well. It is recommended that transcutaneous values be periodically verified by simultaneously taking arterial samples (12).

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1.3.3 Sleep study

The criteria of sleep hypoventilation are defined by the American Academy of Sleep Medicine: $paCO_2 > 55$ mmHg (or surrogate such as $etCO_2$ or $ptcCO_2$), or an increase in carbon dioxide level by at least 10 mmHg for 10 minutes, compared to the daytime value (13). While the definition of OHS suggests diurnal gas exchange impairment, a sleep study (polysomnography or polygraphy) is required to determine the pattern of sleep-disordered breathing, including alveolar hypoventilation and airway obstruction (9) (Figure 2). Approximately 90% of OHS patients have concomitant OSA, defined by the apnea-hypopnea index (AHI ≥ 5 events / hour), and nearly 70% of patients have severe OSA (AHI > 30 / hour). The remaining 10% have non-obstructive sleep hypoventilation. Based on the presence of OSA and sleep-related hypoventilation the European Respiratory Society Task Force recently proposed severity staging for obesity related hypoventilation (Table 2). Although this approach might help understand the different clinical presentations of alveolar hypoventilation in obesity, its clinical significance is yet to be proven.

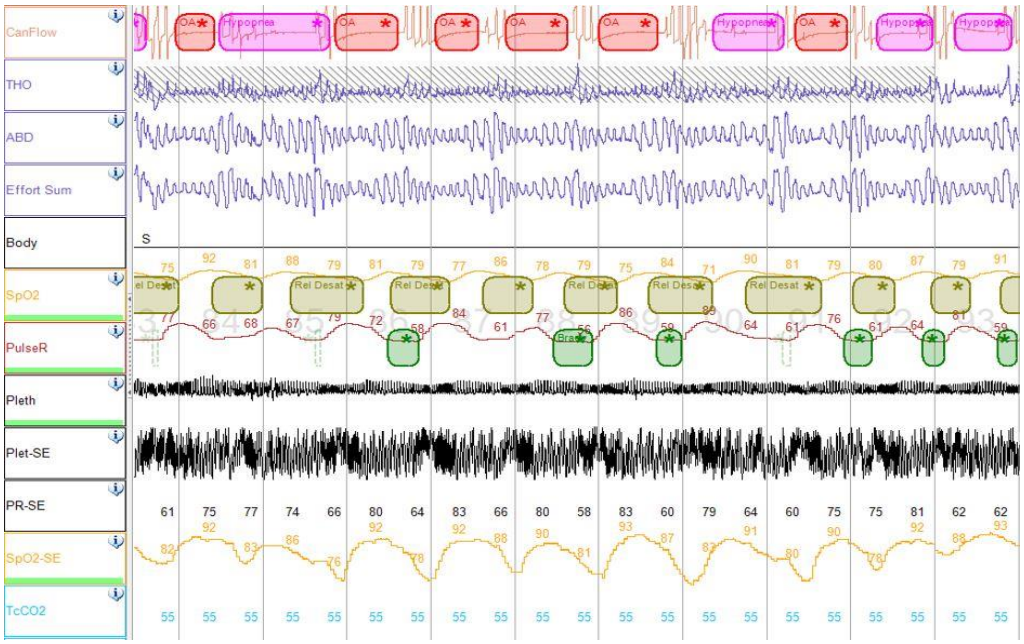

Figure 2 *– Polygraphy of a representative OHS patient with severe OSA. The repetitive airway obstructions led to cessation of airflow, hypoxemia and autonomic instability; meanwhile severe alveolar hypoventilation was also present with elevated carbon dioxide ($\Delta TcCO_2 > 10$ mmHg). Data taken from Semmelweis University Home Ventilation Program records.*

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Table 2 Staging of hypoventilation in obesity according to Randerath et al. (6). OHS = Obesity hypoventilation syndrome, BMI = Body mass index, OSA = Obstructive sleep apnea, HCO_3^- = Bicarbonate, $paCO_2$ = arterial tension of carbon dioxide

0	At risk	BMI > 30 kg˙m^{-2}	OSA	No hypercapnia
I	Obesity-associated sleep hypoventilation	BMI > 30 kg˙m^{-2}	OSA / hypoventilation during sleep	Intermittent hypercapnia during sleep, full recovery during sleep; Serum HCO_3^- < 27 mmol˙L^{-1} during wake
II	Obesity-associated sleep hypoventilation	BMI > 30 kg˙m^{-2}	OSA / hypoventilation during sleep	Intermittent hypercapnia during sleep; Serum HCO_3^- ≥ 27 mmol˙L^{-1} during wake
III	Obesity hypoventilation	BMI > 30 kg˙m^{-2}	OSA / hypoventilation during sleep	Sustained hypercapnia ($paCO_2$ > 45 mmHg) while awake
IV	Obesity hypoventilation syndrome (OHS)	BMI > 30 kg˙m^{-2}	OSA / hypoventilation during sleep	Sustained hypercapnia while awake, cardiometabolic comorbidities

1.4 Long term health consequences

Although the current definition of OHS is based on daytime gas value change, the European Respiratory Society task force has recently suggested to include the presence of so called 'cardiometabolic' comorbidities in the most severe stage of the syndrome, since these comorbidities have a huge impact on health-care resource utilization and on the outcome of OHS patients (6). Previously hospitalized patients with OHS are more likely to need intensive care unit (ICU) admissions compared to eucapnic obese patients (40% versus 25% respectively). Although these patients appear in the health-care system frequently, the formal diagnosis of OHS is usually established with delay, typically in the 5^{th} and 6^{th} decades of life (14).

1.4.1 Comorbidities

Metabolic and cardiovascular comorbidities are prevalent and are usually diagnosed prior to the identification of OHS. Although symptoms indicative of the condition and its comorbidities may be present for years, OHS is frequently diagnosed late in its course as acute-on-chronic hypercapnic respiratory failure (15, 16). Patients who are diagnosed late during an acute exacerbation of chronic respiratory failure usually present with heart failure, ischemic heart disease and right heart failure (Table 3) (9). Thus, generalized edema, labored breathing, reduced exercise tolerance, unstable blood pressure are the initial symptoms with which the patients present for work-up.

Table 3 - Most frequent comorbidities of obesity hypoventilation syndrome patients (14)

Congestive heart failure	60%
Hypertension	55%
Angina	30%
Cor pulmonale	30%
Osteoarthrosis	25%
Hypthyroidism	25%
Diabetes mellitus	10%

Despite the documented increased healthcare utilization of OHS patients as a result of these secondary conditions, physicians frequently fail to recognize the actual culprit, OHS

(14). This is especially concerning, as secondary conditions seldom react to appropriate therapy without the treatment of the underlying condition, chronic respiratory failure.

1.4.2 Acute-on-chronic respiratory failure

OHS with progressive symptoms may lead to acute-on-chronic hypercapnic respiratory failure (16). Acute-on-chronic respiratory failure occurs when relatively minor, although often multiple, insults cause acute deterioration in a patient with chronic respiratory insufficiency. OHS patients without long-term respiratory support are fragile, and frequently have repetitive hospital admissions before definite diagnosis is made. This suggests an unnecessary, avoidable burden of the health care system. In fact, a recent monocentric study highlighted that up to 8% of all the patients admitted to the ICU fulfill the criteria of obesity hypoventilation syndrome (17). All of these patients were admitted with hypercapnic respiratory failure requiring respiratory support. Although many of the patients had prior hospital admissions, they were mostly misdiagnosed and stigmatized as chronic obstructive pulmonary disease (COPD) patients.

The vast majority of OHS patients have classic symptoms of OSA, including loud snoring, nocturnal episodes of witnessed apnea, excessive daytime sleepiness, and morning headaches. In contrast to OSA, OHS patients also frequently complain of dyspnea, orthopnea, and may have signs of chronic right heart failure. With acute-on-chronic hypercapnic respiratory failure, patients who have OHS usually present with progressive shortness of breath (18). Physical examination can find a somnolent, plethoric, obese patient who has increased neck circumference and a compromised oropharynx. Careful inspection can reveal a paradoxical breathing pattern suggestive of diaphragmatic dysfunction. Patients with OHS are typically rapid shallow breathers, and tachypnea may become more prominent during exacerbation.

Several laboratory findings are supportive of OHS, yet none of them are specific. The definitive test for alveolar hypoventilation is arterial blood gas performed on room air. Hypercapnia ($paCO_2$ > 45 mmHg), and compensated or uncompensated respiratory acidosis may be significant with metabolic compensation and elevated bicarbonate level. Secondary erythrocytosis can be a sign of chronic hypoxemia, however, may be absent in multimorbid cases. Chest X-ray can reveal enlargement of the cardiac silhouette, and

pulmonary vascular congestion. Echocardiography usually shows right heart enlargement with pulmonary hypertension (18).

1.4.3 Outcome

In two recent prospective studies focusing on acute and acute-on-chronic hypercapnic respiratory failure, there was no reported in-hospital death among decompensated OHS patients. However, increased mortality rate was reported among patients without long-term respiratory support, once discharged from hospital (11, 19). These results reinforce the fact, that respiratory support has many positive effects on patients with OHS, however this population becomes extremely fragile once they are let go without adequate long-term treatment.

It is known that the mortality rate of OHS after an episode of acute-on-chronic respiratory failure may reach 23 - 46% in the following 18 - 50 months respectively (11, 20). On the other hand, long-term NIV has the potential to decrease the mortality rate to 2.5 – 26.7% in the following 1 to 5 years respectively (21). Moreover, a consistent and significant improvement was reported in the quality of life of this population (22).

1.5 Pathophysiology

The pathophysiology of OHS is complex (9). There are well known disadvantageous changes in the respiratory system that appear in every obese patient. Additionally, there are changes that are more common with obesity but are not a prerequisite of OHS. Finally, there are considerable changes in the respiratory drive, which are not yet clearly understood, but seem to be the culprit of the syndrome. These changes do not occur in all obese patients and are not dependent on actual weight.

1.5.1 General mechanical changes associated with obesity

The high intrathoracic pressure caused by abdominal obesity is a known cause of impaired lung expansion. The abdominal and chest wall adipose tissue reduces functional residual capacity (FRC) at the expense of the expiratory reserve volume (ERV). The shift in FRC may force tidal breathing to reach below closing volume, lung volume declines below the point where small airway closure occurs during tidal breathing. This essentially results in diminished absolute lung volumes, augmented lower airway resistance, and even premature airway closure, atelectasis and ventilation / perfusion ($\Delta V/\Delta Q$) mismatch (9).

Fat deposits also have a direct effect on respiratory function by impending diaphragm motion, reducing the compliance of the respiratory system. A further worsening can be seen in the supine position because of the cephalad projection of the diaphragm. Overall, there is a poor exercise tolerance, and impaired and vulnerable oxygenation in instances when minute volume requirements are increased or restrictive lung pathology (e.g. pneumonia) is present. As a consequence, minute ventilation is limited and is an attribute to exercise intolerance but may also lead to nighttime hypoventilation (see later). Overall, an increased work of breathing (WOB) is seen, leading to elevated respiratory drive and overwhelmed respiratory muscles (23).

1.5.2 Disordered breathing during sleep

These aforementioned changes together predispose the respiratory system to disordered breathing during sleep. Faced with abnormal respiratory workload and impaired gas exchange, the vast majority of obese patients develop increased respiratory drive to compensate and remain eucapnic. If this increased respiratory drive cannot be maintained, alveolar hypoventilation and hypercapnia occurs. This may be the reason of the vulnerable ventilation in obesity during certain sleep stages.

During non-rapid eye movement (NREM) sleep hypoxemic and hypercapnic ventilatory responses typically decline and are further blunted during rapid eye movement (REM) sleep. In this certain stage generalized muscle atonia occurs, and without the postural tone, much of the alveolar ventilation is dependent on the function of the diaphragm and the respiratory drive controlling it. In OHS the REM sleep hypoventilation is hence a consequence of the previously mentioned obesity-related mechanical constraints of the diaphragm in addition to a failing central response. The later one is the culprit of OHS and is thought to be in connection with the relative leptin resistance of the central drive. At first the repetitive hypoventilation is thought to be limited to REM sleep, inducing a secondary depression of the respiratory centers. This may lead to daytime hypercapnia and progress OHS to an advanced stage.

1.5.3 Leptin associated central drive malfunction

The initial central hypoventilation during REM sleep in OHS is thought to be in connection with the so-called leptin axis. Leptin is a protein hormone predominantly secreted by peripheral adipose tissues. Its primary role is likely to regulate long-term

energy balance, controlling hunger and satiety. Numerous (mainly preclinical) studies have investigated the mechanisms of leptin's actions both in the healthy state and in metabolic disorders. Leptin has been associated with the development of obesity in several conditions (24).

Leptin may have a central and complex role acting as a regulator of both neuroendocrine function and energy homeostasis. Leptin produced by adipocytes passes the blood-brain barrier and has central effects, and acts in certain areas of the hypothalamus. Its level is proportional to the overall amount of energy stored as fat in the body. It has important impact on controlling fasting and energy intake, has effects on the hypothalamic-pituarity-gonadal axis, and it is in connection with the sympathetic nervous system as well (25).

Interestingly, leptin is also a powerful stimulant of the ventilator drive adding to the complex metabolic interplay of this hormone. Although not entirely understood, leptin appears to have a role in the normal respiratory control and chemoreceptor sensitization. Significantly higher leptin concentration was observed in obesity and in OHS with impaired effect, implying the existence of leptin resistance. The dysfunction of the leptin axis may be crucial in the development of hypoventilation in OHS and may not only lead to the deterioration of respiratory control but also explain some of the cardiometabolic consequences of the disease (24, 26).

1.5.4 Obstructive sleep apnea

OSA is defined as repeated narrowing or collapse of the upper airways during sleep. Obstructive sleep apnea (OSA) is the most common sleep related breathing disorder. The mechanism by which the upper airway collapses is not fully understood but is thought to be multifactorial. Fat deposits, alteration of upper airway muscle function, fluid shift around the neck may all contribute to the obstructive events during sleep. Severe obesity is a known risk factor for OSA. The apnea-hypopnea index (AHI) is the combined average number of apneas and hypopneas that occur per hour of sleep. According to the American Academy of Sleep Medicine, OSA is categorized into mild (5 – 15 events /hour), moderate (15 – 30 events / hour), and severe (> 30 events / hour) stages (27).

90% of OHS patients experience concomitant repetitive OSA episodes, although OSA is not a prerequisite for the syndrome. Interestingly, cases without OSA are more likely to

result in severe hypoventilation (28). The frequent occurrence of OSA in obesity is explained by a combination of coexisting risk factors. Obesity itself decreases pharyngeal size and increases collapsibility, predisposing upper airway narrowing and closure during sleep. Reduced lung volume and excessive fat deposits around the upper airway are key factors. OHS patients experience obstructive events with relatively long-lasting hypopneas and apneas without effective ventilatory compensation, due to the blunted central respiratory drive. In this situation, the obstructive periods and the carbon dioxide overload contributes to diurnal hypercapnia. It is hypothesized, that there is a phenotype of OHS patients with less severe obesity, and without respiratory muscle impairment, exhibiting long lasting apneas and hypopneas, but free from REM sleep hypoventilation. This subpopulation is more likely to benefit from continuous positive airway pressure (CPAP) (Figure 3) (9).

1.5.5 Other possible contributing factors

To this day no community-based cohort studies of OHS have been conducted and gender distribution is still unknown. Studies dealing with the gender perspective of OHS are sparse, and many of them are focusing on sleep clinics with OSA patients, where men are over-represented (10, 29). On the other hand, in studies investigating hospital settings, women appear to be at least equally affected by OHS as men (11, 17). The facts, however, that prevalence of OSA is twice as high in men, and approximately 90% of OHS patients have concomitant OSA, is provoking. A recent study has shed light on some differences between men and women patients with OHS (30). At the time of diagnosis and start of long-term NIV support women appear to be older, more obese and have more deranged blood gas values compared to men. Long-term therapy also starts more frequently in an acute setting among women. Despite these differences long term mortality rate and improvement in gas exchange appears to be similar in both men and women (30). However, the male predominance is apparent in patients with OSA, and women might be more affected by non-obstructive OHS.

Obesity is a state of chronic systemic low-grade inflammation. On top of obesity, OHS may add several extra stimuli increasing the burden of chronic inflammation. An increased load on the respiratory muscles, hypoxia of the adipose tissue, and OSA all have been demonstrated to increase proinflammatory cytokine release (31, 32, 33).

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Hence, an aggravation in adipose tissue inflammatory state is conceivable in OHS. Adding to this, the leptin resistance, and the increased plasma concentration of leptin may also lead to increased sympathetic tone and cytokine production (26, 34). A recent study showed increased level of proatherogenic chemokines in patients with OHS compared to obese patients with eucapnia (35). These data support the fact that the pathophysiology of OHS is complex with respiratory, cardiovascular and metabolic derangements.

