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Clinical Impact and Therapeutic Outcomes in Obesity–Related Hypoventilation Disorders

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[Redaction]

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Thesis Statement of Originality

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged. This thesis has not been submitted for any other degree or purpose.

Yizhong Zheng (306116111)

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Author Attribution

The work described within this thesis was carried out at the Royal Prince Alfred Hospital under the supervision of Dr Amanda Piper, Associate Professors Keith Wong and Craig Philips and Professors Ron Grunstein and Brendon Yee.

I, Yizhong Zheng, certify that the intellectual content of this thesis is the product of my own work, and I was primarily responsible for the development of the research proposals, selection of research methods, data analysis, interpretation of findings, drafting and revising manuscripts, and drafting and revising the thesis.

For Chapter 2, I was responsible for conceptual development, literature review, synthesis of findings, drafting, and revision of the chapter. Chapters 2.2 and 2.3 have been published as a book chapter [1] (Zheng Y, Piper AJ. Management of Obesity Hypoventilation Syndrome. *Encyclopaedia of Respiratory Medicine (Second Edition).* 2022;215-227) and a review article[2] (Zheng Y, Phillips CL, Sivam S, et al. Cardiovascular disease in obesity hypoventilation syndrome–A review of potential mechanisms and effects of therapy. *Sleep Medicine Reviews*. 2021;60:101530).

For Chapters 3 and 5, I was responsible for concept and research proposal development, review of literature, data analysis, interpretation of results, as well as drafting and revision of manuscripts for publication. These chapters used data from the paper "Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation"[3] and data collected, but not published by Dr Amanda Piper, prior to the commencement of my PhD candidature. Chapter 3 and 5 have been published as original research articles[4, 5] (Zheng Y, Yee BJ, Wong K, Grunstein RR, Piper AJ. A comparison of two obesity-related hypoventilation disorders: Impact on sleep, quality of life and neurocognitive outcomes and the effects of positive airway pressure therapy. *Sleep Advances*. 2024;5(1):zpae016) and (Zheng Y, Yee BJ, Wong K, Grunstein R, Piper A. A pilot randomized trial comparing CPAP vs bilevel PAP spontaneous mode in the treatment of hypoventilation disorder in patients with obesity and obstructive airway disease. *Journal of Clinical Sleep Medicine*. 2022;18(1):99-107).

For Chapters 4 and 6, I was responsible for concept and research proposal development, review of literature, participant recruitment, data collection and analysis, interpretation of results, as well as drafting and revision of manuscripts for publication.

The research presented in this thesis was approved by the Sydney Local Health District Ethics Committee. Written, informed consent was obtained from all participants.

Artificial Intelligence tools were not utilised in the generation of this thesis.

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Yizhong Zheng

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As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Brendon Yee

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Location in thesis	Status	Details
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Conferences and presentations during PhD candidature

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Abstract

This thesis explores the clinical impact and therapeutic outcomes of obesity-related hypoventilation disorders to address some of the research unknowns in this area. It addresses two main clinical questions. Firstly, the symptom burden, neurocognitive and cardiovascular impact of disease at diagnosis and following positive airway pressure (PAP) therapy are evaluated. Secondly, the efficacy of different modes of PAP therapy in addressing respiratory failure is examined. This thesis incorporates three peer-reviewed publications, one book chapter and one submitted journal (currently pending review).

The book chapter serves as a review of obesity hypoventilation syndrome. It is incorporated into the thesis introduction, along with publication 1, which summarises the cardiovascular literature on obesity hypoventilation disorders and research deficiencies.

Publication 2 examines the neurocognitive symptom outcomes between two obesity-related hypoventilation disorders, either with or without airways disease. Findings from this publication show that, despite differences in baseline demographics, lung function, and polysomnographic data, the two disorders have a similar symptom burden and deficiencies in neurocognitive assessment at baseline, as well as similar responses to 3 months of PAP therapy.

Publication 3 is a randomised, parallel study that compares bilevel PAP and fixed CPAP in improving respiratory failure in obesity-related hypoventilation with concurrent airways disease. The study found that bilevel PAP was superior to fixed CPAP in improving hypercapnic respiratory failure over 3 months of therapy.

Finally, publication 4 (accepted, yet to be published) is a pilot, randomised, parallel study that explored the use of auto-titrating CPAP in obesity hypoventilation syndrome. The study found that non-inferiority to fixed pressure CPAP could not be confirmed, but several clinically important outcomes favoured fixed CPAP over auto-titrating CPAP. The feasibility study also provides further study design information for a larger RCT to confirm our preliminary findings.

Data regarding cardiovascular biomarkers in OHS formed the basis for Chapter 4. This study showed that at baseline, participants with obesity hypoventilation syndrome had high rates of abnormal cardiovascular biomarkers, even in those without established cardiovascular diagnosis or traditional risk factors. Furthermore, the use of PAP therapy over a 3-month period did not result in significant changes in these cardiovascular biomarkers, including markers of arterial stiffness.

This thesis highlights the importance of phenotyping patients with obesity and sleep-disordered breathing when deciding the most appropriate type of PAP therapy while also addressing some of the questions surrounding the non-respiratory aspects of the disorder.

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Chapter 6: OHS APAP vs fCPAP RCT

List of Abbreviations

AHI – apnoea hypopnoea index

APAP – auto-titrating CPAP

BMI – body mass index

BP - blood pressure

BPAP – bilevel positive airway pressure

COPD – chronic obstructive pulmonary disease

CPAP – continuous positive airway pressure

CRP – C-reactive protein

CT – computer tomography

CVD - cardiovascular disease

CVD – cardiovascular disease

DEXA – dual energy X-ray absorptiometry

ERV – end-respiratory volume

ESS - Epworth Sleepiness Scale

fCPAP – fixed CPAP

FER – forced expiratory ratio

FEV_1 – forced expiratory volume in 1 second

FVC – forced vital capacity

GIP – gastric inhibitory polypeptide

GLP-1 – glucagon-like peptide-1

HRQoL – health-related quality of life

IHD - ischemic heart disease

IL-6 – interleukin 6

LV – left ventricle

MEP – maximal expiratory pressure

MIP – maximal inspiratory pressure

MRI – magnetic resonance imaging

OCM – obesity cardiomyopathy

OHS – obesity hypoventilation syndrome

OSA – obstructive sleep apnoea

OSAS - obstructive sleep apnoea syndrome

PAP - positive airway pressure

PASP - pulmonary artery systolic pressure

PH - pulmonary hypertension

PSQI - Pittsburgh Sleepiness Quality Index

RV - residual volume

SF36 - Medical Outcomes Survey Short Form 36

TLC - total lung capacity

TNF-a – tumour necrosis factor alpha

TTE - transthoracic echocardiogram

Chapter 1. Introduction

1.1 Rationale for the thesis

Obesity is a growing global epidemic that will continue to have significant societal health burdens. With more extreme obesity, the burden on the respiratory system can lead to hypercapnic respiratory failure. While there is a wealth of research involving the impact of obesity on other body systems, obesity-related hypoventilation has received less attention, with these individuals either under-represented or excluded from clinical research. My thesis examines the clinical impact of obesity-related hypoventilation in terms of symptoms, neurocognitive function and cardiovascular biomarkers as well as treatment outcomes using different positive airway pressure modalities.

1.2 Aims

1. Describe and compare neurocognitive function and symptom impact of two obesity hypoventilation disorders (obesity hypoventilation syndrome and obesity hypoventilation (hypercapnic obesity with airways disease).

2. Describe cardiovascular disease and risk factors in obesity hypoventilation syndrome and explore the use of novel biomarkers for cardiovascular risk assessment.

3. Compare the outcomes of fixed continuous positive airway pressure therapy with bilevel positive airway pressure therapy in addressing respiratory failure in obese hypercapnic patients with airways disease.

4. Compare the outcomes of auto-titrating continuous positive airway pressure therapy with fixed continuous positive airway pressure therapy in obesity hypoventilation with severe obstructive sleep apnoea.

Chapter 2. Background

2.1 Obesity Overview

Despite efforts to curb the obesity epidemic, rates of obesity continue to rise, with around 40% of all adults and 20% of all children overweight or obese[1]. In Australia, 1 in 4 individuals are overweight or living with obesity, including approximately 1.2 million adolescents and children[2]. Two in 3 Australian adults have a body-mass index (BMI) >25kg/m^2, with 31% living with obesity (BMI>30kg/m^2 with rates in men greater than in women) and 12% with severe obesity (BMI>35kg/m^2). Rates are even higher in the Indigenous population (with obesity rates >45%), regional areas and amongst lower socioeconomic groups – people who are already disadvantaged from a healthcare access perspective. Although recent data collection has been curbed by COVID-19, it is expected that the pandemic has further exacerbated the burden of obesity. Globally, obesity rates are rising in low- and middle-income countries due to urbanisation and nutritional transition (from traditional to westernised diets)[3].

Several factors contribute to obesity risk in an individual – genetic, behavioural, sociodemographic and environmental[3]. Genome-wide association studies have so far identified more than 250 genes/loci that are linked with obesity. These genes also correlate with higher BMI, fat mass index and leptin concentration, while a particular gene (fat mass- and obesity-associated gene or FTO) plays a role in the development of obesity and type 2 diabetes mellitus. While genetic factors are not yet readily modifiable, behavioural factors have long been targeted in weight loss intervention. Dietary habits are a major determinant of health in general. Dietary factors associated with obesity include the consumption of ultra-processed and energy-dense foods (confectionaries, sugars, soft drinks, fats), excess alcohol, a monotonous diet, and timing of intake (breakfast versus evening snacking). Non-dietary behavioural factors that promote weight gain include a sedentary lifestyle, prolonged screen time, short sleep duration and shift work. Policy initiatives and obesity prevention measures can promote healthy behaviours and reverse the current obesogenic environment. Unfortunately, efforts so far to curb the global obesity epidemic have fallen short. There is a call to action across regions and sectors of society, prioritising risk factor reduction to minimise the health and psychosocial related harms of obesity[4].

The health impact of obesity is far-reaching. Obesity is associated with a range of comorbidities, including cardiovascular and metabolic disease, cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease, reproductive dysfunction and sleep-disordered breathing. Obesity also increases chronic condition-associated mortality. The more recent entity of sarcopenic obesity (age-related loss of muscle mass with increased amounts of adipose tissue), which is likely prevalent among this thesis study population, is shown to be associated with worse health consequences – higher mortality, worse physical function, increased rates of metabolic disease and other comorbid conditions[5]. On an individual basis, the impact of obesity varies based on biological differences and other traits. In turn, a growing number of biomarkers are either determinants of obesity or increase its association with other comorbidities. These include micro-RNA (links with non-alcoholic fatty liver disease, insulin resistance, cardiovascular diseases), inflammatory biomarkers (C-reactive protein, interleukin-6, tumour necrosis factors), adipocytokines (leptin, resistin, adiponectin, omentin, apelin - highly predictive of adverse cardiovascular conditions), oxidative stress (lipid oxidation, predict cardiovascular disease and atherosclerosis) and gut microbiota (which in turn influences gastrointestinal hormones such as leptin and ghrelin, with ghrelin facilitating food intake and leptin involved in satiety)[3].

As this thesis focuses on obesity-related hypoventilation and associated cardiovascular and cognitive outcomes, the following sub-chapters will focus on the impact of obesity on lung mechanics, upper airway function, cardiovascular morbidity, and neurocognitive function.

2.1.1 Impact of Obesity on Respiratory Mechanics and Upper Airway Physiology

Although the chemical/hormonal interaction between adipose tissue and the lung is not fully understood, the mechanical effects of obesity on pulmonary (summarised in Figure 2.1.1a) and upper airway function (Figure 2.1.1b) are well-recognised.[6] Both the degree of obesity as well as the distribution of adiposity will influence the extent to which respiratory physiology is altered. Upper body and central distribution of adipose tissue have a greater detrimental effect on pulmonary function than lower body fat distribution.

In obesity, the most common finding of obesity on static lung volumes is a reduction in functional residual capacity (FRC)[7]. This is the volume of gas within the lungs at the end of expiration, the resting state where the outward forces of the chest wall are balanced against the inward elastic recoil of the lung. In obesity, the mass load of adipose tissue around the rib cage, the visceral cavity, and the abdomen shifts the balance towards deflation. The reduced FRC is mainly reflected in reduced expiratory residual volume (ERV). Even at extremes of obesity, there is only a modest reduction in residual volume (RV) and total lung capacity (TLC), often just above the lower limit of normal. Adipose tissue deposition in the subpleural spaces and within the chest cavity, and upward displacement of the diaphragm from increased abdominal fat likely explain this small reduction in TLC and RV[8].

Spirometric variables, such as FEV1 and FVC, show an inverse relationship with BMI[7]. The effect is small in otherwise healthy individuals with obesity. The FEV1 to FVC ratio (FER) is usually well-preserved or increased, even in extreme obesity, indicating that the major effect of obesity is on lung volumes, with no direct effect on airway obstruction[9]. The reduction in expiratory flow rate appears to be in proportion to the reduction in vital capacity. Airway resistance is increased in obesity, but specific airway resistance is normal, indicating that the reduction in airway calibre is secondary to a reduction in lung volume. Some studies also suggest there are additional factors that contribute to an increase in airway resistance, potentially related to remodelling by inflammatory adipokines, damage to the small airways by opening and closing during the breathing cycle or lipid deposition in the airway[7].

The greater the BMI, the closer the FRC approaches RV. When the closing capacity exceeds the FRC, airway closure can occur within tidal breathing[8]. This is exacerbated in the supine position when the diaphragm ascends into the chest. Areas of under-ventilation tend to occur in the lower zones of the lung, indicating basal air trapping. Reversal of the normal distribution of ventilation is observed in obesity. Regional ventilation-perfusion mismatch, in turn, can lead to mild hypoxaemia and an increased alveolar-arterial oxygen gradient[8]. Diffusing capacity is normal or even increased in morbid obesity, likely due to an increase in blood volume[7]. A low diffusing capacity, particularly the transfer coefficient, may represent a loss of the pulmonary capillary bed or pulmonary hypertension.

Obesity causes stiffening of the respiratory system due to a combination of reduced lung and chest wall compliance. Reduced lung compliance is thought to be secondary to atelectasis in dependent areas (due to the closure of dependent airways as FRC is less than the closing volume), increased alveolar surface tension (due to reduced FRC) and increased pulmonary blood volume (due to

increased total blood volume with high body mass)[10, 11]. Different studies have produced conflicting results regarding chest wall compliance in obesity, with some suggesting it is reduced[7]. In contrast, others indicate a rightward shift of the chest wall pressure-volume curve without a change in gradient (potentially requiring only a greater inspiratory threshold load to be overcome)[12].

Respiratory muscle strength, reflected in maximum inspiratory and expiratory pressures (MIPs and MEPs), is similar in obese and normal-weight subjects. However, this may be compromised in those with sarcopenic obesity or with comorbid COPD (2.3.3.) and unclear in obesity hypoventilation syndrome (further discussed in 2.2.5.).

The majority of obese subjects can eliminate CO2 to maintain normocapnia even during exercise and sleep. They can increase their minute ventilation to meet their increased metabolic production. The higher ventilatory drive in eucapnic obese subjects may be due to higher levels of leptin, which is a respiratory stimulant. A small portion of patients are unable to compensate, leading to the development of OHS (further discussed in 2.2.5.).