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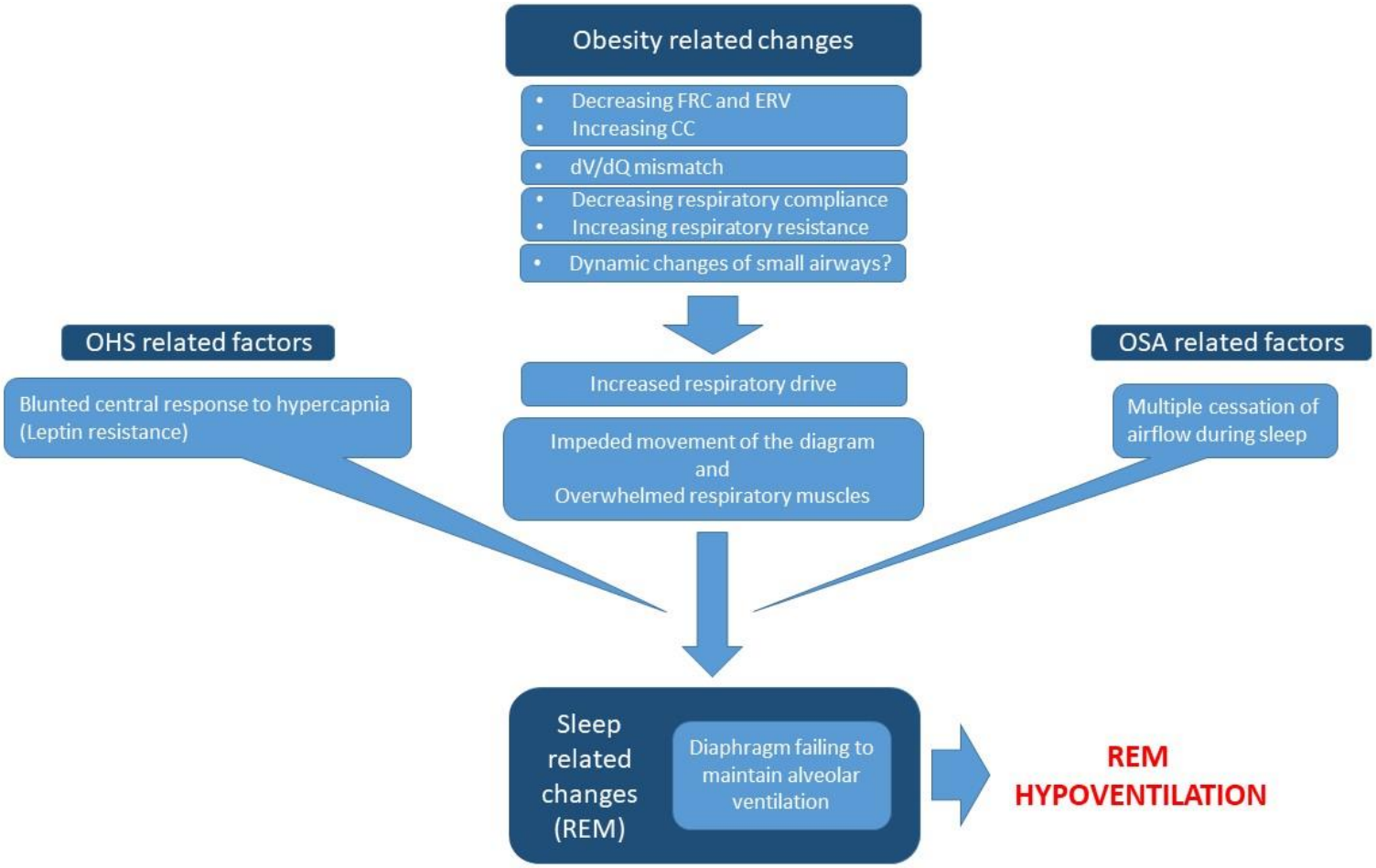

Figure 3 *– The current concept of the underlying pathophysiology of hypoventilation in obesity hypoventilation syndrome.*

OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnea, REM = rapid eye movement, FRC = functional residual capacity, ERV = expiratory reserve volme, CC = closing capacity, dV/dQ = ventilation perfusion ratio,

1.7 Therapy

Due to its complex pathophysiology, optimal therapy for patients with OHS has not yet been clearly established. Given the unknown origin of the disease, there are currently no primary forms of therapy that can reverse the syndrome. Possible therapeutic options involve different types of respiratory support and weight management strategies including lifestyle modification and surgical procedures, although it is not yet known if weight management alone can completely reverse the aforementioned changes in respiratory physiology. Additional therapies may involve the control of cardiovascular and metabolic comorbidities.

Given that the definition of OHS establishes that chronic respiratory failure is present, adequate symptomatic therapy involves respiratory support. Effective use of respiratory support as treatment for a patient with OHS was first reported by Sullivan et. al. in 1983 (36). Since then, many observational and randomized studies have proven the efficacy of this treatment in OHS. Current guidelines, however, show some contradiction in terms of the modality of the respiratory support. Additionally, they provide conditional recommendations only with low level of certainty in the evidence.

1.7.1 Types of respiratory support

Different modalities of respiratory support are possible, all administered through a noninvasive interface (see Figure 4). CPAP therapy consists of a continuous preset pressure application during the whole of the respiratory cycle, meanwhile noninvasive ventilation (NIV) consists of bi-level positive pressure ventilation often referred to as biphasic positive airway pressure (BIPAP).

CPAP has several positive therapeutic effects. Augmented airway pressure has the ability to maintain airway patency, and therefore may prevent obstructive events during sleep. CPAP may also restore lung volumes in obese patients by increasing the end expiratory lung volume (EELV), and therefore improve previously impaired lung compliance and resistance. Moreover, it may counteract with dynamic small airway changes as well, improving airflow throughout the breathing cycle. Increased intrathoracic pressures have favorable effects on the cardiac strain and may be beneficial in congestive heart failure.

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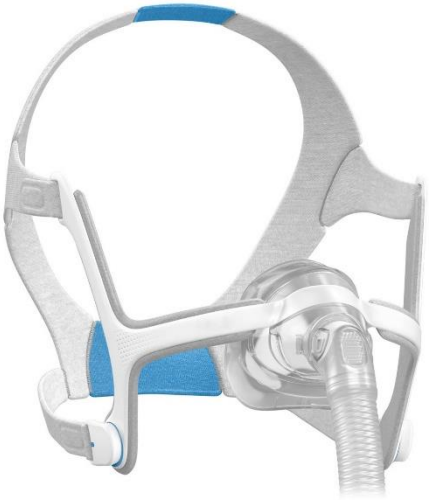

d

Figure 4 *- Different type of masks used for non-invasive respiratory support. Using a proper mask, the treatment can be personalized*

Despite these effects, using CPAP as respiratory support in OHS raises some questions. First, during CPAP the whole work of breathing (WOB) is covered by the patient. WOB, and especially the workload of the diaphragm is usually remarkable in obesity and morbid obesity. Second, the current clinical guidance for the on titration of CPAP is based on airway patency, focusing on OSA patients only, aiming to prevent the cessation of airflow during sleep. To this day no CPAP titration protocol exists specifically for OHS patients.

NIV has all the previously mentioned therapeutic effects of CPAP, but additionally provides inspiratory assistance, meaning some or all of the WOB is covered by the ventilator. NIV has several different modalities that differ mainly on how patient and machine effort are interacting. Currently the most often used NIV modalities favor patient-machine synchrony. It is well known that ventilator settings and efforts to achieve synchrony may be crucial in optimizing work of breathing for the patient (37). However, currently the guideline does not advise on the exact mode of NIV, preferred parameters or exact ventilation goals. Hence the details and particulars of NIV are left for the physician to decide.

1.7.2 Comparison of CPAP and NIV

There is an ongoing clinical debate about the optimal mode to support OHS patients. Studies comparing different therapeutic modalities enrolled OHS patients with stable compensated chronic respiratory failure and were performed in sleep laboratories.

An important study with a small sample size by Piper et al. investigated stable ambulatory OHS patients. Based on clinical consensus they performed an initial CPAP trial before randomization. Patients who displayed significant and prolonged desaturation or carbon dioxide retention during the CPAP trial were excluded from the study and placed on NIV treatment. Patients who succeeded with the CPAP trial were randomized into CPAP and NIV groups. This study concluded that both nocturnal CPAP and NIV were equally effective in improving gas exchange in selected patients with OHS (38).

In the framework of the “Pickwick project” OHS patients were recruited between 2008 and 2016 in 16 tertiary hospitals in Spain. Patients were divided into two subgroups based on the presence of severe OSA (AHI > 30 / h). The 319 stable ambulatory OHS outpatients (221 with and 98 without severe OSA) were recruited in different randomized controlled trials. In the first study (Masa et al. 2015) the OHS patients with severe OSA were randomized into NIV, CPAP, or lifestyle modification groups. They concluded that after two months both NIV and CPAP were sufficient in reducing clinical symptoms, however, the group with NIV exhibited greater respiratory improvements than those with CPAP (39). After a 2-month follow-up they also found that lifestyle modifications were insufficient in improving clinical symptoms, and these patients were re-recruited into the CPAP and NIV groups to a complete follow-up for 36 months. The long-term

investigation of these patients with CPAP or NIV (Masa et al. 2019) found similar long-term effectiveness in terms of hospitalization days, cardiovascular events, mortality, and quality of life (40).

In the third study Masa et al. examined OHS patients without severe OSA (AHI < 30 / h). Based on the concept that CPAP may not be efficient in this subpopulation, and NIV can treat both apneic and non-apneic nocturnal hypoventilation, they randomized patients into NIV and control groups. During the 3-year follow-up they concluded that both groups had similar hospitalization days, cardiovascular events and mortality. The predominant cause of death was related to cardiovascular events in the NIV group and respiratory failure in the control group. Respiratory parameters and quality of life improved significantly in the NIV group compared to the control group (41). It is important to note, that in the study group adherence to the NIV treatment affected the outcome. Subgroup analysis revealed that high adherence to therapy with an average daily NIV use of 6,2 hours (!)) decreased rehospitalization rate, hospitalization days, and even improved mortality rate.

Despite the scarce data and the highly selective inclusion criteria of the studies, current guidance suggests the use of CPAP rather than NIV in stable outpatients with OHS and severe OSA (AHI > 30 / h). However, as agreed in the panel judgement, there is a lack of certainty on the clinical benefits of initiating CPAP, rather than NIV, in patients with OHS who have sleep hypoventilation without severe OSA (AHI < 30/h) (1). The efficacy of CPAP is often monitored over a single night in patients with stable hypercapnic respiratory failure. “Insufficient CPAP therapy” is usually considered as the inability to maintain oxyhemoglobin saturation above 85 – 90%, triggering an indication for long-term NIV (1). It is also noted in the panel judgement that OHS patients with CPAP require close monitoring especially in the first two months of treatment, to ensure improvement is achieved. NIV is currently recommended for long-term respiratory support in cases where it has already been established for acute-on-chronic respiratory failure, ideally for at least 3 months until further work-up in a sleep lab (1).

There are many possible reasons for the lack of evidence of the superiority of NIV in OHS. It is important to note, that in the previously mentioned studies a considerable subpopulation of OHS patients were excluded, who received long-term NIV due to

clinical or ethical decisions. These patients were the ones with the most severe respiratory impairment for whom CPAP would have obviously been insufficient. However, this subpopulation is very relevant in everyday practice, since to this day the majority of OHS patients are recognized after acute-on-chronic respiratory failure, currently often an actual indication for long-term NIV. Patients with serious gas exchange impairment during the CPAP trial were also excluded from these randomized controlled trials and placed on NIV treatment. This suggests that the patients enrolled in these pivotal studies are the ones more likely to benefit from CPAP.

As mentioned, NIV has the ability to produce superior blood gas values. It has also been proven that goal directed ventilation may have a significant impact on mortality (42). This suggests that NIV is most efficient when used in a goal directed manner. It is important to note that in the previously mentioned studies the initiation of NIV was not performed with a defined clinical goal (e.g. normocapnia) and gas exchange during NIV was not observed. In fact, the significant ratio of patients who presented with slightly elevated daytime carbon dioxide and increased bicarbonate during follow-up suggests that NIV settings were less than optimal (41).

Furthermore, given that unintentional leakage has many unfavorable effects on ventilation, including asynchrony, decreased minute ventilation and patient discomfort (43), the choice of mask (nasal mask, oronasal mask, facemask) appears to be crucial. In the aforementioned studies the masks were chosen based on patient comfort, and leakage was not noted, or published.

Symptoms of OHS and OSA may overlap, and as previously mentioned, CPAP and NIV may both have similar effects on OSA and improve OSA associated symptoms. Although this is a clinical improvement, it is not necessarily optimal clinical improvement if hypoventilation is still present for other reasons.

Providing long-term mechanical non-invasive ventilation is challenging, and its efficacy is highly influenced by the experience of the providing team. Patient education, follow-up, reviewing NIV settings and taking care of comorbidities should all be part of long-term treatment. In the “Pickwick project” 16 centers recruited 319 patients for 8 years, corresponding to an average 2.5 patients per year in an individual center. Previous

observations highlighted that centralized management of home mechanical ventilation patients, meaning high case numbers per treatment centers yield optimal results (3).

These uncertainties question the validity of the current recommendation to initially treat patients with CPAP. Further studies are required to clarify the initiation algorithm and the benefits of each modality of respiratory support in OHS subpopulations. To this day there is no demonstration of superiority of either NIV or CPAP in a mixed OHS population. From the pathophysiological point of view, it is clear that NIV is able to unload the overwhelmed respiratory muscles, increase EELV, maintain alveolar ventilation and prevent obstructive events in the same time. Meanwhile, a certain OHS phenotype with less severe obesity, exhibiting long-lasting apneic episodes, but free form respiratory muscle impairment and REM hypoventilation is more likely to benefit from CPAP.

As remarked in the guidance, NIV, compared to CPAP, may require more resources, and equipment training, and areas where skills are necessary for complex respiratory support may be limited (1). From the Hungarian perspective this may highlight the importance of centralized management of patients with chronic respiratory failure, providing complex, goal directed, personalized respiratory support with the required modalities.

1.7.3 Emergency initiation

Effective treatment strategies for OHS in case of hypercapnic acute-on-chronic respiratory failure must relieve upper airway obstruction and increase alveolar ventilation. Hence, for patients with decompensated chronic respiratory insufficiency the cornerstone of the therapeutic effort is adequate respiratory support, namely non-invasive ventilation (NIV). There are no prospective randomized controlled studies (RCTs) demonstrating the efficacy of NIV in the management of acute decompensated OHS. However, the use of NIV in this clinical context has been incorporated into standard practice. Positive pressure should be administered during sleep and wakefulness during acute hospital setting. Bilevel positive airway pressure (BIPAP) ventilation provides inspiratory positive pressure (IPAP), and expiratory positive airway pressure (EPAP), each of which can be set independently. EPAP maintains upper airway patency, while delta between IPAP and EPAP represents pressure support during inspiration. Given that most patients have concomitant severe OSA, the EPAP typically needs to be set at a

higher level (not rarely 10 - 15 - 20 cmH_2O) compared to patients with COPD or neuromuscular disease (NMD) (18).

The use of NIV in patients with acute decompensation of OHS is attractive because it improves ventilation and oxygenation and may avoid invasive mechanical ventilation. The physiological benefits of NIV include decreasing the work of breathing (WOB) by unloading respiratory muscles and improving central chemosensitivity after days of use. Combined with intermittent positive pressure physiotherapy it may also open atelectatic lung regions. NIV can improve somnolence, dyspnea. Moreover, NIV has a beneficial effect on the right ventricular function by restoring absolute lung volume and reducing right ventricular afterload (18).

In an acute setting oronasal or full-face mask is recommended for NIV, and appropriate interface fitting ensures adequate gas exchange. Nasal masks are commonly used in the chronic setting but can lead to mouth breathing with significant leakage. The choice of interface should be highly individualized aiming for comfort, and effective ventilation at the same time (18).

It is known that hospitalized patients suspected of having OHS who develop an acute-on-chronic respiratory failure have increased short-term mortality compared to stable ambulatory OHS patients (44). Given the effectiveness of NIV in OHS, to this day no randomized controlled trial was conducted examining ‘respiratory support’ vs. ‘no respiratory support’ in acute settings due to ethical challenges. Moreover, in case of acute respiratory failure in a previously untreated OHS patient the current guidance suggests initiation of long-term NIV, until they undergo outpatient workup in a sleep lab (1). This practice is supported by previous observational studies reporting improved survival rates after discharging OHS patients with long-term respiratory support, NIV in particular (30, 45).

1.7.4 Other possible additional therapeutic options

Although major developments occurred in the study of respiratory neurobiology over the last two decades, the novel fundamental findings have not been translated into clinical practice. It is also unknown if these efforts have any effect on the central respiratory drive related aspects of OHS. Preclinical studies, however, showed strong connection between leptin concentration and minute ventilation independently of food intake, body weight,

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and CO_2 production (46). Animal data strongly suggest that leptin signaling pathways in respiratory centers are promising targets for future drug development in weight management, and probably in OHS (47).

Efforts to decrease the weight with weight loss surgery or more current options such as glucagon-like peptide (GLP) agonists primarily used in diabetes therapy may help with reducing obesity and related mechanical changes (39, 48). It is unknown how weight loss effects an existing need for respiratory support or how often a previously established therapy needs to be reevaluated. Future studies are warranted focusing on these aspects.

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2. OBJECTIVES

As described in the introduction, there is an apparent gap of data regarding OHS in the Hungarian health care system. It is striking that there have been no public records targeting this particular syndrome, despite OHS being the most common indication for home mechanical ventilation in Hungary. There is an urgent need to draw attention to OHS in the country, the leading indication of long-term respiratory support. The suspected number of OHS patients is high and may increase in the future. OHS patients without therapy may appear in different sites of the Hungarian health-care system and may utilize a significant amount of resources, especially in urgent and critical care settings. On the other hand, state-of the art treatment of the syndrome is available in Hungary, as home mechanical ventilation has been established and is reimbursed by the national health insurance system (2). Understanding current management characteristics is important in order to improve long-term care for these patients.

The centralized nature of the current home mechanical ventilation provision in the country is a great opportunity to evaluate new concepts in OHS management. Introducing evidence based diagnostic and management algorithms is crucial in order to improve long-term outcome for a patient group that is currently facing high mortality rates worldwide.

Despite the complex pathophysiology of OHS, optimal therapy for patients has not yet been clearly established. It is also unclear how the “ideal CPAP” or, in the case of NIV “ideal EPAP” level can be determined and whether CPAP failure can be managed with a more optimized CPAP setting. According to OHS guidelines there are currently no official titration protocols in use. Recent studies have used protocols where gradual increase of CPAP is continued even after obstructive events and flow limitation have ceased, if saturation goals are not reached (49, 50). A recent study has shown the majority of patients with lower AHI (< 30 /h) can still benefit from CPAP values of 8 - 14 cmH_2O (50). This effect is probably attributable to restored absolute lung volumes. While hypoventilation and upper airway patency issues can be assessed using polysomnography, changes in the absolute lung volume and subsequent airway dynamics are currently not evaluated during routine therapy induction for OHS. Optimizing therapy by restoring EELV might improve long-term outcomes in this patient population.

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Small airway closure due to the reduction in absolute lung volumes during normal tidal breathing has been demonstrated using several methods in obese patients, including the negative expiratory pressure (NEP) technique and oscillometry (51, 52, 53). Intra-breath oscillometry detects dynamic changes in large and small airways, as well as in peripheral inhomogeneity during tidal breathing (54). As an additional benefit, tidal expiratory flow limitation (tEFL) can be revealed even during therapeutic intervention (55, 56).

The objective of the current thesis is to evaluate the current health care burden derived from undiagnosed OHS in Hungary, establish what outcomes characterize state of the art long-term respiratory support for this patient group and lay the groundwork to move respiratory therapy towards a more evidence-based management of the disease.