Obese people are more likely to experience breathlessness and exercise limitation even when there is no obvious lung function impairment or respiratory disease[7]. Obesity is a risk factor for self-reported dyspnoea[13]. Although a clear explanation for this is yet to be identified, prior studies have either suggested mechanisms or refuted this claim[7]. Obesity is associated with a higher basal metabolic rate and oxygen consumption for any workload during exercise. To meet the oxygen demands, a greater minute ventilation augmentation is required for a given workload. In obese subjects, this is mainly achieved by a higher respiratory rate rather than altering tidal volume[14]. This breathing pattern could be related to the effects of obesity on diaphragmatic excursion, supported by a study showing that subjects with upper body adiposity had a significantly higher respiratory rate and lower anaerobic threshold when compared to those with lower body adiposity[15]. As the oxygen cost of breathing increases parabolically with breathing frequency, breathlessness and poor exercise performance may also be linked to the increased oxygen cost of the respiratory system[16]. In healthy obesity, subjects have the same peak work rate and peak oxygen consumption, are able to increase ventilation to avoid hypercapnia, and have normal ventilatory responses to inhaled CO2 compared to a normal-weight group[7].

The deposition of fat around the pharyngeal airway is a key mechanism in the development of obstructive sleep apnoea. The pharyngeal airway shares space with soft tissues within the confines of the maxillomandibular bony enclosure. Hence, greater upper airway fat deposition reduces

luminal pharyngeal airway space, which in turn, increases upper airway collapsibility (i.e. higher Pcrit – pharyngeal critical pressure; a greater Pcrit indicates more collapsible and unstable airway).[17, 18] While there is a significant correlation between Pcrit and BMI, there is also considerable scatter. This is indicative of the relationship between excess soft tissue and maxillomandibular enclosure size – a patient with a small maxilla and mandible is at risk of OSA with mild obesity. In contrast, a proportion of patients, even with extreme obesity, are unaffected by OSA (see 2.2.1 and 2.2.5). While the correlation between upper airway collapsibility and obesity is apparent for both genders, this is particularly striking for men.[19] The increased risk may be partly related to the differences in the distribution of adipose tissue – the central visceral fat deposition is a potent risk for the presence and progression of OSA[20].

Adipose deposition can lead to both macroglossia and thickening of the lateral pharyngeal walls. There are two distinct primary regions of pharyngeal collapse/closure.[21] In around half of OSA patients, critical luminal narrowing occurs exclusively in the retropalatal space, whereas in the other half luminal collapse occurs in both the retropalatal and retroglossal space.[17] Hence, obesity is more frequently associated with retropalatal airway collapse, whereas retroglossal closure is more frequently observed in craniofacial abnormalities. This may be due to the fact that the retropalatal airway is naturally narrower with the tongue located more anterior than the soft palate.[17] In addition, accumulation of fat outside of the bony enclosure, such as in the submandibular space, is also predictive of OSA. Caudal displacement of excessive soft tissue with the loss of upper airway dilator muscle activity, observed during sleep, further increases upper airway collapsibility. The reduction in FRC observed in obesity is thought to contribute to pharyngeal airway obstruction. Static and dynamic inflation of the lung produces tonic and phasic tracheal traction forces. The tonic traction force appears reduced in obese individuals with OSA, tipping the balance towards an increase pharyngeal airway collapsibility.[17]

There are also a number of non-upper airway influences of obesity on OSA. Having a decreased FRC, and hence a smaller oxygen reservoir, underlies the development of more severe hypoxaemia during obstructive events. This is compounded by a lower baseline oxygen saturation due to a combination of hypoventilation and V-Q mismatch, observed in extremes of obesity, and further exacerbated with supine positioning during sleep. Obesity is associated with increased levels of circulating leptin, a respiratory stimulant. Along with hypoxia, this may promote increased loop gain and ventilatory instability.

2.1.2 Consequences of Obesity: Cardiovascular Disease

The American Heart Association classifies obesity as a major modifiable risk factor for cardiovascular disease (CVD)[22]. There is a wealth of evidence linking obesity to a variety of cardiovascular diseases, including atherosclerosis, ischaemic heart disease, atrial fibrillation, heart failure, stroke, ventricular arrhythmias and sudden cardiac death (summarised in Figure 2.1.2a).[23]

Adipose tissue is not only an energy storage organ but also regulates metabolic homeostasis and interacts with other organs, both locally and systemically. The local effects of adipose tissue expansion include hypoxia, inflammation, fibrosis and dysregulated adipokine secretion. Systemically, dysfunctional adipose tissue can promote insulin resistance, endothelial dysfunction, and abnormal glucose and lipid metabolism.[24]

In the past, there was debate around whether increased CVD can be attributed to the association and causative influence of obesity with other cardiovascular risk factors. However, based on data from large epidemiological studies, such as the Framingham Heart[25] and Manitoba Study[26], obesity-related CVD risk persists even after adjustment for co-morbid risk factors, i.e. obesity appears to have both direct and indirect pathophysiological mechanisms leading to CVD. Even in the absence of metabolic syndrome, patients with obesity have a higher risk of coronary heart disease than those with a healthy weight.[27] Direct mechanisms include the proinflammatory, prothrombic state observed in obesity, in addition to its associated functional and structural adaptation of the cardiovascular system.[28]

Adipose tissue deposition is associated with inflammation, and there are significant associations between visceral adipose tissue and circulating levels of interleukin (IL)-6, tumour necrosis factor-a (TNF-a) and C-reactive protein (CRP).[29] The density of macrophages increases with obesity, reducing the production of anti-inflammatory adipokines (adiponectin). This is particularly the case in hypertrophic obesity, a type of obesity characterised by an increase in the size of existing adipocytes, rather than proliferation of new adipocytes.[29] The interaction between macrophages and adipocytes also leads to the release of free fatty acids. This, in turn, activates toll-like receptors, contributing to a state of sustained activation/inflammation and production of cytokines like TNF-a and acute phase proteins, including CRP (which is currently the most reliable and accessible biomarker of inflammation).[30, 31] There is further cross-talk between macrophages and adipose tissue via cytokines, propagating positive feedback loops.[29] Inflammation promotes the development of

atherosclerosis and, during vascular injury, increases fibrin deposition while inhibiting nitric oxide (a vasoactive peptide that suppresses vasoconstriction and platelet aggregation).[31]

There is a strong link between obesity and thrombosis—obesity is a risk factor for the development of arterial thrombosis and venous thromboembolism. In obesity, various pro-thrombotic molecules, such as plasminogen activator inhibitor-1 (PAI-1), tissue factor, fibrinogen, and factor VII, are expressed more strongly. There is also increased thrombin generation, platelet hyperactivity, and reduced fibrinolysis.[32]

Obesity has detrimental haemodynamic effects. To meet the increased metabolic demands from an increased body mass, cardiac adaptations result in increases in total circulating blood volumes, cardiac output, systemic vascular resistance from sodium retention and sympathetic activation. The increased left ventricular filling pressures and volumes, in turn, lead to a leftward shift in the Frank-Starling curve. Over time, this leads to progressive left ventricular remodelling (ventricular dilation to accommodate increased venous return, ventricular hypertrophy to combat wall stress). Diastolic dysfunction is common in obesity and can lead to heart failure with preserved ejection fraction. The functional, morphological, and metabolic changes to the heart observed in obesity ultimately contribute to the development of obesity cardiomyopathy, OCM (LV systolic, diastolic dysfunction and right ventricular dysfunction in the setting of morbid obesity, in the absence of other cardiac risk factors). The risk of developing heart failure in the setting of OCM includes the duration of morbid obesity, LV internal dimension, LV end-systolic wall stress, left atrial dimension and right ventricular internal dimension. The increased risk of sudden cardiac death, pulmonary hypertension and congestive heart failure is thus linked to OCM.[33]

Obesity indirectly increases cardiovascular risk as it leads to the development of other classical risk factors for cardiovascular morbidity, such as hypertension, insulin resistance, type 2 diabetes mellitus, dyslipidaemia, and chronic kidney disease.[34] Compared to normal weight, Class 3 obesity (BMI > 40 kg/m^2) is associated with a 7.37-, 6.38-, and 1.88-fold increase in rates of diabetes, hypertension, and hypercholesterolaemia, once adjusted for age, ethnicity, and gender.[35]

While obesity is a strong risk factor for the development of CVD, in patients who develop symptomatic CVD, BMI is not a consistent risk factor for adverse short-term CVD outcomes. The cause of this phenomenon, known as the obesity paradox, is unclear. Some of the proposed explanations include earlier diagnosis and treatment of CVD in obese populations (lead-time bias),

lower reserve in lean patients to avoid cardiac cachexia and differences in cardiopulmonary fitness (physically active obese individual versus sedentary lean individual).[22]

The use of BMI to define and classify obesity to risk-stratify cardiovascular risk has several limitations, and may partly explain the finding of the obesity paradox.[22] It also accounts for some of the influence of gender and age on cardiovascular risk and the feature of metabolically healthy obese phenotype. BMI does not differentiate fat and lean body mass, nor the distribution and composition of adipose tissue. Various epidemiological studies have shown that the central/visceral distribution of adipose tissue is more strongly related to cardiovascular risk than total adiposity.[22] Hence, anthropometric measurements of central fat distribution (waist-to-hip ratio, waist-to-thigh circumference, waist-height ratio) are better predictors of higher cardiometabolic risk.[36] The development of imaging technologies, including computed tomography (CT), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DEXA), and bioimpedance analysis, has enabled more accurate quantification of obesity and assessment of adipose tissue deposition.[22]

There have been mixed results in weight loss studies on cardiovascular mortality.[37] In the Look AHEAD trial, intensive lifestyle intervention in obese diabetics did not show significant reductions in cardiovascular disease incidence across 10 years.[38] The Sibutramine Cardiovascular Outcomes Trial demonstrated an increased risk of non-fatal myocardial infarction in the pharmacotherapy arm.[39] However, in the post-hoc analysis of both arms, weight loss responders had lower rates of incident cardiovascular events.[37] Weight loss by bariatric surgery has also been shown to reduce the number of cardiovascular deaths and events.[40] The recent development of GLP-1, GIP, and glucagon receptor agonists has transformed the field of medical weight loss management. Consistent findings of reduced major adverse cardiovascular events with the use of these incretin mimetics compared to placebo in both diabetic and non-diabetic populations have been reported. In addition to weight loss and improved glycaemic control, these medications also appear to exert their cardioprotective effects by reducing systemic inflammation.[37]

2.1.3 Consequences of Obesity: Neurocognitive Function

While the physical health impact of obesity is well recognised, there is recent evidence that obesity may impact on brain function.[41] Obesity is considered a modifiable risk factor for the prevention of dementia.[42] Obesity, in particular, abdominal obesity leads to other metabolic conditions (insulin

resistance, hypertension, dyslipidaemia, systemic inflammation). These metabolic disorders, individually or in synergy, are thought to affect the cerebrovascular system and lead to cerebral hypoperfusion and blood brain barrier dysfunction.[43]

There is limited data on the impact of obesity on general cognitive performance. One study used Mini Mental State Examination (MMSE), showing no significant differences between groups (normal, overweight and obese), but the MMSE is a screening tool for dementia and lacks sensitivity to mild cognitive deficits[44]. Several studies that used various Wechsler Scales (WAIS-III, WAIS-R, WASI) to assess intellectual functioning had variable outcomes. Studies that showed an association with obesity did not control for education, while the studies that showed a non-significant relationship matched or controlled for education and age.[43]

Multiple studies have explored the effects of obesity on various cognitive domains. Without accounting for obesity's influence on other comorbidities, these studies found that mid-life obese individuals exhibit cognitive issues in visual construction (combine motor response, perceptual and spatial abilities) and visual memory (encode, store and retrieve visual information), complex attention, concept formation and set shifting (ability to use abstraction, flexibility and novel problem solving), verbal fluency and memory (ease and quantity of speech production), psychomotor performance and speed (indicative of the coordination of sensory or cognitive activity with motor performance), and decision making (ability to select an option or action out of several alternatives).[43 45] However, once obesity-related comorbidities were considered, the effects of obesity on cognitive function are less clear, and strong evidence of an independent relationship between obesity and various cognitive domains is no longer apparent. Some evidence of an independent relationship persists for psychomotor performance and speed, verbal memory, visual construction, concept formation and set shifting.[43, 45, 46]

Recent research interests have also focused on identifying intermediary mechanisms between obesity and cognitive dysfunction. Obesity is considered a risk factor for neurodegenerative and structural changes, such as frontal atrophy, decreased grey matter volumes and increased white matter hyperdensities.[47] Obesity has also been observed to alter the size and cellular density of the nucleus accumbens[48]. As the nucleus accumbens is linked to motivation and addiction, alterations in its structure may promote overeating and, in turn, drive further weight gain.[48-50]

Another proposed mechanism is impaired cerebral metabolism, as a negative correlation is identified between prefrontal cerebral metabolism and BMI.[51] Obese individuals have higher levels

of leptin and leptin resistance. Leptin resistance and reduced levels of adiponectin can lead to amyloid-beta production and deposition, microglia-mediated neuroinflammation, neuronal insulin resistance, impaired synaptic plasticity, synapse loss and Tau hyperphosphorylation. These are all intermediary pathways that are linked to cognitive decline, memory loss and Alzheimer's dementia.[52] Finally, inflammatory proteins, e.g. CRP and IL-6, have been linked with reduced brain volume and cognitive scores.[53]

Intentional weight loss in obese individuals is associated with cognitive improvements across multiple domains in randomised clinical trials and observational studies[54, 55]. There appear to be variations in neurocognitive outcomes between different weight loss interventions. Nutritional interventions most consistently showed positive outcomes. Some proposed mechanisms include improving insulin resistance (associated with lower cerebral glucose metabolism) and reducing inflammatory and oxidative stress. Bariatric surgical outcomes are also positive, with improvements in neurocognitive function and the additional proposed mechanism of changing the gut microbiota. [54-56]

2.1.4 Consequences of Obesity: Quality of Life

Obesity is associated with worse quality of life when compared with the general population, supported by data from large national registries (such as the Swedish Obese Subjects, SOS)[57]. It is also associated with poorer functional status (capacity to perform various activities), increased pain, negative general health perception and reduced activity compared to non-obese participants. The degree of impairment correlates with the degree of obesity. Obese persons are also more likely to have elevated levels of anxiety and depression.[57, 58]

Although various instruments have been used in obesity studies, the Short-form-36 (SF-36) is the most widely used health-related quality of life instrument and is recommended by the US Task Force. SF-36 is a comprehensive assessment tool that includes multiple domains (physical functioning, role limitations, bodily pain, general health perception, vitality, social functioning, emotional role limitations, general mental health) and emphasises that health has dimensionality.[59] Obese persons score significantly lower than population norms in all 8 domains.[60] The greatest effects of obesity on health-related quality of life (HRQOL) appear to be in the domains of vitality and bodily pain scales of the SF-36. Individuals with greater obesity have the poorest quality of life.