In order to meet these objectives, this thesis will explore the following themes:

2.1 The prevalence of OHS risk factors and outcomes in general ICUs in Hungary

The objective of our first study was to assess suspected OHS prevalence and associated outcomes among critically ill patients. As the study was conducted during the COVID-19 pandemic, our study not only aimed to describe the Hungarian health care burden of the disease, but also uncover how the COVID-19 pandemic might have impacted care. We planned to conduct a multicenter cross-sectional investigation in general ICUs. Primary outcomes were the prevalence and mortality of suspected OHS in critically ill patients. Secondary outcomes were relative risk of suspected OHS prevalence and mortality due to COVID-positive status, pneumonia, or need for invasive ventilation (IV).

2.2 Outcomes of home mechanical ventilation in OHS patients in Hungary

The objective of our second study was to uncover the characteristics and long-term outcomes of mechanical ventilation treatment available to OHS patients in Hungary. In order to characterize the patient group receiving treatment, evaluate the quality of care and describe the expected mortality, we planned to conduct a prospective observational study of patients starting home mechanical ventilation care for OHS in the Semmelweis University Home Mechanical Ventilation Program.

2.3 Intra-breath oscillometry in OHS, and a potential marker to optimize therapy

The objective of our third observational study was to assess the viability of intra-breath oscillometry in optimizing CPAP therapy for OHS by measuring tEFL in awake OHS

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patients in different body positions and at different CPAP settings. We hypothesized that, using this method, we could accurately detect tEFL and its reversal when applying the “optimal CPAP” level.

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3. METHODS

3.1 The prevalence of OHS risk factors and outcomes in general ICUs in Hungary

3.1.1 Design of the study

We conducted a multicenter cross-sectional investigation in Hungarian general ICUs. Eleven high case number (minimal bed number of 12), mixed case patient population ICUs participating in COVID-19 management were invited to take part in the study. Out of the eleven, five ICU sites took part in the study. Investigating physicians were asked to screen all critical care patients for risk factors of OHS during the study period between the 1st of October and the 30th of November 2020 and again between the 1st of October and 30th of November 2021. Overall patient number, COVID-19 prevalence and mortality were recorded for all participating units during the study period. Patients qualifying as suspected OHS were included in the study. Patients were excluded if they developed OHS related symptoms due to acute illness. We also excluded patients aged under 18 years. Written informed consent was provided by all participating patients or their next of kin. Data were collected via web - based questionnaire anonymously. The study protocol was approved by the regional ethical committee of Semmelweis University (SE RKEB 52/2020.).

3.1.2 Screening

Suspected OHS was defined as a BMI of ≥ 30 $kg \cdot m^{-2}$ and the presence of at least one OHS related risk factor before the current acute illness (Table 4).

Table 4 - Risk factors related to obesity hypoventilation syndrome (28)

- Daytime sleepiness
- Symptoms of right heart failure
- Daytime hypoxemia on room air (Sat 92 - 95%)
- Night-time hypoxemia on room air (Sat < 90%)
- Loud snoring
- Witnessed apnea

Epworth Sleepiness Scale (Table 5) was calculated to evaluate daytime sleepiness, a score of ≥ 6 was considered abnormal (57). Symptoms of right heart failure were considered

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according to European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure (58). Daytime and night-time hypoxemia was based on previous outpatient or in-hospital medical records. The presence of loud snoring and witnessed apnea was based on history collected from next of kin. In case of missing data, the risk factor was assumed to be absent.

Table 5 - Epworth Sleepiness Scale

How likely are you to doze or fall asleep in the following situation, in contrast to feeling just tired?

This refers to your usual way of life in recent times. Even if you haven't done some of these things recently try to work out how they would have affected you! Use the following scale to choose the most appropriate number for each situation!

0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing

Situation	
• Sitting and reading	……
• Watching TV	……
• Sitting, inactive in a public place (e.g. theatre or meeting)	……
• As a passenger in a car for an hour without a break	……
• Lying down to rest in the afternoon when circumstances permit	……
• Sitting and talking to someone	……
• Sitting quietly after a lunch without alcohol	……
• In a car, while stopped for a few minutes in the traffic	……

3.1.3 Data collection

Data collected included anthropometry data (sex, age, BMI), past medical history (comorbidities, previous hospitalization), COVID-19 status, ICU length of stay (LOS), length of invasive ventilation (LOV), ICU mortality, ICU readmission rate and abnormal arterial blood gas values indicative of hypoventilation (hypercapnia, elevated bicarbonate).

Anthropometry data was collected by critical care physicians based on the medical records of the patients, and information given by the patients or relatives. BMI was calculated on admission.

Information about past medical history, comorbidities such as diabetes, congestive heart disease, pulmonary hypertension, and ischemic heart disease was based on information provided by healthcare professionals, information in previous medical reports, and information based on findings during critical care treatment. Chronic kidney disease nomenclature was used according to Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease (59). Hospital admission and ICU admission data in the last 12 months were based on the electronic medical record of the patient. COVID-19 status was based on a PCR test (sputum, tracheal aspirate, or nasopharyngeal swab) performed at any time during the course of the acute illness resulting in the study hospital admission. The total number of days spent in the ICU defined the ICU LOS. The total number of days spent with invasive respiratory support defined LOV. Hypercapnia ($paCO_2 \geq 45$ mmHg) and increased bicarbonate (HCO_3^-) levels (≥ 27 $mmol \cdot L^{-1}$) on arterial blood gas measured at the time of discharge from ICU defined alveolar hypoventilation.

3.2 Outcomes of home mechanical ventilation in OHS patients in Hungary

3.2.1 Design of the study

We performed a prospective long-term follow-up investigation among the OHS patients of the Semmelweis University Home Mechanical Ventilation Program. We screened patients with chronic respiratory insufficiency during an enrollment period between the 1st of January 2018 and the 30th of January 2023. After confirming the diagnosis of OHS we performed a six-month follow-up. We started data collection after obtaining written informed consent.

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We excluded patients with neuromuscular disease, diaphragm paralysis, kyphoscoliosis, COPD, COPD-OSA overlap syndrome, and patients under 18 years (Figure 5).

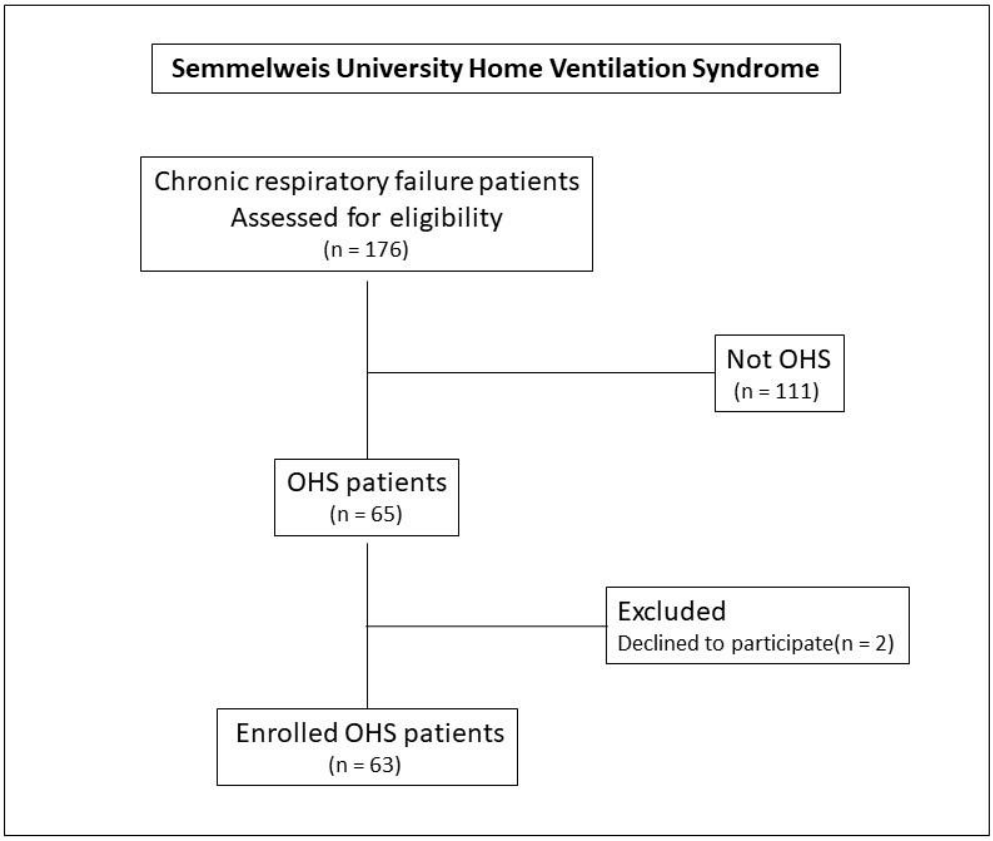

Figure 5 *- Enrollment of study patients. OHS = Obesity hypoventilation syndrome*

The local committee of Semmelweis University approved this study in agreement with the Scientific and Human Research Ethics Committee of the Hungarian Medical Research Council (SE RKEB 251/2017).

After diagnostic work-up long-term intermittent noninvasive mechanical ventilation was initiated. We used the institutional protocol based on the Canadian and German guidelines to personalize home mechanical ventilation for each patient (7, 60, 61). For long-term respiratory support we used noninvasive ventilators (Philips Respironics A40, and Trilogy 100 [Philips Respironics, Murrysville, Pennsylvania, US]; Löwenstein Prisma VENT40 [Löwenstein Medical Technology GmbH, Hamburg, Germany]) with total facemasks or oronasal masks covering the nose and the mouth. Consecutive sleep studies (polysomnography or polygraphy) with real-time noninvasive monitoring of gas

exchange were performed to titrate the parameters of noninvasive ventilation. The parameters were personalized to avoid obstructive events and maintain minute ventilation to achieve normocapnia during NIV. Oxygen supplementation was given in case of sustained hypoxemia. After discharge patients had regular follow-up at predefined dates and emergency consultations were performed if necessary.

After informed consent demographic and anthropometric data (age, gender, weight, height, BMI) were collected at the time of the initiation of long-term therapy. Arterial blood sample was taken, and gas exchange parameters were collected ($paCO_2$, HCO_3^-, paO_2). The patient was considered normocapnic in case of $paCO_2 < 45$ mmHg, and $HCO_3^- < 27$ $mmol \cdot L^{-1}$. AHI was recorded and collected during a sleep study. Severe OSA was considered in case of AHI > 30 / hour.

We collected data regarding comorbidities according to WHO ICD 11 criteria (62). We recorded the OHS stage according to the state of the patient and the known comorbidities at the time of diagnosis (6, 63).

We classified the patients into two subgroups according to the initiation of long-term therapy. Elective initiation was considered in cases of chronic respiratory insufficiency in stable condition. Emergency initiation was considered if the respiratory support was started after an onset of acute-on-chronic respiratory failure.

After six-month follow-up data collection was performed. We collected anthropometric data (weight, height, BMI), arterial blood gas was taken and $paCO_2$, HCO_3^-, paO_2 were recorded. Data from the noninvasive ventilators were also collected (IPAP, EPAP, AHI, daily usage). We used the national electronic health service database to collect hospitalization data from a six-month period before and after therapy was initiated.

We collected the total length of treatment and the number of days spent hospitalized during the whole treatment time. We registered the time of death in case of deceased patients.

3.3 Intra-breath oscillometry in OHS, and a potential marker to optimize therapy

3.3.1 Design of the study

We performed a cross-sectional observational investigation among OHS patients. We screened patients receiving therapy for OHS through the Semmelweis University Home

Ventilation Program (Budapest, Hungary) from the 1st of May 2021 to the 31st of January 2022. After obtaining written informed consent, we collected demographic data and performed arterial blood gas analysis and forced spirometry tests. We then used intra-breath oscillometry in sitting and supine positions to assess the baseline tEFL of the study patients. A second measurement was performed in the supine position with stepwise application of CPAP to determine the CPAP level that could obliterate tEFL (e.g. "optimal CPAP"). We examined the correlation of tEFL with forced spirometry test values, BMI, and AHI. The local committee of Semmelweis University approved this study in agreement with the Scientific and Human Research Ethics Committee of the Hungarian Medical Research Council (SE RKEB 239/2018).

3.3.2 Inclusion and exclusion criteria

Adult (> 18 years) patients with previously confirmed OHS (as per the Task Force Report of the European Respiratory Society) (6) already established on intermittent CPAP or bilevel ventilation were eligible for the study. Exclusion criteria included unstable condition (worsening of respiratory symptoms in the previous 30 days), coexisting chronic obstructive lung disease, and chronic cough or sputum production.

3.3.3 Data collection

The data collected at screening included diagnostic criteria, OHS stage, OSA level, and long-term ventilation therapy settings. The OHS stage was identified at the time of the initiation of long-term respiratory support. The OSA level was based on the AHI values recorded during the initial polysomnography at the time of diagnosis. We collected demographic data (including age, sex, and BMI) at the time of oscillometry and spirometry measurements. Arterial blood gas sampling was performed on room air at least 15 min after discontinuing contingent oxygen supplementation. Patients underwent forced spirometry tests following oscillometry in both body positions using the Piston PinkFlow spirometer (Piston Medical Ltd, Budapest, Hungary), according to the American Thoracic Society and European Respiratory Society guidelines (64). The forced vital capacity (FVC), FVC predicted %, forced expiratory volume in 1 s (FEV1), FEV1 predicted %, and FEV1/FVC ratio were recorded.

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3.3.4 Oscillometry

Respiratory oscillometry employs external small-amplitude oscillations on spontaneous breathing while measuring the mechanical response of the respiratory system, expressed as respiratory impedance (Zrs). The two components of Zrs reflect the sum of the total airway and tissue resistances (resistance of the respiratory system - Rrs) and the elastic and inertial components, describing the ability to store energy and promote passive exhalation (reactance of the respiratory system – Xrs). In contrast to conventional multiple-frequency oscillometry determining mean Zrs over multiple breaths, the novel mono-frequency intra-breath modality follows the changes in Rrs and Xrs with volume (V) and flow (V') within the breathing cycle (54). The intra-breath decrease in Xrs during tidal expiration is a sensitive marker of the dynamic changes in small airway mechanical properties, reflecting tEFL (55, 56). The difference between the mean values of expiratory and inspiratory reactance (ΔXmean) has been used by several studies to identify tEFL, however, measurements under CPAP therapy may require a more complex assessment of the Xrs vs. V and Xrs vs. V' relationships (55, 56, 65, 66). In particular, the high CPAP levels used for OHS may result in glottal interference of impedance values, which might interfere with the ability of ΔXmean to accurately reflect tEFL (67). To better characterize the Xrs vs. V and Xrs vs. V' relationships and possibly identify glottal interference at high CPAP levels, we measured a variety of intra-breath parameters (see Table 6). In addition to measuring Zrs variables at certain time points of the breathing cycle (ReE, ReI, ΔR, XeE, XeI, ΔX), we calculated established (ΔXmean) and newly proposed tEFL markers (AXV and, AXV').

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Table 6 - Definition of intra-breath oscillometry variables		
Parameter	**Unit**	**Definition**
Vt	**Liter**	Tidal volume
Frequency	**min^{-1}**	Breathing frequency
Ti/Ttot		Inspiratory time divided by breathing cycle time
ReE	**$cmH_2O \cdot s \cdot L^{-1}$**	Resistance of the respiratory system at the end of expiration
ReI	**$cmH_2O \cdot s \cdot L^{-1}$**	Resistance of the respiratory system at the end of inspiration
ΔR	**$cmH_2O \cdot s \cdot L^{-1}$**	Difference between ReE and ReI
ΔXmean	**$cmH_2O \cdot s \cdot L^{-1}$**	Difference between the mean values of expiratory and inspiratory reactance
XeE	**$cmH_2O \cdot s \cdot L^{-1}$**	Respiratory reactance at the end of expiration
XeI	**$cmH_2O \cdot s \cdot L^{-1}$**	Respiratory reactance at the end of inspiration
ΔX	**$cmH_2O \cdot s \cdot L^{-1}$**	Difference between XeE and XeI
AXV	**$cmH_2O \cdot s$**	Area of the reactance vs. volume diagram
AXV'	**cmH_2O**	Area of the reactance vs. flow diagram
ARV	**$cmH_2O \cdot s$**	Area of the resistance vs. volume diagram
ARV'	**$cmH_2O \cdot s \cdot L^{-1}$**	Area of the resistance vs. flow diagram

We measured Zrs using a custom-made oscillometry setup (Figure 6). The system consisted of a loudspeaker-in-box system for the generation of an oscillatory signal (frequency: 10 Hz, amplitude: 1 cmH_2O), pressure sensors (Honeywell model 26PCAFA6D, Golden Valley, MN, USA), and a screen pneumotachograph to measure P and V'. We used a noninvasive respiratory device (A40; Philips Respironics, Murrysville, PA, USA) to generate CPAP.

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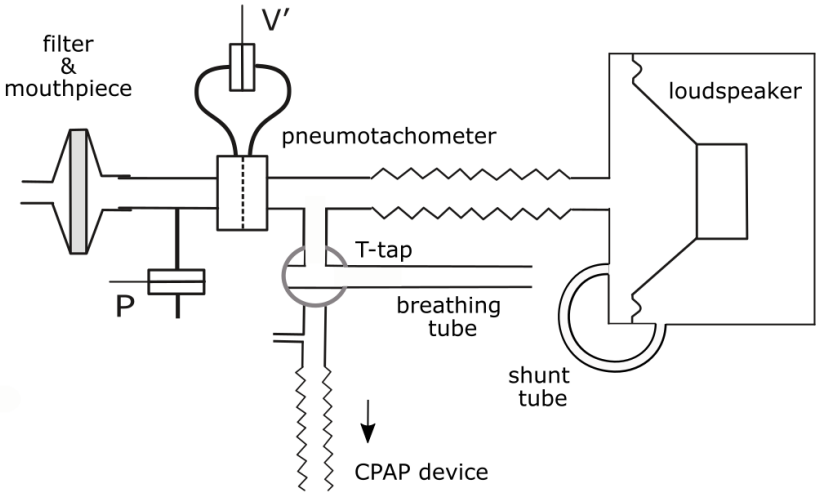

Figure 6 *- Schematics of the oscillometry setup.*
Antibacterial/viral filter and mouthpiece assembly: PBF-100 (Piston Medical Inc. Budapest. Hungary). Pressure (P) and airflow (V') sensors: Honeywell model 26PCAFA6D (Golden Valley. MN. USA). Breathing tube and non-invasive respiratory device (A40; Philips Respironics. Murrysville. PA. USA) were alternately connected to the setup via a T-tap for measurements for "no CPAP" and at CPAP ≥ 5 cmH_2O. respectively. The shunt tube allowed for equilibration of static pressures between the front and back chambers of the loudspeaker-in-box system.