Increasing weight gain is associated with worse physical function but not necessarily worse emotional outcomes. Similarly, weight loss tends to improve physical function more than the mental components of HRQOL. Gender (females worse than males), but not age and ethnicity, appears to influence HRQOL in obesity.[61]

2.2 Obesity Hypoventilation Syndrome

The following has been published in a book chapter[62]

2.2.1 Diagnostic Criteria

Obesity hypoventilation syndrome (OHS) occurs when obesity is complicated by and is the main contributor to awake hypercapnic respiratory failure. The definition is based on the tri-factor of obesity, chronic hypoventilation and sleep-disordered breathing[63, 64]. Unlike other sleep-related hypoventilation disorders, which only require evidence of sleep hypoventilation (rise in $PaCO_2$ to 55mmHg for at least 10 minutes or rise by at least 10mmHg in comparison to an awake supine value to a value exceeding 50mmHg for at least 10 minutes), obesity hypoventilation syndrome requires evidence of daytime hypercapnia ($PaCO_2$ > 45mmHg)[64]. The presence of chronic hypercapnia is often the limiting factor in meeting OHS diagnostic criteria. Although the criteria for obesity in OHS is a BMI $\geq$30kg/m^2, the likelihood of OHS between BMIs of 30-40kg/m^2 is relatively uncommon (except in Asian OHS populations). Most OHS patients have at least class 3 obesity (BMI $\geq$ 40kg/m^2). Sleep-disordered breathing in OHS can manifest as varying degrees of obstructive sleep apnoea and sleep hypoventilation. Around 90% of OHS patients have obstructive sleep apnoea[63]. All OHS patients have sleep hypoventilation, where nocturnal CO_2 accumulation contributes towards the gradual modification of the ventilatory drive and development of persistent daytime hypoventilation. An OHS diagnosis also requires the exclusion of other alternative pathologies that would more likely be causing hypoventilation. This includes significant lung disease, such as COPD and interstitial lung disease; neuromuscular and chest wall disorders; severe hypothyroidism; respiratory depressant medications, such as benzodiazepines and narcotics; and congenital hypoventilation disorders.

2.2.2 Epidemiology

The prevalence of OHS in the general population is unknown. However, based on the global estimates of obesity and OSA, estimates of around 0.15-0.3% in Western society have been suggested[63], with expectations that this will rise in parallel with the obesity epidemic. Prevalence rates of OHS are higher amongst specific subgroups such as patients attending sleep laboratories (11-20%) or those referred for bariatric surgery (7-22%)[65]. Based on medical records, one study showed that 31% of hospitalised patients with BMI>35kg/m^2 will meet criteria for diagnosis of OHS.

The major risk factor for the development of OHS is obesity, with prevalence rates increasing with BMI – from around 10% in patients with a BMI 30-35kg/m^2 [63, 66] to 50% in those with a BMI > 50kg/m^2 [66]. The odds of having OHS increase by 1.5% per unit increase in BMI[67].

The median age of OHS diagnosis appears to be around 52 years old, with an interquartile range of 42-61 years old. It appears women are at least as likely to develop OHS as men [68-70], with the highest prevalence seen in post-menopausal women with OSA[68]. This contrasts with OSAS, where rates are much higher in men than women. Although there is no clear ethnic predisposition, OHS may be present in Asians at a lower BMI (mean BMI in studies ranging from 35-38kg/m^2 versus 44kg/m^2) than Caucasians[71], similar to what is observed in OSA. This is likely due to differences in fat distribution and upper airway anatomy.

2.2.3 Clinical Features and Diagnostic Workup

OHS was first well described in the medical literature in 1956 and termed Pickwickian syndrome after the character 'fat boy Joe' in Dickens' novel The Pickwick Papers[72] who exhibited similar clinical features of obesity and hypersomnolence[73].

Patients may present to sleep clinics with symptoms primarily related to obstructive sleep apnoea (snoring, hypersomnolence, non-restorative sleep). The clinical symptoms do not distinguish OHS from OSA. However, OHS patients are more likely to report morning headaches, dyspnoea and have features of pulmonary hypertension. A high proportion of individuals are diagnosed after presenting with acute-on-chronic hypercapnic respiratory failure requiring hospitalisation and potential ICU admission[74-76], and often only after multiple presentations with respiratory failure[77]. Observational studies have previously shown that 8% of ICU admissions met criteria for OHS diagnosis. When the diagnosis is delayed, more significant comorbid conditions can develop, including severe pulmonary hypertension, right heart failure and polycythaemia. With advanced disease, severe obesity-related multisystem organ dysfunction in conjunction with respiratory failure can occur, involving left ventricular hypertrophy and dysfunction, chronic renal insufficiency and non-alcoholic steatohepatitis. This constellation of features has been termed malignant OHS and is associated with poor outcomes[78].

Sleep-disordered breathing is seen in all OHS, but the nature of the breathing abnormality varies between individuals. About 70% will have severe obstructive sleep apnoea in addition to hypoventilation[79], ranging from repetitive frank obstruction to prolonged periods of partial flow limitation (obstructive hypoventilation)[80]. At the other end of the spectrum, around 10% will demonstrate pure sleep hypoventilation without evidence of obstructive airflow limitation. There are no reliable clinical or blood gas features which distinguish between these two phenotypes. However, a large cross-sectional study found that the highest OSA severity OHS phenotype was associated with reduced risk of cardiovascular disease[81]. The OHS+OSA phenotype tended to be younger, sleepier males with worse nocturnal and daytime gas exchange, who experienced fewer days hospitalised prior to intervention than patients with the OHS phenotype without significant OSA.

While early recognition and intervention are considered vital, misdiagnosis or a delayed diagnosis are common[77]. In obese patients with suspected or known OSA, the possibility of OHS being present should be considered in those with unexplained awake hypoxemia (peripheral $SpO_2 \leq 94\%$), features of pulmonary hypertension/right heart failure, a raised serum bicarbonate (>27mmol/L) or polycythemia,[82, 83] and spirometry/lung volumes indicative of mild restrictive ventilatory impairment (more severe impairment may indicate an alternative diagnosis or complicating comorbidity). The use of serum bicarbonate (with a cutoff of 27mmol/L) has a good negative predictive value in those with low-moderate suspicion of OHS (97%) but a poor positive predictive value (15-50%)[84, 85]. Hence, where bicarbonate is $\geq$ 27mmol/L, an arterialized blood gas is required to confirm the diagnosis.

Staging of obesity hypoventilation has been recently proposed (for patients with BMI>30kg/m^2). The staging ranges from stage 0 (at risk), where the only feature is OSA without any evidence of hypercapnia, to stage IV (OHS with cardiometabolic comorbidities,). Stage III meets the usual criteria for OHS with sustained hypercapnia when awake. Stage I and II have intermittent hypercapnia during sleep, which does not persist during wakefulness, differentiated by serum bicarbonate (less than or greater than 27mmol/L).[86, 87] A recent study showed that OHS can be predicted based on saturation changes in the supine position during wakefulness[87]. Ultimately, the goal is to identify those at risk of later developing OHS to direct early intervention and focus attention on those who will most benefit from preventative medicine.

2.2.4 Clinical Consequences

Regardless of phenotype, OHS is associated with significant morbidity and mortality. Untreated OHS is also associated with poor longer-term survival[66, 88, 89]. Even with positive airway pressure (PAP) therapy, mortality rates of OHS exceed those of obese OSA patients[76].

In addition to its detrimental impact on the respiratory system (reduced lung volumes, increased work of breathing, mechanical disadvantage, sleep-disordered breathing and altered ventilatory drive), OHS is also associated with significant cardiovascular, metabolic and hormonal abnormalities. The cardiovascular consequences of OHS will be discussed in further detail in Chapter 4, but to summarise, higher rates of congestive heart failure and arrhythmia are seen in patient with OHS compared to eucapnic OSA patients, while the data around ischaemic heart disease is conflicting between studies. The rates of pulmonary hypertension are very high and often underdiagnosed among the OHS population (43%-81% based on transthoracic echocardiogram (TTE) or right heart catheterisation (RHC), compared with 8-20% on medical records). There are both pre- and post-capillary factors driving the development of pulmonary hypertension. Increased left ventricular filling pressures are due to high rates of ventricular dysfunction (diastolic more than systolic dysfunction based on previous echocardiographic data), while increased pulmonary vascular resistance is presumed secondary to ventilatory failure and abnormal gas exchange. This may not completely reverse with PAP therapy, suggesting long-term arterial remodelling. OHS patients have high rates of cardiovascular risk factors (hypertension 55-88%, type 2 diabetes mellitus 36-55%, dyslipidaemia 16-43%) (see summary of reported rates in Table 2.2). Although mortality rates of OHS have improved with treatment of their respiratory failure, PAP-adherent OHS still have higher rates of mortality compared to eucapnic obese patients, which has been attributed to their higher cardio-metabolic disease[90]. Other predictors of a poorer prognosis include baseline alkalosis (reflecting the higher burden of nocturnal hypercapnia), severe baseline hypoxemia (SpO_2 < 83%), the need for ongoing oxygen therapy and the presence of diabetes[74, 76, 91].

OHS patients have reduced quality of life[92], impacted by excessive daytime sleepiness, exercise intolerance limiting participation in daily life activities and social stigma. Compared to eucapnic OSA or controls, OHS patients have higher rates of hospitalisation, healthcare utilisation[93], and higher socioeconomic deprivation[94].

2.2.5 Pathophysiology

Daytime hypercapnia distinguishes OHS from simple obesity or obese OSA. Although obesity is a major factor in the pathogenesis of this disorder, only a proportion of those with morbid obesity develop hypercapnia. It is not entirely clear why some people develop hypoventilation while others of similar body habitus are spared. Undoubtedly, the cause of hypoventilation in OHS is complex and multifactorial, with mechanisms varying from individual to individual. Compared with eucapnic obese people, those with OHS present with more severe upper airway obstruction, greater restrictive pulmonary physiology and more attenuated respiratory drive[95-97]. The summary of OHS pathophysiological mechanisms are illustrated in figure 2.2.5a.

Respiratory Mechanics

Morbid obesity induces unfavourable changes in respiratory mechanics and respiratory muscle performance, which are more marked in those with OHS compared to eucapnic obesity[96]. The effects of obesity on pulmonary function were discussed previously in Chapter 2.1.

Excessive fat accumulation around the chest and abdomen leads to lower lung volumes, particularly expiratory reserve volume (ERV) and functional residual capacity (FRC). Lower chest wall and lung compliance[98] and higher airway resistance[99] contribute to a higher work of breathing. The low ERV promotes small airway closure on exhalation, creating greater ventilation-perfusion mismatch as well as expiratory flow limitation and intrinsic PEEP, all worsened when lying supine[100, 101]. These factors contribute to a more marked ventilatory limitation and gas exchange impairment compared to similarly obese eucapnic individuals.

Previous studies comparing respiratory muscle function between OHS patients and eucapnic obese subjects have reported mixed results[83, 102]. Therefore, it is not clear the extent to which reduced respiratory muscle function contributes to the pathogenesis of OHS, although the presence of intramuscular adiposity could reduce muscle strength[103] as would the development of hypercapnia.

However, not all studies have shown an association between regional fat distribution and a propensity for hypoventilation in the morbidly obese[104], highlighting that obesity alone is not the only mechanism underlying the development of hypoventilation.

Sleep Disordered Breathing

Excessive upper airway soft tissue and reduced lung volumes associated with obesity contribute to increased pharyngeal collapsibility[105]. A significant association between AHI and the development of daytime hypercapnia in obesity has been demonstrated[97]. While the majority of OHS patients have concurrent obstructive sleep apnoea, only a minority of obese patients with OSA will develop awake hypercapnia. The reasons for this were unclear until Berger et al.[106] developed a unifying theory connecting sleep breathing events and acute CO_2 retention with the failure of compensatory mechanisms, allowing the development of chronic awake hypoventilation.

During sleep, small transient rises in CO_2 occur during episodes of apnoea or hypopnoea, with subsequent CO_2 unloading between episodes by compensatory hyperventilation. However, if the ventilatory response for a given CO_2 load is reduced and/or the time between apnoeic periods is shortened, less effective clearance of CO2 between periods of abnormal breathing occurs, allowing a gradual accumulation of CO_2 (illustrated in Figure 2.2.5b). This is compensated for by a rise in serum bicarbonate levels to normalise pH, but high bicarbonate will also reduce the ventilatory responsiveness to carbon dioxide permitting the eventual emergence of chronic daytime hypercapnia[106].

Moreover, the retention of CO2 itself may further worsen obesity, with evidence from an in vitro study hypercapnia may accelerate adipogenesis. The authors proposed a positive feedback mechanism involving a vicious cycle of hypercapnia, worsening weight gain which promotes more sleep-disordered breathing, and more CO2 retention[107].

Central Respiratory Drive

In severe obesity, respiratory drive increases to maintain eucapnia in the face of unfavourable respiratory mechanics[101]. However, in OHS this expected compensatory response to the added respiratory load and increase in CO_2 production[108] is not seen. Indeed, patients with OHS exhibit impaired central chemosensitivity to hypoxemia and hypercapnia, as well as a reduced ventilatory drive[109, 110].

In addition to sleep-disordered breathing contributing to the alterations in ventilatory control seen in OHS, neurohormonal influences may also play a role. Leptin is a protein produced by adipose tissue, controlling satiety and energy expenditure as well as acting as a respiratory stimulant. Leptin levels are increased in obese individuals[111], which should aid in compensating for the increased loads placed on respiratory and upper airway structures by excessive adipose tissue. Although serum

leptin levels are higher again in patients with OHS, the stimulatory effects appear to be lost [112, 113], likely due to a state of leptin resistance associated with reduced leptin permeability of the blood-brain barrier[114]. A deficiency of leptin in the CNS would promote the development of awake hypoventilation by altering respiratory drive to both the diaphragm and upper airway muscles, as well as reducing chemo-responsiveness to hypoxia and hypercapnia, thereby attenuating the normal compensatory mechanisms used by individuals to cope with obesity-related respiratory loads and increased CO_2 production.

2.2.6 Management

The mainstay of treatment for OHS has been to address sleep-related breathing abnormalities through positive airway pressure (PAP) therapy. PAP therapy can improve the control of OSA, reduce nocturnal hypoxemia, correct respiratory failure, and improve sleep quality and daytime symptoms.[79, 115-117]

Therapy can be delivered as continuous positive airway pressure (CPAP) or non-invasive ventilation, most commonly in the form of bilevel PAP (BPAP) therapy.

Patients need to undergo titration of device settings with respiratory monitoring to optimise therapy. Previously this has involved performing an attended overnight polysomnogram[118]. However, with improvements in automated device technology, options for titration are broadening[116, 119]. However, data regarding optimal ventilation targets for titration of PAP are lacking. Education and training on device care and interface fit are important elements of home management, as is patient adherence to therapy. Patients require regular follow up for assessment of symptoms, objective measurement of ventilatory status and determination of therapy use. At present, PAP therapy is likely to be lifelong unless significant weight loss is achieved.

2.2.6.1 Positive Airway Pressure

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is the most common therapy used for OHS and is also the simplest. It involves the application of a single level of positive pressure to the airway throughout the respiratory cycle to 'splint' the upper airway open. Since the majority of individuals with OHS have concomitant severe upper airway obstruction, minimising or preventing airway closure during sleep should assist CO_2 unloading. This is turn would lead to a reduction in bicarbonate levels. So while CPAP does not directly augment ventilation by allowing the unloading of CO2 improved ventilation can be achieved. In addition, the volume-inflating effects of CPAP will improve respiratory system compliance and lung volumes, specifically FRC. Not only will this diminish expiratory flow limitation and hence the need for high diaphragmatic effort[101], the attenuation of small airway closure will also improve ventilation-perfusion matching and oxygenation.