We conducted oscillometry in awake patients during tidal breathing in sitting and supine positions. Before recording, we instructed the patients according to technical standards (68) and applied a nose clip and cheek support. The baseline recording was started when a consistent, homogeneous breathing pattern was established and lasted for 30 s. We then recorded for 120 - 240 s in the supine position with stepwise elevations of CPAP levels from 0 to 5, 10, 15, and 20 cmH_2O. At each CPAP level, we selected 3 - 8 regular, artefact-free breathing cycles for intra-breath analysis. We discontinued measurements after two unsuccessful attempts in case of discomfort or intolerance (e.g., inability to maintain CPAP without leakage around the mouthpiece).

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An optimal CPAP level was defined after the measurement during data processing. The discrete CPAP level was considered optimal when the typical anticlockwise looping of AXV' diminished below the threshold as $|AXV'| < 1$ cmH_2O.

We computed the auto- and cross-correlation spectra of the recorded P and V' signals using the fast Fourier transform algorithm and retained a bandwidth of ± 2 Hz at 10 Hz oscillation frequency for further analysis. V was obtained by numerical integration of V'. Definitions of measured and derived intra-breath variables are presented in Figure 7 and Table 6. We computed the values of Rrs and Xrs for each oscillation period (0.1 s) smoothed by a moving average over 0.5 s. We identified the different phases of the breathing cycle according to the interpolated zero crossings of V'. We determined the corresponding end-expiratory and end-inspiratory (i.e., zero-flow) Rrs values (ReE and ReI) and Xrs values (XeE and XeI), as well as their corresponding differences (ΔR and ΔX).

Intra-breath oscillometry variables were pooled and compared in the sitting and supine positions to identify tEFL worsening in the supine body position (characteristic of severe obesity). We then identified diminishing tEFL with stepwise application of CPAP. We calculated the correlation between previously used marker of tEFL (ΔXmean from our 10 Hz data) and the newly proposed parameters (XeE, ΔX, AXV, and AXV').

We further analyzed intra-breath oscillometry variables according to patient subgroups (OSA vs. no OSA and severe OSA vs. no severe OSA).

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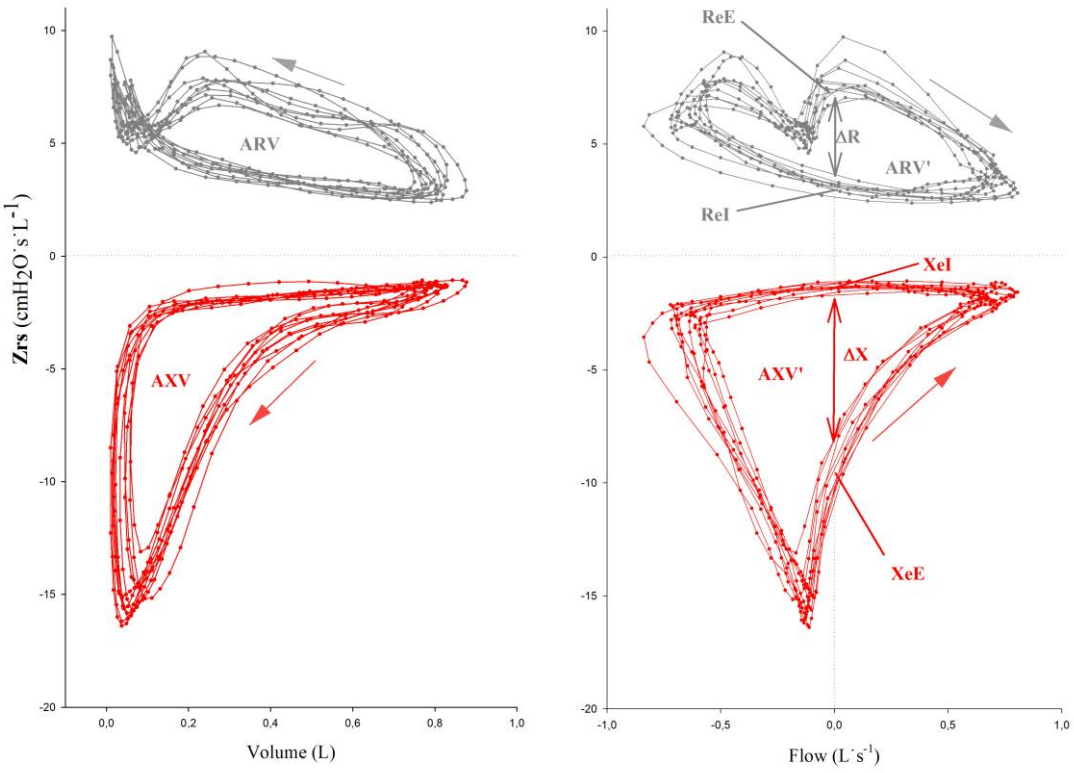

Figure 7 - *Measured and derived intra-breath oscillometry variables*

The two parts of the respiratory impedance (Zrs), the resistance (Rrs) and the reactance (Xrs), are plotted in grey and red, respectively. Rrs reflects the sum of total airway and tissue resistances, whereas Xrs, which consists of elastic and inertial components, describes the ability to store energy and promote passive exhalation. A single patient's Rrs and Xrs recordings are mapped against tidal volume and flow parameters. The arrows mark the direction of looping during a single breathing cycle. Positive flow indicates inspiration and negative flow indicates expiration. Plotting Rrs and Xrs against volume and flow permits insight into the intra-breath changes of airway mechanics in a detailed manner. To describe complex intra-breath changes in respiratory mechanics the following measured and derived variables were used: ReE = end expiratory resistance; ReI = end inspiratory resistance; ΔR = difference between ReE and ReI; XeE = end expiratory reactance; XeI = end inspiratory reactance; ΔX = difference between XeE and XeI; AXV = area of Xrs vs V diagram; AXV' = area of Xrs vs V' diagram;

3.4 Statistical analysis

The results are expressed as median (± standard deviation) for continuous variables and as frequency (percentage) for categorical variables.

Statistical significance was set at $p < 0.05$.

The normality of the collected data was analyzed with the Kolmogorov-Smirnov test.

Different patient groups (OHS suspected vs. OHS not suspected, COVID-19 positive vs. negative patients, IV required vs. not required, survivors vs. non-survivors, different BMI and age groups) were compared with 2 x 2 or 3 x 2 Pearson's Chi-square tests.

The values of the follow-up data (BMI, pO_2, $paCO_2$ HCO_3^-, AHI) and intra-breath oscillometry variables (ReE, ReI, ΔR, XeE, XeI, ΔX, ΔXmean, AXV, AXV') in the two body positions were analyzed with the Wilcoxon signed rank test.

The values between subgroups (acute vs. elective; men vs. women; presence of OSA vs. absence of OSA; presence of severe OSA vs. absence of severe OSA) such as days hospitalized, demographic data (age, BMI, AHI) and oscillometry parameters (XeE, ΔX, AXV, AXV') were analyzed with the Mann-Whitney U test.

The effect of CPAP level on the measured intra-breath oscillometry variables was analyzed using the Friedman ANOVA and Kendall's concordance tests.

The correlation between oscillometry and spirometry parameters (FEV1, FEV1%, FEV1/FVC, and XeE, ΔX, AXV, AXV') and between respiratory support parameters ('optimal' CPAP vs. actual EPAP / CPAP) were analyzed using the Spearman rank order correlation.

Mortality data was analyzed using the Kaplan-Meier method. The difference in mortality between subgroups was analyzed with the Cox regression.

Data analysis was conducted using Statistica 13 software (Tibco Data Science, Hamburg, Germany), and SPSS (IBM Corp., Armonk, NY, United States). We did not use the missing data for the calculations. Figures were created using SigmaPlot 14.5 (Systat Software, San Jose, United States).

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4. RESULTS

4.1 The prevalence of OHS risk factors and outcomes in general ICUs in Hungary

The 5 participating ICUs treated a total of 904 patients during the study period. Overall mortality reported by the units was 35.4%. Overall COVID-19 prevalence of the ICUs was 58.7% during the study period.

Out of the 904 ICU patients screened, 79 patients (8.7 ± 5.5%) were reported to have risk factors for OHS. Prevalence of suspected OHS varied by site and a significant difference was observed between ICU sites ($p < 0.001$) (see Figure 8).

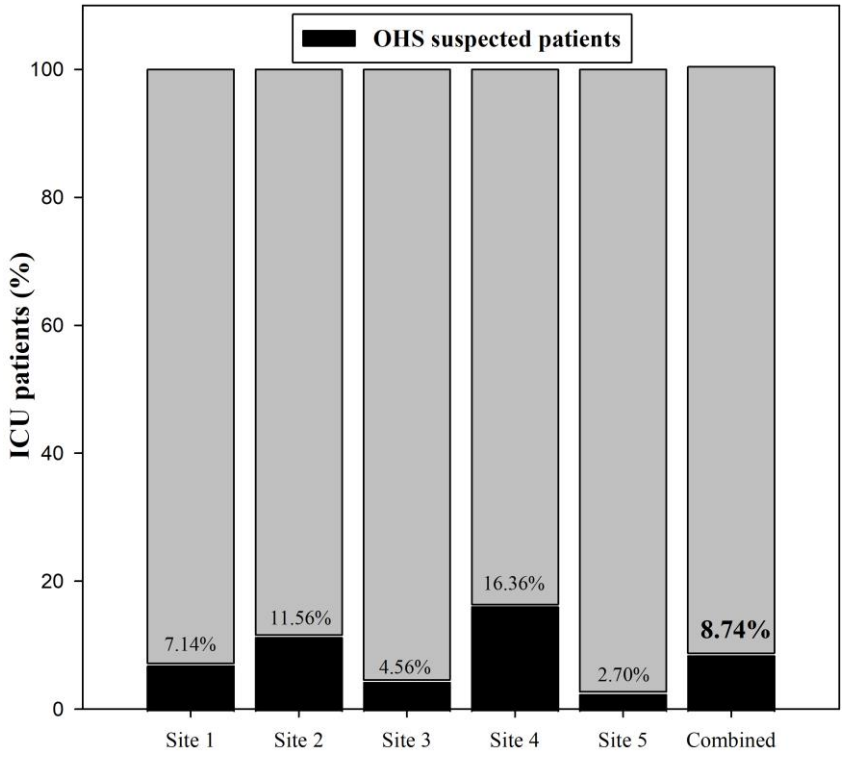

Figure 8 *- The overall prevalence of patients with suspected obesity hypoventilation syndrome in intensive care units*

Characteristics of the study patients are listed in Table 7. More than two-third of suspected OHS patients (72.2%) were male, and the mean age was 62.9 (± 11.9) years. The two most frequent indications for ICU admission were pneumonia (46 patients, 58.2%) and congestive heart failure (12 patients, 15.2%).

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Table 7 – The clinical characteristics of suspected obesity hypoventilation syndrome patients (mean, SD / N, %)
BMI = Body Mass Index, WHO = World Health Organization, ICU = Intensive Care Unit, LOS = Length of Stay, LOV = Length of Ventilation, COVID = Coronavirus disease, CPR = Cardiopulmonary Resuscitation

Anthropometry	
Total (n, %)	79 (100%)
Male (n, %)	57 (72.2%)
Age (years) (Mean, SD)	62.9 (± 11.9)
BMI ($kg \cdot m^{-2}$) (Mean, SD)	37.6 (± 6.4)
Obesity WHO Class I (n, %)	33 (41.8%)
Obesity WHO Class II (n, %)	24 (30.4%)
Obesity WHO Class III (n, %)	22 (27.8%)
ICU LOS (days) (Mean, SD)	11.5 (± 9.3)
Invasive ventilation required (n, %)	60 (75.9%)
LOV (days) (Mean, SD)	8.7 (± 9.5)
Mortality (n, %)	32 (40.5%)
COVID positive (n, %)	38 (48.1%)
Diagnosis at admission	
Pneumonia (n, %)	46 (58.2%)
Congestive heart failure (n, %)	12 (15.2%)
Acute exacerbation of COPD (n, %)	6 (7.6%)
Acute kidney failure (n, %)	3 (3.8%)
Pulmonary embolism (n, %)	3 (3.8%)
St. p. CPR (n, %)	3 (3.8%)
Other nonsurgical (n, %)	4 (5.1%)
Surgical / Trauma (n, %)	10 (12.7%)
OHS related symptoms (23) (n = 59)	
Epworth sleepiness score > 5 (n, %)	49 (83.05%)
Pitting oedema (n, %)	52 (65.8%)
Nocturia (n, %)	55 (69.6%)
Loud snoring (n, %)	68 (86.1%)
Witnessed apnoea (n, %)	17 (21.5%)
Comorbidities (28)	
Congestive Heart Failure (n, %)	27 (34.2%)
Pulmonary Hypertension (n, %)	10 (12.7%)
Ischaemic Heart Disease (n, %)	19 (24.1%)
Diabetes Mellitus (n, %)	33 (41.8%)
Chronic Renal Failure (n, %)	7 (8.9%)
No comorbidities (n, %)	27 (34.2%)
Hospital admission in the last 12 months (n, %)	23 (29.1%)

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Daytime sleepiness scores were reported for 55 out of 79 patients and were abnormal for 45 patients (81.8%). Snoring, nocturia, and pitting edema were the most frequent symptoms among the reported individuals (86.1%, 69.6%, and 65.8% respectively). 17 patients (21.5%) had witnessed apnea by relatives. 69% of the cohort displayed at least 3 symptoms related to OHS (Figure 9).

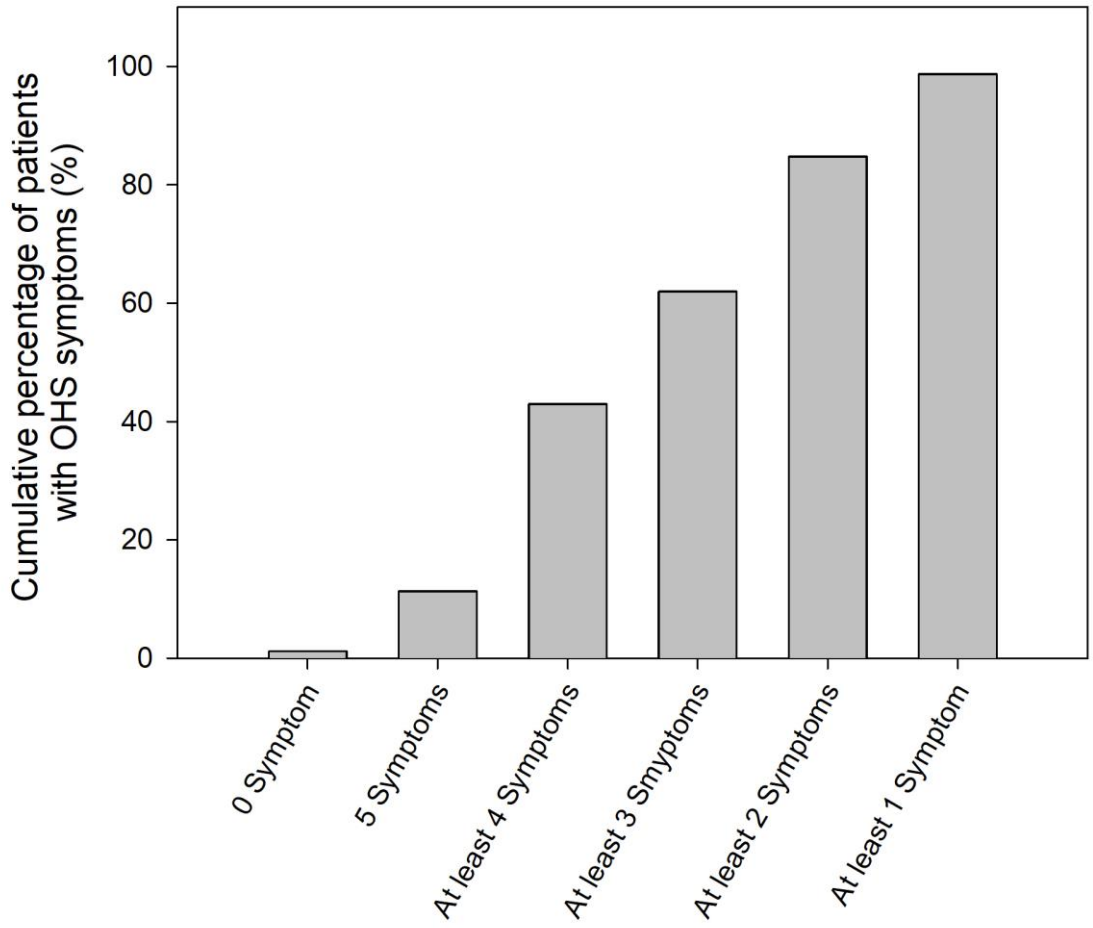

Figure 9 *– Cumulative percentage of study patients with obesity hypoventilation syndrome related symptoms*

Almost half of the patients (48.1%) had confirmed SARS-CoV-2 infection. On the day of discharge, 14 (29.9%) survivors had elevated HCO_3^- and 12 (25.5%) had elevated $paCO_2$ levels despite normal pH, indicating potential hypoventilation. 10 (21.3%) patients had confirmed overnight hypoventilation and elevated $paCO_2$ levels during spontaneous breathing.

Table 8 – Combined mortality rate in the intensive care unit sites and among the suspected obesity hypoventilation patients					
ICU cohort	Overall (n = 904)	OHS suspected (n = 79)	OHS not suspected (n = 825)	OR (CI 95%)	*P* χ^2 test
Mortality	320 (35.4%)	32 (40.5%)	288 (34.9%)	1.270 (0.792-2.034)	0.988

LOS was 11.5 (± 9.3), and LOV was 8.7 (± 9.5). Mortality rate for suspected OHS patients was 40.5%. There was no reported readmission of suspected OHS patients during the study period. As Table 8 shows, the mortality rate did not differ in OHS-suspected patients compared to the ICU patients without OHS risk factors. The mortality rate was similar in both study periods (37.8% vs. 40%; p > 0.05).