Observational studies have demonstrated the effectiveness of CPAP therapy in acutely improving sleep-disordered breathing in OHS, reducing AHI and arousal index, increasing REM duration, and decreasing sleep time with oxygen saturation below 90%.[109, 120, 121] With more extended periods of treatment, CPAP improves daytime gas exchange, ventilatory response to hypoxia and hypercapnia, OHS symptoms and health-related quality of life.[79, 80, 109, 122-124]

Although the treatment of OSA has clear targets concerning CPAP titration (i.e. eliminating obstructive apnoeas and hypopnoeas), this is less clear in OHS. Generally, pressure settings are increased until the elimination of obstructive events and flow limitation (around 10-16cmH_2O).[96] Residual sleep hypoxemia despite the absence of obstructive events may sometimes respond to further increases in pressure.[80] Generally, the goal is to maintain nocturnal SpO_2 above 88-90%.

Failure rates of CPAP range from 20-50%, depending on the criteria used. Some are based on the initial overnight response to CPAP titration in terms of residual nocturnal hypoxaemia or degree of nocturnal rise in $PaCO_2$.[120-122] However, initial CPAP titration failure does not equate to CPAP treatment failure, as this subset of patients can still have marked improvement in their gas exchange during sleep if they persist with CPAP. Persistent chronic hypercapnia ($PaCO_2$>45mmHg) or long-term nocturnal hypoxemia can still occur, despite elimination of obstructive events and good CPAP adherence, and is used to define CPAP failure in some criteria.[70, 123, 125] In general, non-responders to CPAP are more obese[120] with more marked chest wall restriction[121, 124] and have more pronounced sleep hypoxemia during baseline studies.[120, 125] Perhaps not surprisingly, they are also less likely to

have significant upper airway obstruction.[121, 124] A retrospective study found that the rate of acute CPAP response decreased significantly as awake baseline $PaCO_2$ increased, with 60% of OHS patients with a $PaCO_2$ of 46-50 mmHg responding to CPAP compared to just 21% of those with a $PaCO_2$ of 56mmHg or above.[126] However, at present, there are no specific thresholds for any of these parameters to predict who will be a long-term CPAP responder at therapy onset. Up until recently, there has also been a paucity of data regarding longer-term clinical and cardiovascular outcomes in OHS patients managed with CPAP compared to untreated individuals or those managed with BPAP.

Auto-titrating CPAP

The American Academy of Sleep Medicine (AASM) has recommended that auto-titrating CPAP (APAP) not be used in the treatment of obesity hypoventilation syndrome.[127] However, this recommendation is based on expert consensus, with a concern that the APAP algorithm may not detect and respond appropriately to partial airway obstruction, resulting in undertreatment of events and failure to adequately unload CO_2. Nevertheless, to date, no study has been published that identifies any harms associated with using APAP in stable OHS with concurrent OSA. No prior study has compared the efficacy of APAP with fixed CPAP in the treatment of stable OHS with concurrent OSA, although based on observation studies, it appears APAP is used in this population against manufacturers and AASM guidelines. Given the underdiagnosis and misdiagnosis of OHS patients, some OHS patients may be placed on auto-titrating CPAP for pressure determination and long-term therapy.

A recent prospective observational study examining the long-term outcomes of PAP therapy in OHS utilised APAP extensively, with 69 of the 84 patients allocated to CPAP being managed with APAP. Although no direct comparisons of outcomes were made between fixed CPAP and APAP, there did not appear to be any significant differences in gas exchange, mortality or change in sleepiness between CPAP users (of which the majority were on APAP) and the BPAP group, suggesting APAP may have a role in the management of OHS with significant OSA, although well-controlled studies are required to determine the efficacy of therapy.[70]

Bilevel positive airway pressure therapy

Bilevel PAP is a common mode of non-invasive ventilation and is used to treat various causes of acute and chronic respiratory failure, including OHS. With BPAP, two levels of positive pressure are applied to the airway during the respiratory cycle, with a higher pressure during inspiration dropping to a lower airway pressure during exhalation. The latter pressure provides upper airway splinting, while the inspiratory pressure support assists inspiratory efforts in the face of reduced respiratory system compliance, thereby improving ventilation, reducing the work of breathing, and increasing clearance of carbon dioxide. Inspiratory support can be triggered solely by the patient (spontaneous or S mode) or by a combination of spontaneous and machine-triggered breaths (S/T mode). Modes with a more complex algorithm to ensure greater tidal volume stability are also available (volume-assured pressure support or V_APS). The cost of a BPAP device is often several folds higher than that of a standard CPAP device and requires a higher skill level to set appropriate ventilatory parameters.

Bilevel PAP therapy has been shown in both observational studies and randomised control trials to improve daytime gas exchange, sleep parameters, clinical symptoms and quality of life.[70, 74, 79, 91, 115] Long-term data confirm improvements in respiratory function[79, 91] and CO_2 sensitivity[128, 129] and a reduction in the need for hospitalisation[130].

Although some guidelines suggest commencing bilevel therapy in the spontaneous mode[131], this can lead to the emergence of central events in some cases. In a randomised crossover trial, 10 stable OHS patients established on home BPAP therapy were evaluated overnight during therapy in spontaneous and spontaneous-timed (S/T) modes of support.[132] In comparison with the S/T mode, significant increases in abnormal respiratory events (central and mixed), along with greater fluctuations in tidal volumes, were observed in the spontaneous mode. Most published studies have used the S/T mode in the setting of OHS,[79, 116, 133] although there are exceptions[70, 122]. Post hoc analysis from one study found OHS patients ventilated with a higher percentage of machine-triggered breaths experienced greater improvements in nocturnal and awake gas exchange as well as quality of life compared to those in whom more breaths were patient-triggered.[116]

When titrating BPAP for OHS, the end-expiratory pressure (EPAP) is set to stabilise the upper airway, with levels of 8-12 cmH2O or higher often required.[116, 124] The level of inspiratory pressure support (IPAP) is then adjusted upward above this to correct nocturnal hypoventilation and reduce and normalise nocturnal CO2 levels. A target tidal volume of 8-10ml/kg of ideal body weight appears to

be an appropriate goal.[116] Inspiratory pressures of 25 cmH_2O or more may be needed in some individuals to overcome the high chest wall impedance.

Volume-assured pressure support has frequently been used in trials of BPAP therapy in OHS. [79, 116, 133] In this mode, the device automatically adjusts the IPAP level within a pre-determined range to maintain a clinician-set target tidal volume. However, there does not appear to be any greater clinical benefit from using this mode routinely over standard fixed pressure BPAP therapy, so long as both modes are set to deliver similar target tidal volumes and maximum IPAP level.[116, 133, 134] More recently, modes of support which permit automatic adjustment of EPAP (AutoEPAP) in response to upper airway obstruction have been incorporated into some home bilevel devices. At present, this feature has not been widely studied, but a small randomised study comparing BPAP with V_APS with and without AutoEPAP over two separate nights found AutoEPAP was not inferior to standard fixed EPAP in patients with hypoventilation and significant OSA, including those with OHS.[119] Such a feature offers the opportunity to determine an appropriate level of expiratory pressure without the need for an attended sleep study, potentially reducing waiting times for therapy and providing more dynamic control of the upper airway despite changes in sleep stage, body position and weight. However, longer-term studies are needed to confirm these potential benefits.

CPAP vs Bilevel PAP

There remains considerable variation in the way sleep disordered breathing is managed in patients with OHS and concomitant OSA. Bilevel PAP therapy is associated with higher equipment costs and the need for greater skills and resources to initiate and titrate therapy compared to CPAP. However, if longer-term CPAP-treated individuals utilise more health resources, any initial cost savings would be lost, and indirect social costs would be higher. While observational studies report 40-80% of OHS patients are treated with CPAP therapy[70, 123], there have been relatively few randomised trials comparing clinical outcomes between CPAP and BPAP.[79, 122, 124, 135]

In a single-centre study comparing the short-term efficacy of CPAP and BPAP-S mode in 36 OHS patients, improvements in awake $PaCO_2$ were similar between groups, with no significant difference in weight loss, therapy adherence, or daytime sleepiness after 3 months of treatment.[122] However, those allocated to BPAP reported better subjective sleep quality and performed slightly better on a psychomotor vigilance task compared to the CPAP-treated group. It should be noted that nine of the

initially 45 enrolled participants were excluded from the trial due to prolonged desaturation and/or significant rises in nocturnal CO_2.