Table 9 - The impact of anthropometric data, admitting diagnosis, and past medical history on outcome					
	Suspected OHS patients n = 79	ICU survivors n = 47	Non-survivors n = 32	OR (CI 95%)	*p* χ^2 test
Anthropometry					
Sex (male)	57 (72.2%)	33 (70.2%)	24 (75%)	0.79 (0.29-2.17)	0.64
Age > 65 years	35 (44.3%)	20 (42.6%)	15 (46.9%)	1.91 (0.48-2.9)	0.70
ICU Diagnosis					
Pneumonia	46 (58.2%)	18 (39.1%)	28 (87.5%)	11.28 (3.39-37.50)	**<0.001**
Congestive heart failure	12 (15.2%)	11 (23.4%)	1 (3.1%)	0.11 (0.01-0.86)	**0.01**
AE-COPD	6 (7.6%)	6 (12.8%)	0 (0%)	0.87 (0.78-0.97)	**0.03**
Acute Kidney Failure	3 (3.8%)	3 (6.4%)	0 (0%)	0.94 (0.87-1.01)	0.15
Pulmonary embolism	3 (3.8%)	3 (6.4%)	0 (0%)	0.94 (0.87-1.01)	0.15
Post cardiac arrest	3 (3.8%)	1 (2.1%)	2 (6.3%)	3.07 (0.27-35.33)	0.35
Other non-surgical	4 (8.5%)	4 (8.5%)	0 (0%)	0.915 (0.84-0.99)	0.09
Surgical / Trauma	10 (12.7%)	9 (19.1%)	1 (3.1%)	0.14 (0.16 -1.13)	**0.04**
COVID-19	38 (48.1%)	11 (23.4%)	27 (84.4%)	17.67 (5.49-56.88)	**<0.001**
Medical history					
Chronic heart failure	27 (34.2%)	18 (38.3%)	9 (28.1%)	0.63 (0.239-1.66)	0.35
Pulmonary hypertension	10 (12.7%)	5 (10.6%)	5 (15.6%)	1.56 (0.41-5.89)	0.51
Ischaemic heart disease	19 (24.1%)	8 (17.0%)	11 (34.4%)	2.55 (0.89-7.33)	0.08
Diabetes mellitus	33 (41.8%)	16 (34.0%)	17 (53.1%)	2.20 (0.88-5.51)	0.09
Chronic kidney disease	7 (8.9%)	4 (8.5%)	3 (8.9%)	1.11 (0.23-5.34)	0.90

In the suspected OHS group, patients with COVID-19 infection and pneumonia had increased mortality (OR 17.67; 95% CI 5.49 - 56.88; p < 0.001 and OR 11.28; 95% CI 3.39 - 37.50; p < 0.001 respectively) and a higher rate of invasive mechanical ventilation (OR 7.47; 95% CI 1.97 - 28.39; p = 0.001 and OR 4.33; 95% CI 1.43 - 13.1; p = 0.007 respectively) compared to those without these factors (Table 9, Table 10).

Table 10 – The impact of anthropometric data, admitting diagnosis, and past medical history on the need for invasive mechanical ventilation

	All patients n = 79	IV required n = 60	IV not required n = 19	OR (CI 95%)	*p* χ^2 test
Anthropometry					
Sex (male)	57 (72.2%)	42 (70%)	15 (78.9%)	1.61 (0.47-5.52)	0.45
Age > 65 years	35 (44.3%)	28 (46.7%)	7 (36.8%)	1.5 (0.52-4.33)	0.45
ICU Diagnosis					
Pneumonia	46 (58.2%)	40 (66.7%)	6 (31.6%)	4.33 (1.43-13.1)	**0.007**
Congestive heart failure	12 (15.2%)	7 (17.5%)	5 (26.3%)	0.37 (0.10-1.34)	0.12
AE-COPD	6 (7.6%)	4 (6.7%)	2 (10.5%)	0.61 (0.10-3.6)	0.58
Acute kidney injury	3 (3.8%)	2 (3.3%)	1 (5.3%)	0.62 (0.53-7.25)	0.70
Pulmonary embolism	3 (3.8%)	0 (0%)	3 (15.8%)	0.84 (0.69-1.02)	**0.002**
Post cardiac arrest	3 (3.8%)	3 (5%)	0 (0%)	1.05 (0.99-1.11)	0.32
Other nonsurgical	4 (5.1%)	3 (5%)	1 (5.3%)	0.95 (0.93-9.68)	0.96
Surgical / trauma	10 (12.7%)	6 (10%)	4 (21.1%)	0.42 (0.10-1.67)	0.21
COVID-19	38 (48.1%)	35 (58.3%)	3 (15.8%)	7.47 (1.97-28.39)	**0.001**
Medical history					
Chronic heart failure	27 (34.2%)	20 (33.3%)	7 (36.8%)	0.86 (0.29-2.51)	0.78
Pulmonary hypertension	10 (12.7%)	8 (13.3%)	2 (10.5%)	1.31 (0.25-6.76)	0.75
Ischaemic heart disease	19 (24.1%)	17 (28.3%)	2 (10.5%)	3.36 (0.70-16.14)	0.11
Diabetes mellitus	33 (41.8%)	26 (43.3%)	7 (36.8%)	1.31 (0.45-3.79)	0.62
Chronic kidney disease	7 (8.9%)	6 (10%)	1 (5.3%)	2.00 (0.26-17.75)	0.53

COVID-19 infection increased mortality in each BMI category [BMI 30 - 35 $kg.m^{-2}$ OR 14.4; 95% CI 2.29-90.60; BMI 35.1 - 40 $kg.m^{-2}$ OR 11,0 95% CI 1.60 - 75.50; BMI > 40 $kg.m^{-2}$ OR 38.5 95% CI 2.91 - 508.46]. However, in the COVID-19-positive cohort there was no difference in mortality rate based on BMI categories (p = 0.374) (Figure 10).

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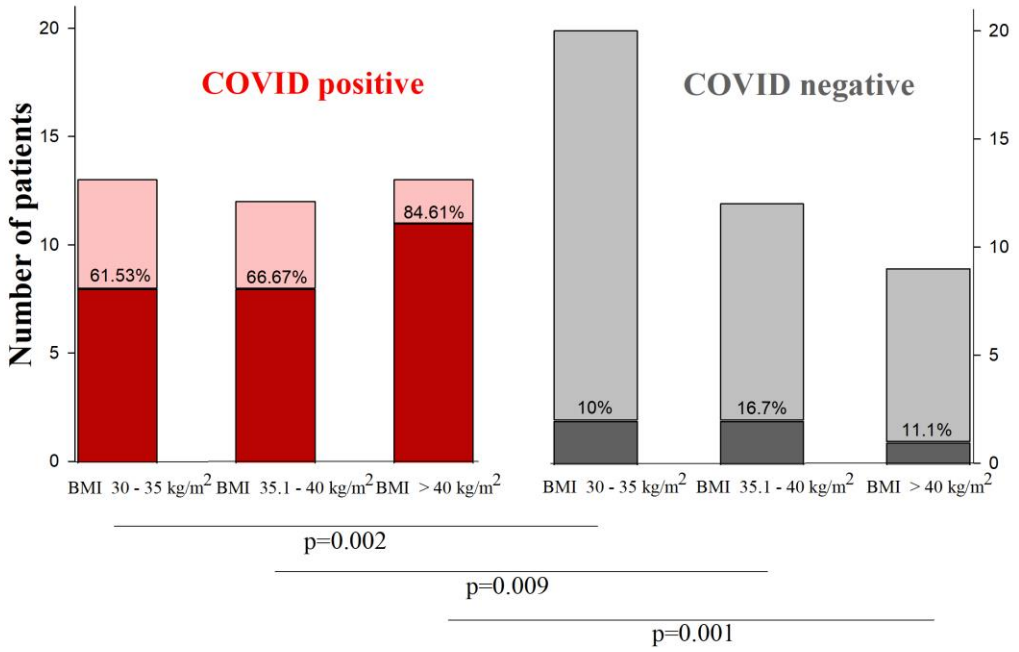

Figure 10 *- Impact of COVID-19 on the mortality of suspected obesity hypoventilation syndrome patients. Red bars indicate the number of patients with COVID-19 infection in each BMI category, and grey bars correspond to COVID-19 negative patients. Dark shading represents the mortality rate in each category.*

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4.2 Outcomes of home mechanical ventilation in OHS patients in Hungary

Sixty-three patients were enrolled in the study. The demographic and anthropometric data are presented in Table 11. The distribution of BMI and age are presented in Figure 11 and Figure 12.

Table 11 – The demographic and anthropometric data of the enrolled patients (n = 63) (mean ± SD / n, %)	
Age (years)	55.37 (± 9.7)
Female	21 (33.3%)
Male	42 (66.7%)
Severe OSA (AHI > 30 / hour)	38 (60.3%)
Average daily use of the ventilator (hours)	7.5 (± 3.0)
IPAP (cmH_2O)	22.4 (± 4.1)
EPAP (cmH_2O)	12.7 (± 3.0)
Normocapnia after six months	54 (85.7%)

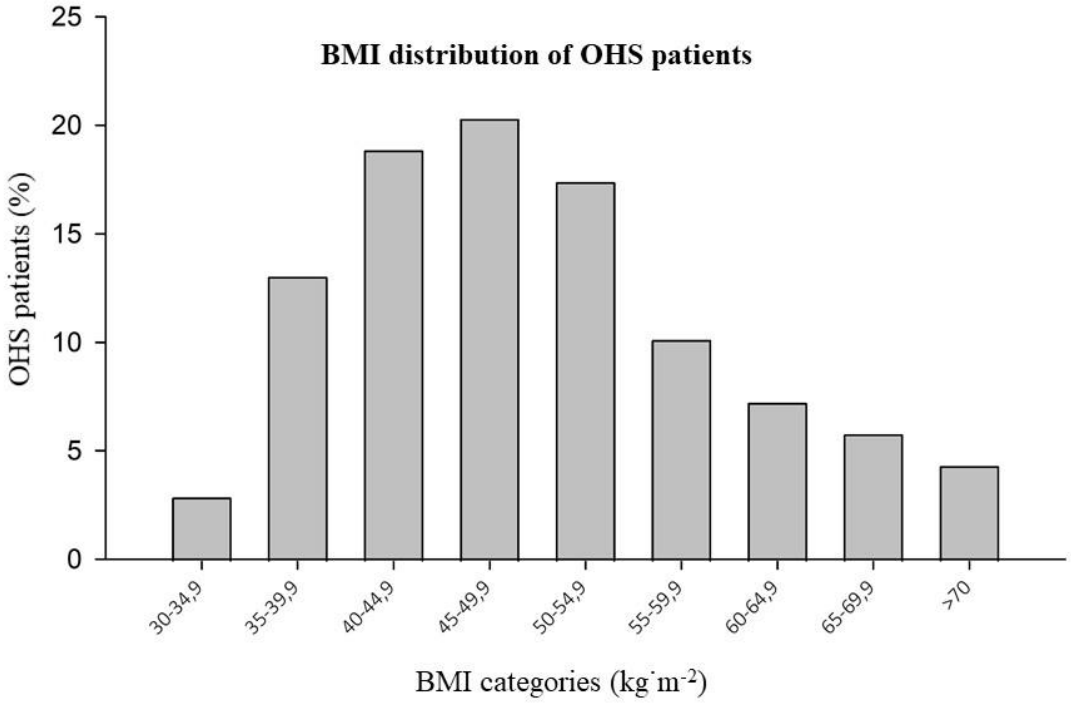

Figure 11 *- Body mass index distribution of study patients (n = 63)*

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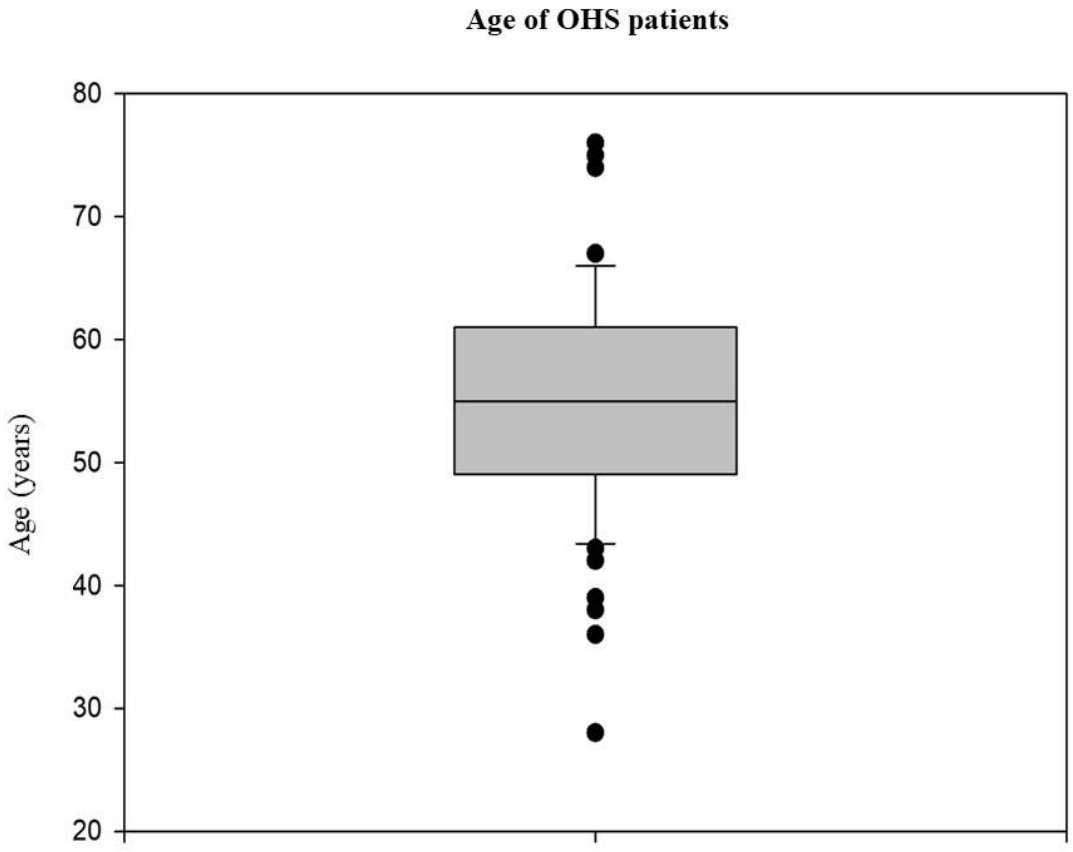

Figure 12 *- Age of study patients (n = 63)*

As can be seen, the population mainly consisted of extremely obese patients and had a male dominance (66.7%). According to the sleep studies 60.3% of patients 38 had severe OSA (AHI > 30 / h). The long-term respiratory support was initiated electively in 25 patients (40%), and after an episode of acute-on-chronic respiratory failure in 38 patients (60.3%). All respiratory support was provided noninvasively (63 patients, 100%). The comorbidities of the patients are presented in Table 12.

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Table 12 – Comorbidities of OHS patients according to WHO ICD 11 (n, %)	
Disease of the circulatory system	*60 (95.2%)*
Essential hypertension	59 (93.7%)
Chronic ischaemic heart disease	5 (7.9%)
Congestive heart failure	31 (49.2%)
Atrial fibrillation	8 (12.7%)
Pulmonary embolism	6 (9.5%)
Chronic arterial occlusive disease	3 (4.8%)
Endocrine diseases	*37 (58.7%)*
Diabetes mellitus	31 (49.2%)
Hypothyroidism	3 (4.8%)
Hypolipoproteinaemia	10 (15.9%)
Chronic kidney disease	*3 (4.8%)*

After six months of treatment 96.8% (61) of the patients had good compliance with the home ventilation program, using the ventilator with an average of 7.5 (± 2.9) hours per day. 54 patients (85.7%) reached normocapnia.

According to the hospitalization data the patients had spent an average of 7.6 days in hospital before therapy, and this decreased significantly to an average of 0.7 days after respiratory support was started ($p < 0.001$) (Figure 13). We did not find a difference in the hospitalization (6.9 ± 9.6 vs. 8.5 ± 12.4 days) and rehospitalization (0.4 ± 1.7 vs. 1.2 ± 4.4 days) data between emergency and elective initiation groups.

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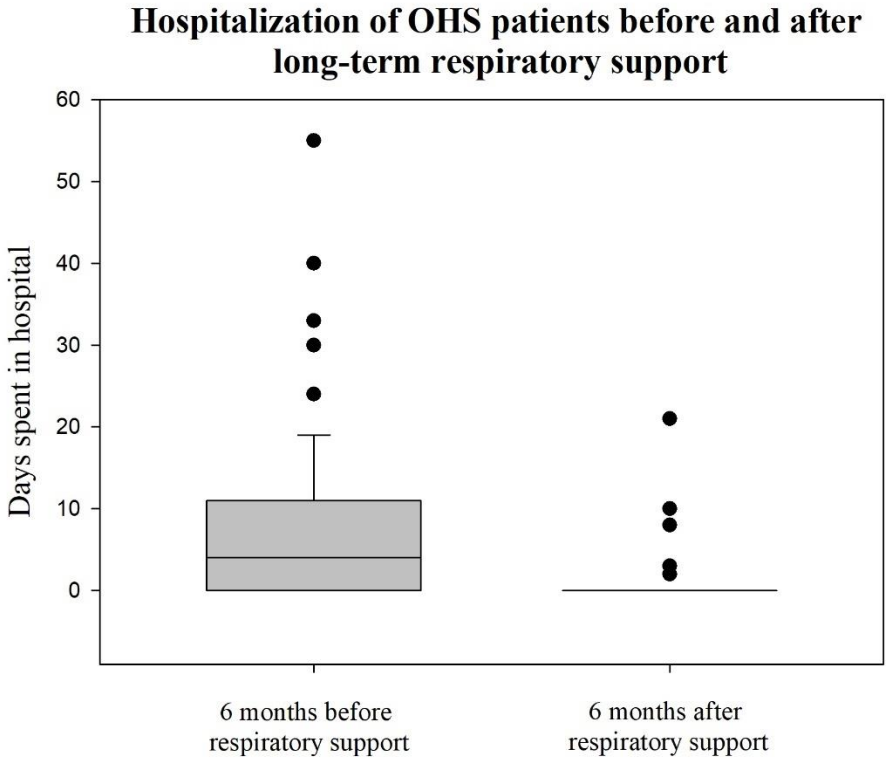

Figure 13 *- Hospitalization of study patients before and after initiation of long-term therapy. The days spent in hospital decreased significantly after respiratory support (p<0.001)*

The length of follow-up varied among patients between 6 and 66 months. Adherence of the patients to the home ventilation program was 88.9% (56 patients). During the observation period 5 patients were deceased (7.9%). According to our calculation the expected cumulative mortality rate was 98.2% in six months, 96.3% in one year, 94.1% in three years, and 86.7% in five years. The Kaplan-Meier survival plots are shown in Figure 14 and Figure 15. When comparing mortality rates we observed a favorable trend for the elective group ($p > 0.05$).

During the observational period the normalized rehospitalization rate was 2.2 (± 4.1) days / year.

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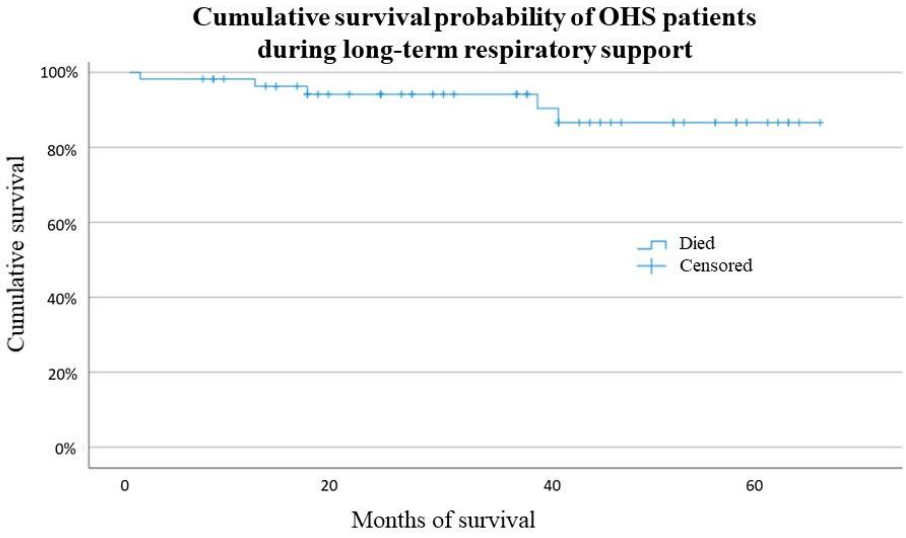

Figure 14 *- Kaplan-Meier plot of study patients.*

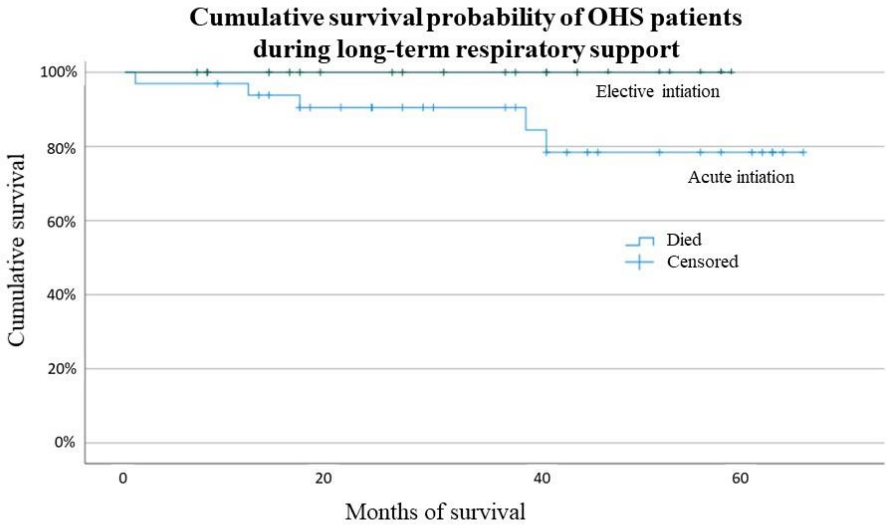

Figure 15 *- Kaplan-Meier plot of 'acute' and 'elective' study patients.*

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4.3 Intra-breath oscillometry in OHS, and a potential marker to optimize therapy

Thirty-five patients were measured in the sitting and supine position, and 33 completed the CPAP measurements. The demographic data are summarized in Table 13. Mean BMI was 49.3 $kg \cdot m^{-2}$ (range 32.3 - 91.1 $kg \cdot m^{-2}$). Note that 88.6% of patients had severe (III-IV stage) OHS and that blood gas values reflected adequate treatment (63). Demographic data (age, BMI, baseline AHI) did not differ in the two sexes (data not shown).

Table 13 - Demographic data of study patients (N = 35) are presented as mean (± SD) or n (%);
† AHI was measured at the time when NIV treatment was initiated
# Note the normalized values of arterial blood gas as a result of the NIV treatment
BMI = body mass index; OHS = obesity hypoventilation syndrome; $paCO_2$ = partial pressure of arterial carbon dioxide; paO_2 = partial pressure of arterial oxygen; HCO_3^- = bicarbonate; FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 s;

	Mean (SD, or %)
Male N	23 (65.7%)
Age years	56.3 (± 8.6)
BMI $kg \cdot m^{-2}$	49.3 (± 10.9)
Baseline AHI /h†	23.9 (± 28.1)
AHI ≥ 5/h N	24 (77.4%)
AHI > 30/h N	7 (22.6%)
OHS stage (according to Shah NM et al) (63)	
I	3 (8.6%)
II	1 (2.9%)
III	19 (54.3%)
IV	12 (34.3%)
Arterial blood gas#	
pH	7.42 (± 0.0)
$paCO_2$ mmHg	42.89 (± 8.9)
paO_2 mmHg	71.41 (± 11.9)
HCO_3^- $mmol \cdot L^{-1}$	26.53 (± 2.5)
Forced spirometry test	
FVC Liter	2.7 (± 0.8)
FVC %	74.3 (± 15.9)
FEV_1 Liter	1.9 (± 0.7)
FEV_1 %	65.9 (± 18.1)
FEV_1/FVC %	70.9 (± 9.4)

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Figures 16a and 16b illustrate the changes in Zrs in two representative patients with OHS. During expiration, Xrs departs gradually from the inspiratory path with an increasing negative slope, thus creating a clockwise loop with a significant area (AXV). The corresponding Xrs vs V' diagram reveals a gradual decrease in Xrs with increasing expiratory V', followed by a further fall in both Xrs and expiratory V' in the second half of expiration where Xrs approaches its lowest point with decreased V'. This characteristic pattern is considered the manifestation of tEFL. Inspiratory effort leads to a sharp increase in Xrs and, eventually, the formation of a loop. The value of the area (AXV') is negative by definition due to the counterclockwise change in Xrs. In connection with tEFL, a characteristic phenomenon appears in the Rrs vs. V diagram. When inspiratory activity starts, although still at a net expiratory flow, tEFL resolves, flow is abruptly restored, causing a transient increase in Rrs, likely via upper airway nonlinearities.

The position dependence of the intra-breath oscillometry data is summarized in Table 14 and illustrated in Figure 17a and Figure 17b. The change in Xrs loop areas between body positions (Figure 17b) revealed notable inter-individual variability.

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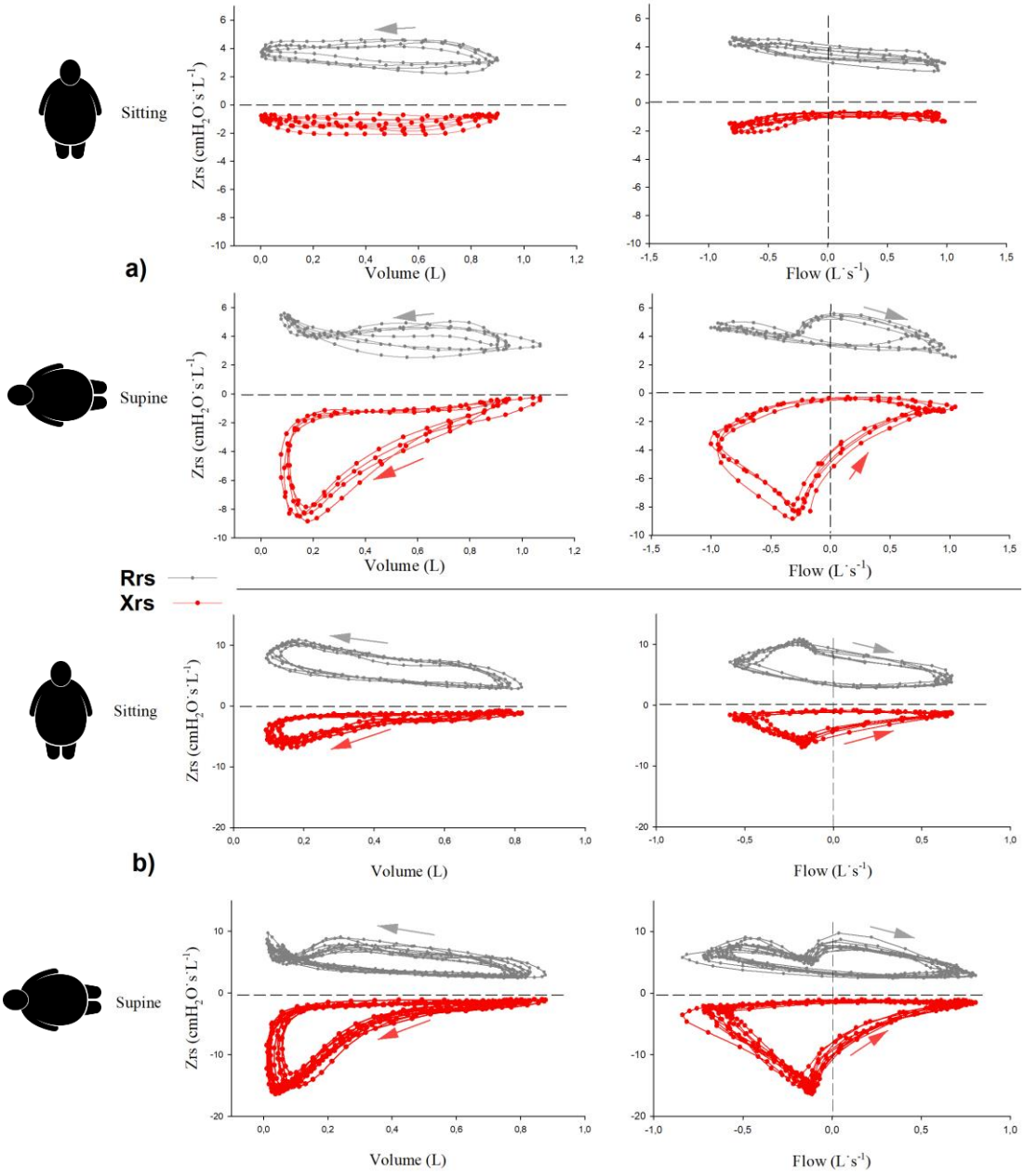

Figure 16 - *Intra-breath changes of impedance values of two representative patients with OHS. The first patient (Figure 16a) exhibits minimal intra-breath changes in Rrs and Xrs in the sitting position, while in the supine position, a marked looping develops in the Xrs vs V plot. In another subject (Figure 16b), tEFL was already present in the sitting position with both decreased Xrs and V' at late expiration. The change in position augmented this looping pattern of tEFL.*

Zrs = respiratory impedance; Rrs = respiratory resistance; Xrs = respiratory reactance;

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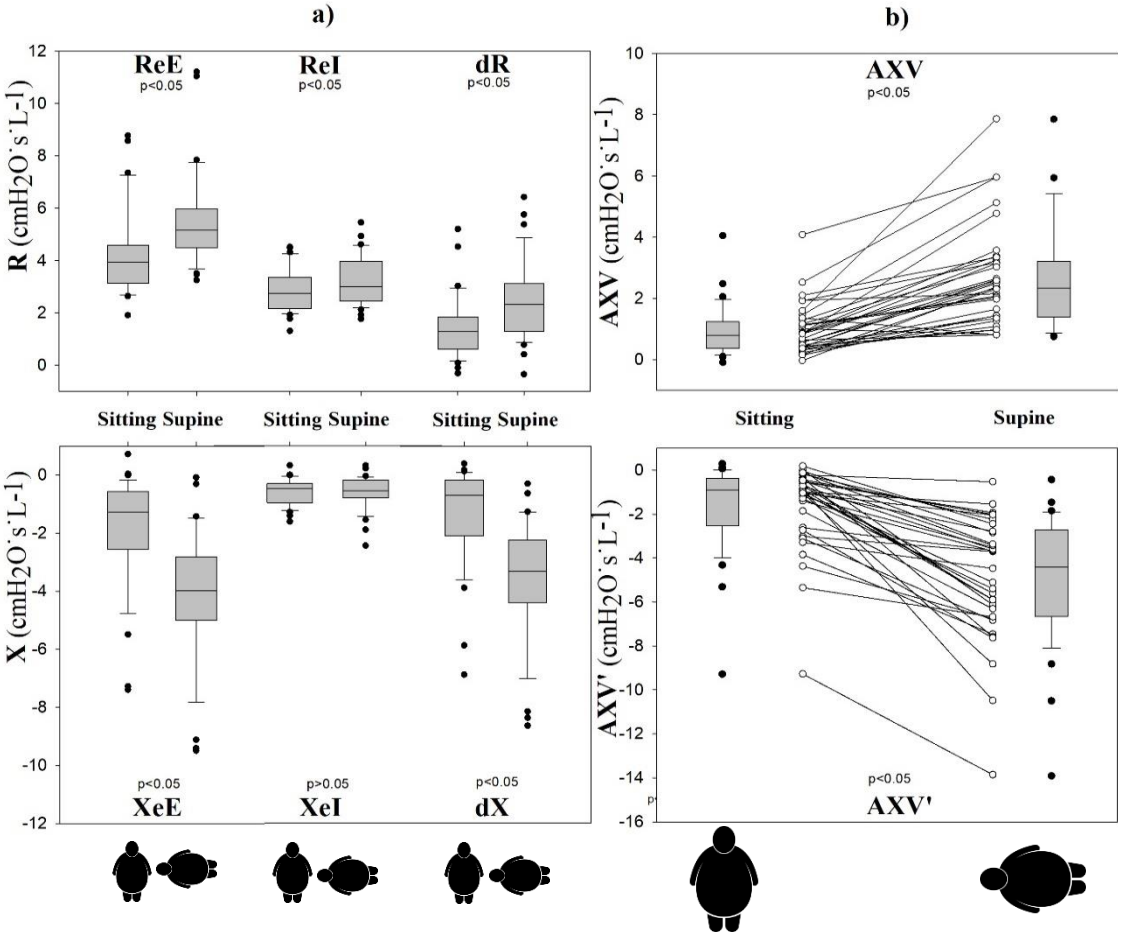

Figure 17 - *The effect of body position on the intra-breath oscillometry values*

The effects of the body position on different oscillometry variables are depicted as (a) box-plot diagrams (ReE, ReI, ΔR, XeE, XeI, ΔX), and (b) individual changes and box-plot diagrams (AXV, AXV'). The supine position has a significant effect on Xrs during expiration indicating EFL during tidal breathing (tEFL). P values are established by the Wilcoxon signed rank test. (n = 35)

ReE = end expiratory resistance; ReI= end inspiratory resistance; ΔR = difference between ReE and ReI; XeE = end expiratory reactance; XeI = end inspiratory reactance; ΔX = difference between XeE and XeI; AXV = area of Xrs vs V diagram; AXV' = area of Xrs vs V' diagram;

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Table 14 - Spirogram and intra-breath oscillometry variables of study patients
Comparison of spirogram and intra-breath oscillometry variables of study patients (n = 35) in the sitting and the supine position. Data are presented as mean (± SD); The definitions of intra-breath variables are listed in Table 6

	Sitting	**Supine**	***p***
Vt (L)	0.92 (± 0.30)	0.95 (± 0.26)	0.10
Frequency (min^{-1})	16.49 (± 4.10)	16.72 (± 4.53)	0.77
Ti/Ttot	0.44 (± 0.04)	0.44 (± 0.04)	0.77
ReE ($cmH_2O \cdot s \cdot L^{-1}$)	4.26 (± 1.63)	5.56 (± 1.80)	<0.001
ReI ($cmH_2O \cdot s \cdot L^{-1}$)	2.81 (± 0.81)	3.37 (± 1.62)	<0.001
ΔR ($cmH_2O \cdot s \cdot L^{-1}$)	1.45 (± 1.18)	2.37 (± 1.48)	<0.001
ΔXmean ($cmH_2O \cdot s \cdot L^{-1}$)	1.19 (± 1.24)	3.33 (± 2.11)	<0.001
XeE ($cmH_2O \cdot s \cdot L^{-1}$)	-1.85 (± 1.89)	-4.17 (± 2.22)	<0.001
XeI ($cmH_2O \cdot s \cdot L^{-1}$)	-0.58 (± 0.46)	-0.61 (± 0.58)	0.71
ΔX ($cmH_2O \cdot s \cdot L^{-1}$)	-1.27 (± 1.68)	-3.56 (± 2.02)	<0.001
AXV (cmH_2O)	0.93 (± 0.81)	2.53 (± 1.40)	<0.001
AXV' ($cmH_2O \cdot s \cdot L^{-1}$)	-1.52 (± 1.92)	-4.95 (± 2.89)	<0.001
ARV (cmH_2O)	-1.27 (± 0.81)	-1.46 (± 1.21)	0.34
ARV' ($cmH_2O \cdot s \cdot L^{-1}$)	1.87 (± 1.26)	2.77 (± 1.83)	<0.001

We found tEFL (based on the presence of the Xrs vs. V' loop and the absolute value of AXV') in 19 patients in the sitting position and all 35 patients in the supine position.

All variables reflecting an expiratory decrease in Xrs as a potential marker of tEFL (XeE, ΔX, AXV, AXV', and ΔXmean) changed significantly between body positions (Table 14). ΔXmean showed a strong correlation with XeE ($r = 0.86$), ΔX ($r = 0.87$), AXV ($r = -0.93$), and AXV' ($r = -0.95$) ($p < 0.05$).

We found no correlation between oscillometry parameters indicating tEFL (XeE, ΔX, AXV, AXV', and ΔXmean) and age, BMI, AHI, OHS stage, or spirometry parameters (FEV1, FEV1% and FEV1/FVC) ($p > 0.05$).

When comparing the two sexes, the oscillometry parameters reflecting tEFL were more pronounced in females compared to males in the supine position (XeE: -5.99 vs -3.22, p<0.001; ΔX: -5.11 vs -2.76, p = 0.003; AXV: 3.42 vs 2.07, p = 0.017 and AXV': -6.89 vs -3.94, p = 0.006 in females and males respectively). These differences were not present in the sitting position.

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When comparing subgroups with or without OSA and patients with or without severe OSA, we observed no difference in oscillometry parameters reflecting tEFL in the supine position (XeE, ΔX, AXV, AXV', $p > 0.05$).

During increasing CPAP level measurements, the anticlockwise looping of AXV' was reversible in 32 out of 33 patients. One patient showed significant looping even at a CPAP level of 20 cmH_2O. The "optimal CPAP" (required to stop tEFL) in the study group, exhibiting significant individual differences, was 14.84 ± 4.11 cmH_2O. The mean CPAP / EPAP used by study patients during long term treatment was 13.01 (± 2.97) cmH_2O. We found no correlation between the defined 'optimal' CPAP and the actual CPAP / EPAP ($p = 0.555$).

A gradual decrease in the Rrs values was also observed with increasing CPAP.

A representative example of a change in the looping pattern during stepwise elevation CPAP is presented in Figure 18. The changes in intra-breath oscillometry values are shown in Figure 19.

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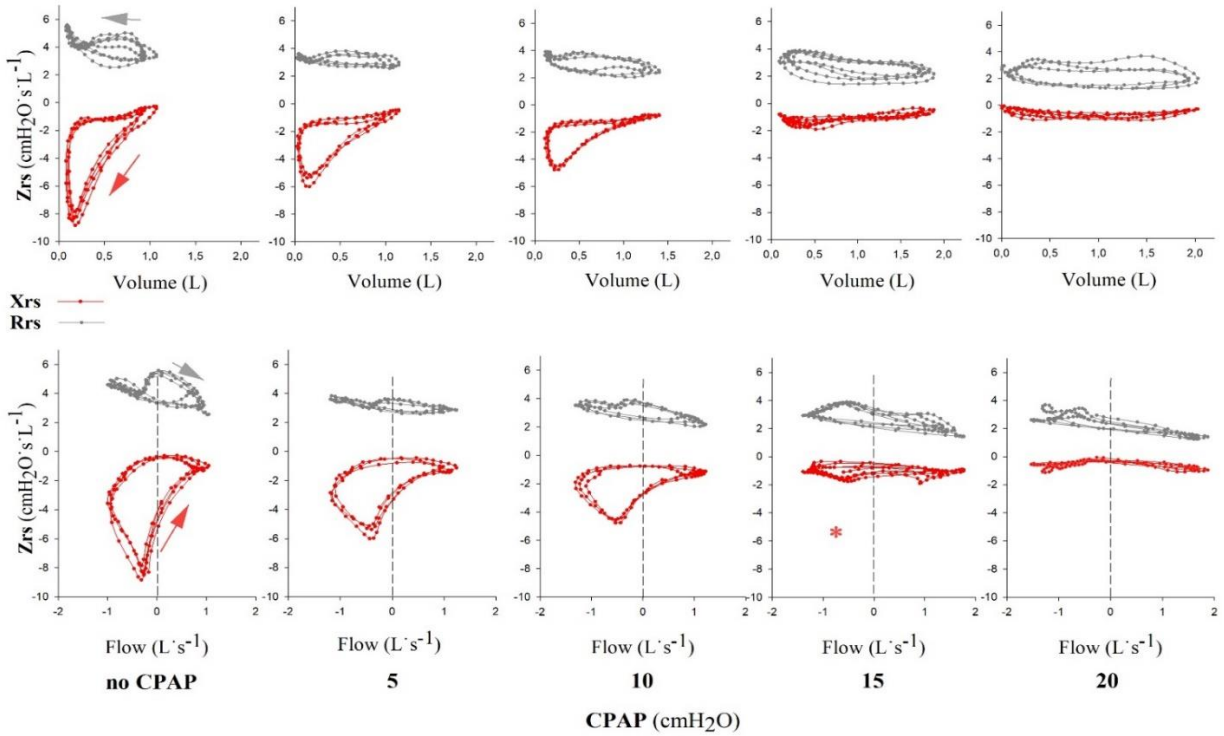

Figure 18 - *Intra-breath changes of impedance values in one representative patient with OHS*
The two parts of the respiratory impedance (Zrs), the resistance (Rrs) and the reactance (Xrs) are marked in grey and red, respectively. The Rrs and Xrs data are plotted against tidal volume and tidal flow parameters. The arrows mark the direction of looping during a single breathing cycle. With a stepwise elevation of CPAP, increasing expiratory Xrs values and decreasing AXV and AXV' loop areas indicate the gradual release from tEFL. At CPAP 10 cmH_2O the tidal volume dependence of Xrs starts in the second half of expiration, and in this particular patient, the flow and volume dependence of Xrs was almost eliminated between CPAP 10 and 15 cmH_2O. Small gradual intra-breath changes can be seen in Rrs. The CPAP level required to reduce the flow and volume dependence of Xrs was highly variable between patients.
Zrs = respiratory impedance; Rrs = respiratory resistance; Xrs = respiratory reactance;

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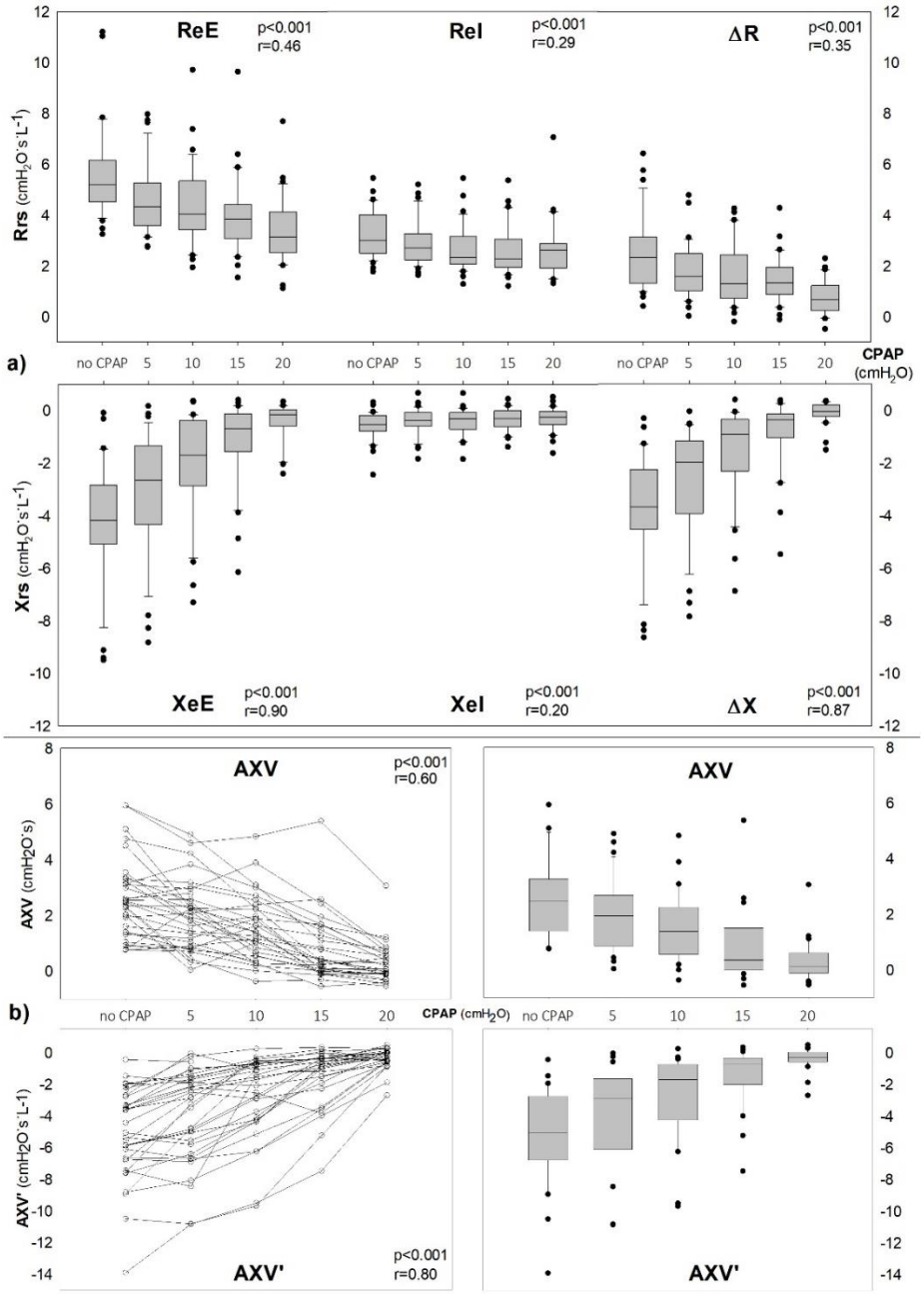

Figure 19 - *The effect of CPAP on the intra-breath oscillometry values*

The effects of different CPAP levels on oscillometry variables are depicted as (a) box-plot diagrams (ReE, ReI, ΔR, XeE, XeI, ΔX) and (b) individual changes and box-plot diagrams (AXV, AXV'). With increasing CPAP levels stepwise change was visible on the Xrs during expiration indicating decreasing tEFL during tidal breathing. The CPAP level required to diminish expiratory Xrs was highly variable between patients. P values are established by the Friedman ANOVA test; the r values are established by Kendall's concordance test. (n = 33)

ReE = end-expiratory resistance; ReI end-inspiratory resistance; ΔR = difference between ReE and ReI; XeE = end-expiratory reactance; XeI end-inspiratory reactance; ΔX = difference between XeE and XeI; AXV = area of the Xrs vs volume loop; AXV'= area of Xrs vs flow loop; CPAP = continuous positive airway pressure;

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We observed the expected glottal interference at high CPAP values (> 5 – 15 cmH_2O) in 19 out of 33 patients (see also Figure 19 and Figure 20). The high temporal resolution displays of CPAP measurements in all subjects revealed two types of dynamic elevations in Rrs during expiration (e.g. glottal interference), which were present in 19 of the 33 patients. One of these patterns is a trapezoid or oval loop shape in the Rrs vs V diagram reflecting steadily increasing Rrs during the whole expiration, whereas the other one exhibits a gradual increase in Rrs in the second part of expiration and sudden fall coinciding with sharp minima of Xrs at the expiratory limit V'. It is noteworthy that these elevations in expiratory Rrs, also reflected by the loop area ARV, persist during elevations in CPAP even when the clear indicators of tEFL gradually disappear in Xrs.

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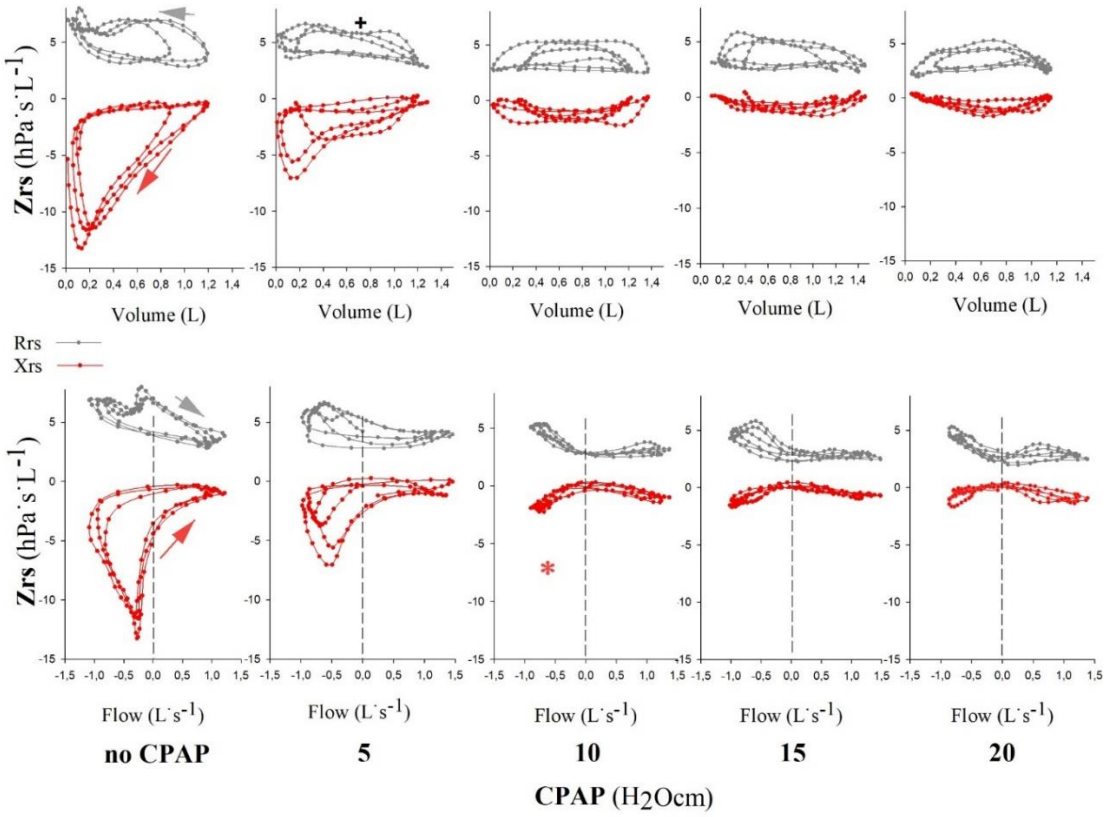

Figure 19 *- Intra-breath changes of impedance values of the study patients during different CPAP levels.*
As an important finding of our study, visual depiction of the respiratory impedance vs. flow and volume are also helpful in recognizing different patterns of dynamic shifts in Xrs and Rrs during tidal breathing, indicative of glottal narrowing during CPAP measurements. A representative patient presents with a trapezoid or oval loop shape in the Rrs vs V diagram reflecting steadily increasing Rrs during the whole expiration (marked with a "+"). These elevations in expiratory Rrs, also reflected by the loop area ARV, persist during elevations in CPAP even when the clear indicators of tEFL gradually disappear in Xrs. The optimal CPAP value is marked with "".*
Zrs = respiratory impedance. Rrs = respiratory resistance. Xrs = respiratory reactance

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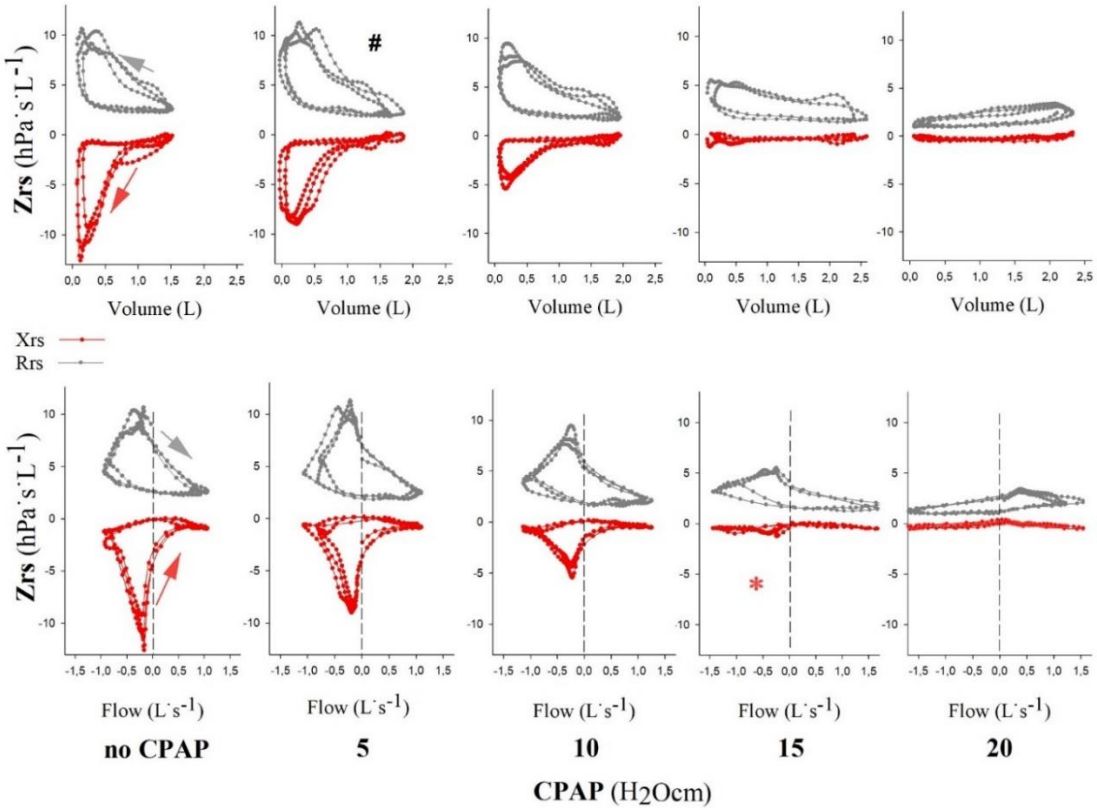

Figure 20 *- Intra-breath changes of impedance values of the study patients during different CPAP levels.*
As an important finding of our study, visual depiction of the respiratory impedance vs. flow and volume are also helpful in recognizing different patterns of dynamic shifts in Xrs and Rrs during tidal breathing, indicative of glottal narrowing during CPAP measurements. Another representative patient shows a gradual increase in Rrs towards the end of expiration (marked with '#'). These elevations in expiratory Rrs, also reflected by the loop area ARV, persist during elevations in CPAP even when the clear indicators of tEFL gradually disappear in Xrs. The optimal CPAP value is marked with "".*
Zrs = respiratory impedance. Rrs = respiratory resistance. Xrs = respiratory reactance

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5. DISCUSSION

5.1 The prevalence of OHS risk factors and outcomes in general ICUs in Hungary

The first study of this thesis is the first multicenter, cross-sectional observational study assessing the prevalence and mortality of suspected OHS patients in Hungarian ICUs during the COVID-19 pandemic (69). The mean prevalence of suspected OHS was 8.74% in our examined sites, with patients showing frequent persisting symptoms, and potential signs of chronic hypoventilation at discharge. Mortality of patients with suspected OHS was similar to patients without OHS risk factors but increased significantly if COVID-19 infection was present.

The overall prevalence of OHS is 0.15 - 0.3% in the general population (4, 70). This data is based on the United States (US) population and is highly dependent on the prevalence of morbid obesity. Obesity rates are documented to be lower in Europe but are closer to US rates in Hungary (US: 33%; Europe: 23%; Hungary: 25%) (71, 72). A previously cited study from Marik et al. observed that 8% of the ICU population met the criteria of OHS in the US, however, they used BMI $\geq$ 40 $kg \cdot m^{-2}$ as inclusion criteria (17). COVID-19 greatly increased the prevalence of obesity in the ICU population, suggesting a subsequent increase in OHS prevalence as well during this period (73). Despite this, we found an overall 8.74% prevalence of suspected OHS among ICU patients during the COVID-19 pandemic, with about 50% of our study patients presenting as COVID-19 negative. This suggests that COVID-19 infection did not result in increased ICU admission of OHS suspected patients.

As previous studies have shown, patients with obesity are admitted to the ICU frequently, and increased BMI categories are associated with comorbidities such as diabetes mellitus, cardiac failure, and respiratory failure (74). During the COVID-19 pandemic, the prevalence of obesity in ICUs reached almost 50%, moreover, in higher BMI categories increased mortality rate and frequent need for invasive mechanical ventilation was observed (73, 75). In our study both pneumonia and COVID-19 infection were risk factors for mortality, and the need for invasive mechanical ventilation. However, the actual mortality rate was independent of BMI categories. These findings suggest that the presence of the risk factors for OHS and chronic respiratory failure may carry an increased risk in COVID-19 independently of the actual body weight.

Among critically ill patients obesity may be associated with greater survival (74). This paradoxical protective effect was negatively affected by COVID-19 (73). In our study, OHS-suspected patients displayed higher mortality rates than was expected by the obesity paradox. This was mainly driven by COVID-19 infections, as suspected OHS patients without COVID-19 had similar mortality rates to previously reported historical data (10 - 16.7%) (74, 76). We also found that COVID-19-positive status increased mortality independent of actual BMI. These data suggest that the presence of suspected OHS is a risk factor for mortality in COVID-19 positive patients independent of actual body weight. This is a strong indication that obese patients with risk factors of chronic respiratory failure may be more fragile during the pandemic era.

As previous studies highlighted, OHS patients are predominantly diagnosed late, during an episode of acute hypercapnic respiratory failure (9). It is also known that some of these patients, even in this stage, are falsely diagnosed with COPD rather than OHS (17). Our study highlighted that more than 60% of OHS-suspected patients carry at least three symptoms connected to OHS besides obesity. It is also noteworthy, that more than 60% of patients had at least one documented comorbidity related to OHS, meaning OHS could have been suspected and diagnosed before their current hospitalization (70). There is an urgent need to draw attention to this population of patients who might benefit from advanced screening for OHS.

Additionally, even before the pandemic, the mortality of ICU survivors with subsequently untreated OHS was 24 - 46% in the years following ICU discharge (9, 70). According to the American Thoracic Society guideline, OHS patients with persisting hypercapnia should receive non-invasive ventilation after an episode of hypercapnic respiratory failure until further evaluation in a sleep laboratory (1). It has been shown that long-term non-invasive ventilation (NIV) treatment initiated after acute hospitalization can improve the quality of life significantly in this patient group (22). Almost one-third of survivors in our study had elevated $paCO_2$ and/or HCO_3^- levels at the time of discharge from the ICU, potentially qualifying them for long-term respiratory support (1, 7). This reinforces that ICUs are important sites for flagging patients with suspected OHS.

In summary, we found that the overall ICU prevalence of suspected OHS during the COVID-19 pandemic was similar to historical data, despite the higher prevalence of the

obese in critically ill patients. Several reasons may be suspected behind this apparent "protective" effect, most obviously that multimorbid patients were more likely to take precautionary measures and avoid infection during the pandemic. Mortality of COVID-19-positive OHS suspected patients was significantly higher than mortality of COVID-19-negative patients, independent of BMI categories, highlighting the fragility of this population during the pandemic.

Despite these important findings, our study has some limitations. The relatively short observational period might have influenced our results, as seasonal fluctuation of patients with respiratory insufficiency in ICUs is well known (77). The markedly different prevalence of suspected OHS at the different study sites might indicate different clinical practices during the pandemic, but our study did not focus on uncovering reasons for this occurrence. Additionally, the study was executed during the second and fourth wave of the COVID-19 pandemic in Hungary with different dominant strains, which might have influenced the prevalence of obesity, and mortality rates observed in our study.

5.2 Outcomes of home mechanical ventilation in OHS patients in Hungary

The aim of the second study was to characterize OHS patients at the time of initiation of long-term respiratory therapy and evaluate the effect of respiratory support on gas exchange, rehospitalization and mortality. Our data shows that the majority of the OHS patients requiring respiratory support were between 40 and 60 years of age and had extreme obesity (average BMI was 49.47 [± 10.39] $kg \cdot m^{-2}$). Our data reinforce the fact that protocol based long-term therapy may lead to high adherence and excellent clinical outcome. In 85.7% of the patients the gas exchange abnormality was completely reversible. Additionally, our follow-up evaluation showed that 86% five-year survival rate can be achieved in an OHS population in Hungary.

Our current data shows that the survival rate in Hungary can be in line or even superior to international data (21, 78). There may be several reasons for this. Our local institutional protocol aiming to personalize the home mechanical ventilation for each patient is based on the German and Canadian guidelines (7, 60, 61). Additionally, our patient care is led by clincians and supported by nursing staff requiring patient - physician appointments every 1 – 6 months (markedly more frequent than what the guidelines usually advise). This may improve the adherence of the patients to the program. Presently the availability

of long-term respiratory support is limited in Hungary, and it can be assumed that mainly OHS patients willing to cooperate are represented. It is worth mentioning that the follow-up of the patients is an important part of our institutional protocol. Regular patient - clinician visit creates the opportunity to notice OHS related symptoms and to optimize respiratory therapy if needed. The importance of regular visits is also highlighted by the fact that in case of hypercapnia at the six months follow up (9 patients, 14.3%) with further optimazition of respiratory support (solving technical issues, increasing daily usage of ventilator, or changing the settings) normocapnia was reached in almost every case.

The other possible cause of the outstanding survival rate may be the fact, that all of the OHS patients received complex noninvasive respiratory support aiming for normocapnia. As mentioned before, previous studies showed clinical improvement with CPAP therapy in some of the OHS patients. There is a higher chance, however, that biphasic positive pressure ventilation may correct hypoventilation and improve gas exchange. Our study population mainly consisted of OHS patients with complex respiratory failure. According to our institutional protocoll all of these patients were treated with NIV. Our data may highlight that in a subpopulation of OHS a personalized, goal directed NIV therapy may improve outcome compared to CPAP.

It is important to stress that what we see today may just be the tip of the iceberg. It would be important to recognize these patients before serious complications. Screening of extreme obese patients with OHS related symptoms (somnolence, restless sleep, headache) may help in early recognition. Our data also shows that both elective and acute patients appeared frequently in the healthcare system before starting long-term respiratory therapy.

Previous studies showed that OHS patients without treatment are heavy users of health-care resources (14). It is also known that long-term respiratory therapy may reduce hospitalization of these patients, moreover, survival and quality of life can be improved (6, 14, 22). Our data reinforce these findings, the rehospitalisation of OHS patients decreased significantly after initiation of therapy.

Finally, it is worth noting, that treating this population may have a positive economic effect as well. In line with our data previous studies showed that OHS is recognized in an

advanced state, but in a young age, typically in the fifth, or sixth decade of life. Chronic illness in this age group may prevent many years spent working. Having in mind that long-term treatment may improve survival, rehospitalisation and quality of life, personalized therapy and care in OHS may result in outstanding health gain.

5.3 Intra-breath oscillometry in OHS, and a potential marker to optimize therapy

The third study of this thesis aimed to assess whether intra-breath oscillometry can be used to detect tEFL and optimize CPAP therapy in patients with OHS (79). We found that tEFL measured by intra-breath oscillometry is present during normal tidal breathing, becomes more pronounced in the supine position, and is reversed by CPAP in patients with OHS. Our results show that tEFL and the "optimal CPAP" value needed to diminish it (14.84 ± 4.11 cmH_2O), are highly variable between subjects and independent of the AHI and BMI values.

tEFL is associated with tidal ventilation inhomogeneity as well as impairment of gas exchange and acts as an extra workload on the diaphragm during expiration (resulting in eccentric contraction) (80, 81, 82). Previous studies have implied that airway function abnormalities and tEFL, in particular, are present in severely obese and OHS patients and worsen in the supine position. This has been proposed as part of the pathophysiology leading to respiratory impairment in OHS (52, 83, 84, 85, 86). The results of our study corroborate these findings. We found that all patients with OHS present with tEFL that worsens in the supine position, although the change between the sitting and supine positions is highly variable. Additionally, we found that the newly proposed markers (XeE, ΔX, AXV, and AXV') showed a strong correlation with the previously used tEFL marker (ΔXmean).

Interestingly, despite similar BMI ranges, females displayed oscillometry patterns corresponding with more intense tEFL. Given that the more intense tEFL in women is mainly present in the supine position, this phenomenon is probably independent of actual weight, although muscle mass, muscle tone or its distribution might play a role. No previous study has noted differences in tEFL in female and male obese patients, but this phenomenon might further our understanding of the development of tEFL.

Indeed, tEFL measures were found to be independent of the severity of obesity in all OHS patients in our cohort. This seems contradictory to a previous study that found that FRC

and ERV decreased exponentially with increasing BMI in an obese population (87). However, it is well known that not every obese patient will develop hypoventilation and our results suggest that other factors independent of BMI might contribute to increased tEFL in patients with OHS. Further studies are warranted to clarify whether the presence and level of tEFL correlates with respiratory impairment and gas exchange abnormalities in the obese population.

As anticipated, we found that the body position-related worsening of respiratory mechanics could be counteracted by CPAP (56, 80). Reversal of tEFL could be achieved in almost all patients; however, the CPAP level required to eliminate tEFL (the "optimal CPAP") varied between patients in our study.

The documented therapeutic effect of CPAP in OHS is thought to be the result of its ability to counteract both nocturnal upper airway collapse and small airway closure during tidal breathing (51, 88, 89). Coexisting OSA is frequent in patients with OHS, but airway patency issues and reduction of lung volumes are not directly related, and OHS may appear without morbid obesity (BMI < 40 $kg \cdot m^{-2}$) or a high AHI (9). This is further supported by the fact that we found no correlation between AHI and BMI or between AHI and awake supine oscillometry variables reflecting tEFL. Moreover, subgroup analysis did not show an association between OSA severity (AHI ≥ 5 /h or AHI > 30 /h) or BMI and awake supine oscillometry variables reflecting tEFL. Despite this, CPAP therapy is usually titrated based on airway patency during sleep studies in OHS, and its effect on absolute lung volume is not monitored. While airway patency is required for maintaining ventilation during sleep, CPAP levels based on this may be insufficient to restore EELV, adequately improve $\Delta V/\Delta Q$, and unload respiratory muscles overloaded in OHS. Studies establishing CPAP as a viable treatment for OHS used settings acquired during AHI based CPAP titration, with mean values ranging from 10-15 cmH_2O (38, 39, 90, 91). As a noteworthy finding in our study, these CPAP levels were not sufficient to eliminate tEFL in all OHS patients in our cohort. Additionally, 'optimal' CPAP values based on oscillometry measurements did not correlate with the settings used by study patients during their long-term ventilation therapy. Transcutaneous CO_2 monitoring during therapy titration might provide more reliable values for effective CPAP, although whether this results in clinically improved outcomes remains to be seen (92). Our results suggest that intra-breath oscillometry measurements provide important additional information for

optimizing CPAP treatment in patients with OHS. This is in line with recent findings suggesting that CPAP may be helpful even in patients without severe OSA (50). Further studies are needed to determine whether CPAP levels based on awake supine intra-breath oscillometry variables are effective in achieving clinical goals and improving long-term outcomes in patients with OHS.

Glottal interference, previously described in animal models, was present in close to 60% of patients with OHS in our study during CPAP measurements (67). These patients exhibited increased Rrs during expiration with similar kinetics to voluntary glottal narrowing (93). As it has been previously noted and reinforced by our results here, resistance fluctuations in the upper airway can appear parallel with intrapulmonary and small airway mechanical changes (93). We found that the values of expiratory Rrs, ARV and ARV' typically persist during increasing CPAP settings, meanwhile Xrs variables improve gradually with stepwise elevation of CPAP. Therefore, XeE, ΔX, AXV and AXV' appear to be reliable indicators of the presence of tEFL during CPAP measurements. Further research is warranted to analyze the mechanical effect of glottal activity on small airway mechanics via elevation of intrabronchial pressure; however, characterization of this phenomenon was not the aim of this study. Visualization of the dynamic change in Rrs during expiration with intra-breath mapping allows clear distinction between glottal origin and other possible causes. It is also important to note that glottal interference might explain intolerance of high initial airway pressures and stresses the need for gradual stepwise increase in CPAP values both during titration and long-term therapy to increase adherence.

Our study had some limitations. tEFL was assumed to be the result of reduced lung volume in our study; however, ERV and FRC were not measured, as this would have required plethysmography impractical in the supine position. Patients with a possible obstructive pathophysiology were excluded to rule out other contributors to tEFL. Forced expiratory spirometry did not identify any significant obstruction in the study group. Additionally, oscillometry detection of tEFL may be hindered by glottal interference, as resistance fluctuations in the upper airway can appear parallel to intrapulmonary and small airway mechanical changes (93). To eliminate the effects of upper airway obstruction, we performed a study in awake patients. To identify the glottal narrowing potentially accompanying higher levels of PEEP previously described in animal models

(67), we used a visual depiction of the respiratory Xrs vs. V’ and V relationships and tEFL markers that more accurately assess the different patterns of dynamic shifts in Xrs and Rrs during tidal breathing. We identified possible glottal narrowing accompanying CPAP measurements in 19 of 33 patients; however, further studies are needed to verify which tEFL markers can accurately identify this phenomenon.

Finally, the current study used a stepwise elevation of CPAP measurements with quite large jumps in order to quickly and efficiently distinguish between levels of tEFL. The stepwise application of CPAP is important to avoid hyperinflation related bias and patient discomfort, however a more precise titration of CPAP could yield more optimal CPAP settings. Further studies are needed to identify the ideal CPAP titration protocol during oscillometry measurements and polysomnography verification of oscillometry results for a clinically feasible, precise diagnostic algorithm.

In the context of oscillometry employed in a number of clinical scenarios, the general application of this 30-60 minute test during OHS assessment seems feasible and might optimize treatment in a disease where long-term survival is still poor (94, 95). However, implementation of our technique in clinical studies is hindered by the fact that the currently available commercial oscillometry devices do not operate at elevated airway pressures.

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6. CONCLUSIONS

Despite being the leading cause of long-term respiratory support, OHS is frequently unrecognized, and remains untreated. OHS without treatment is associated with increased health-care resource utilization. Our results suggest a significant ICU subpopulation (8.74%) with OHS symptoms, remains to be flagged. It can be suspected that these patients are present in the ICU during pandemics, and during 'peace time' as well. Thus, ICUs are important sites for flagging patients with symptoms of OHS. The overall mortality rate of patients with OHS symptoms was 40.5% independently of BMI, but highly influenced by COVID-19 infection. Based on our findings, OHS symptoms appeared to be protective against hospitalization during the COVID-19 era, however, in cases of actual COVID-19 infection increased mortality rates can be expected. It is noteworthy that more than 60% of the screened patients had at least one documented comorbidity related to OHS, meaning OHS could have been suspected and diagnosed before their current hospitalization. Further studies are warranted to clarify other sites of the health-care system, where screening for OHS related symptoms could help in early recognition of this population.

Characterizing OHS patients may help clinicians in all fields to recognize the untreated OHS patients in Hungary. Our second study highlights that OHS patients are mainly diagnosed in their fifth or sixth decade, and they usually are extremely obese. Our data reinforce the fact that protocol based long-term respiratory support and close monitoring of patients may lead to outstanding adherence to therapy, and excellent clinical outcome, including normalized blood gas values, reduced hospitalization rates and improved survival. Our study showed an 86% five-year cumulative survival probability for OHS patients treated with long term respiratory support in Hungary.

The current management strategies for long-term respiratory support are poorly defined in OHS. Based on our results, we can propose tEFL as a possible marker to optimize CPAP therapy in OHS patients. Our study is the first to detect tEFL with intra-breath oscillometry in an OHS population, also showing that tEFL can be diminished with augmented airway pressures. Based on this examination, in terms of small airway dynamics an 'optimal CPAP' level can be identified. Our results show that tEFL and the "optimal CPAP" value are highly variable between subjects and independent of the AHI

and BMI values. General application of intra-breath oscillometry seems to be a feasible additional test in OHS to achieve optimal respiratory support. As an important additional finding, our results highlighted that the dynamic change in the resistance of the upper airways (e.g. the glottal interference) during CPAP measurements might interfere with some of the intra-breath oscillometry values. Further studies are warranted to investigate how oscillometry based therapy initiation effects outcome in OHS patients. However, implementation of our technique in clinical studies is hindered by the fact that the currently available commercial oscillometry devices do not operate at elevated airway pressures.

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7. SUMMARY

Despite the facts that respiratory support can decrease the significant mortality and morbidity associated with OHS, and that the financial and therapeutic conditions have been established in Hungary for almost a decade, this syndrome is still frequently undiagnosed and remains inadequately managed. There is an urgent need to draw attention to this population of patients. Increased vigilance of clinicians can lead to early recognition of the syndrome and initiation of appropriate therapy.

Untreated OHS is associated with increased use of health-care resources including ICU admission and need for respiratory support. As our results have shown, OHS suspected patients have a high prevalence in Hungarian ICUs and are associated with a high mortality rate. This phenomenon is worsened by COVID-19 infection but is independent of BMI. Based on our results, ICUs are important sites for flagging patients with symptoms of OHS and ensuring appropriate screening. Initiation of long-term respiratory support may lead to a significant mortality rate reduction in the following years after ICU discharge.

As we uncovered, in line with the high ICU prevalence, most Hungarian patients start long term respiratory support after an acute respiratory failure hospitalization. Despite this, a protocol based long-term respiratory support program with close monitoring of patients leads to excellent adherence to therapy, and it can improve clinical outcome. According to our results, the five-year cumulative survival of OHS patients treated with long term respiratory support is comparable to international rates in Hungary.

Although the syndrome has been extensively studied, the complex pathophysiology of OHS requires further exploration. As our results show, expiratory flow limitation, a surrogate marker of absolute lung volume reduction, is identifiable using oscillometry during calm tidal breathing in OHS patients, especially in the supine position. Our results demonstrate that by monitoring tEFL during the stepwise augmentation of airway pressure, an optimal CPAP level can be identified. Thus, the general application of intra-breath oscillometry during CPAP initiation may help optimize respiratory support setup in OHS patients, which so far is not well-defined in practice guidelines. Despite frequent glottal interference, a selection of intra-breath oscillometry values appear to be reliable indicators of small airway dynamics during CPAP measurements.

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9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1 Publications included in the thesis

Baglyas S, Valkó L, Donka D, Fodor G, Hansági E, Méhész I, et al. Prevalence of suspected obesity hypoventilation syndrome in Hungarian Intensive Care Units during the COVID-19 pandemic. The clinical respiratory journal. 2023;17(8):771-9. **IF 1.7**

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9.2 Other publications by the author

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