A subsequent larger, multicenter study compared ST mode to CPAP in 60 OHS patients over 3 months.[124] This study recruited patients with more severe ventilatory failure, including those who had recently recovered from acute respiratory acidosis. No difference in treatment failure (defined as hospital admission, persistent or worsening ventilatory failure, or non-adherence) was observed between therapies (CPAP, 13.3% vs. BPAP, 14.8%, p = 0.87). Furthermore, both treatment modes provided similar rates of improvement in health-related quality of life, cardiovascular risk markers and weight loss. Again, adherence rates were similar between groups at around 5 hours per night. However, there was a trend towards respiratory failure improving more rapidly in the BPAP group over the first month of therapy.[124]

The largest trial to date is the Pickwick Study, randomizing 221 patients with OHS and severe OSA to one of three groups: BPAP (ST mode with V_APS), CPAP or lifestyle modification (control) over 2 months.[79] The primary outcome of this trial was the change in awake $PaCO_2$. Participants were older with a lower BMI than the previously described studies. A more significant improvement in $PaCO_2$ was seen in the BPAP group compared to the control group, with no significant difference between the CPAP and BPAP groups. Clinical symptoms and polysomnographic parameters improved similarly with BPAP and CPAP relative to controls. However, BPAP resulted in greater improvements in spirometric indices (FEV_1 and FVC) and six-minute walk distance compared to CPAP. In a secondary analysis of the data, Corral and colleagues[136] examined the structural and functional echocardiographic changes associated with therapy, finding that BPAP was more effective than CPAP and lifestyle modification in improving pulmonary hypertension and left ventricular hypertrophy. However, given the small differences between therapies and the short period of intervention, the impact on cardiovascular burden and clinical outcomes was unclear.

Publication of data from the long-term follow-up of the Pickwick Study has provided important insights into this issue. Following the completion of the 2-month phase of the trial,[79] participants in the lifestyle group were re-randomised to either the established CPAP or BPAP groups,[135] with both groups then continued to be followed for a median of 5.42 years. Data from 202 patients was available for final analysis. No difference between groups in the primary outcome measure of hospitalisation days was seen, nor were there differences in healthcare resource utilisation, incident cardiovascular events or mortality between the two PAP groups.

In light of available current evidence,[137] CPAP should be considered as the initial treatment choice in stable OHS patients with concurrent severe OSA. However, close monitoring of an individual's response to therapy in the initial 4-8 weeks of therapy is critical, recognising that a proportion of patients with OHS and concurrent OSA will fail CPAP and will need to be treated with BPAP long-term. Those presenting with high baseline $PaCO_2$[124] and more severe obesity[126] are more likely to be CPAP non-responders.

Adherence to PAP therapy

Irrespective of the mode of PAP therapy used, adherence to treatment is key to improving clinical outcomes. In most reported studies, OHS patients have generally used PAP for 5-6 hours per night.[70, 79, 122, 124] In a study comparing two different modes of BPAP, a significant correlation between hours of use and improvement in daytime CO_2 was seen, with at least 4 hrs nocturnal use required to achieve a reduction in awake CO_2.[116] Mokhlesi and colleagues[123] reported a plateau in $PaCO_2$ improvements after 7 hours mean nightly use, regardless of mode. In a more recent observational study, patients using PAP therapy ≥ 6 hours per night had considerably greater improvements in blood gases and quality of life than those using PAP less than this. Moreover, these individuals also had a lower likelihood of experiencing a serious cardiovascular event during the follow-up period. Finally, Masa et al.[138] reported significantly improved hospital resource utilization and survival in both BPAP and CPAP users who were more adherent to therapy.

PAP Therapy in OHS without OSA

Around 20-30% of OHS patients do not have significant OSA, showing primarily sleep hypoventilation and an AHI <30 events/hour.[79] This sleep hypoventilation phenotype is indistinguishable from those with OHS-OSA in terms of symptoms and blood gases. However, a cross-sectional analysis of a large cohort of OHS patients found that those with the more pure OHS phenotype were more likely to be older and female, with a lower BMI, less nocturnal hypoxemia, but have a higher cardiovascular comorbidity burden.[81]

Few studies have evaluated treatment or outcomes in this group, with patients generally managed with long-term BPAP. One randomised trial compared bilevel PAP to lifestyle measures over 2 months in this select group of patients.[117] More significant improvements in $PaCO_2$ and serum bicarbonate, sleepiness and some health-related quality of life assessments were seen in the BPAP group compared to those receiving lifestyle modification alone. The long-term follow-up of this group of patients (median duration of 4.98 years) also indicates that BPAP therapy, in contrast to the control group, had sustained improvements in $Paco_2$, pH, bicarbonate, quality of life, and daytime sleepiness. However, there was no difference in hospitalisation days between the two groups (per-protocol analysis did favour BPAP arm).[139]

A prospective longitudinal study followed 83 patients with OHS who were part of a home ventilation program over a 12-year observational period.[69] Fifty of these individuals were classified as pure sleep hypoventilation OHS. Despite similar improvements in blood gases in both groups, survival after the third year of therapy was lower in the sleep hypoventilation-only group. It is unclear why this would be the case, and longer-term data from well-designed studies are needed to confirm and explain this finding.

Oxygen therapy

Although a significant number of OHS patients exhibit daytime hypoxemia and severe nocturnal oxygen desaturation prior to intervention,[70, 140] oxygen therapy should not be used as the sole treatment as it does not address the underlying cause of ventilatory failure. Used alone, supplemental oxygen may worsen hypercapnia[141] and extend symptoms of sleep hypoventilation, including morning headaches and confusion[140]. Once PAP therapy is established, oxygen therapy is often no longer required,[121 70, 74] reducing overall healthcare costs. Post hoc analysis of data from phase one of the Pickwick study found that hospital resource utilisation was higher over a 2-month period in OHS patients requiring supplemental oxygen, although this did not reach statistical significance. Baseline hypoxemia and the need for ongoing oxygen therapy have been found to be predictors of poorer outcomes in patients with OHS in several observational studies.[74, 76, 91] It is likely those individuals requiring supplemental oxygen long term have more severe disease or worse

comorbidities[70, 74] and therefore warrant closer monitoring and attention to minimize comorbid cardiovascular risk[90].

Tracheostomy

Before the availability of PAP therapy delivered non-invasively by masks, tracheostomy was the main treatment for OHS patients with severe symptoms and life-threatening complications. The bypass of upper airway obstruction via tracheostomy resolves nocturnal obstruction and reduces hypoventilation, although the need for ventilator support may persist.[142] Currently, tracheostomy is reserved for those who cannot tolerate mask PAP therapy, and is rarely used as it creates its own problems and clinical issues.

Placement of tracheostomy can be challenging in the very obese patient. The increased distance from the anterior neck skin to the tracheal wall increases the risk of complications, such as tube misplacement, false passages, and accidental decannulation. Customised tubes may be required.

Acute Hypercapnic Respiratory Failure

Forty percent or more of OHS patients are first diagnosed during a hospital admission with acute hypercapnic respiratory failure (AHRF)[74, 76, 124], although multiple admissions may be needed before the condition is recognized and correctly labelled[78]. Decompensation may arise from various causes, including worsening heart failure, pharmacotherapy (e.g. opioids), inappropriate oxygen use and infection. However, no clear precipitant is found in a significant proportion of patients.[143]

No controlled trials comparing CPAP and BPAP for decompensated respiratory acidosis in OHS have been reported. Although one observational study reported significant improvements in respiratory acidosis and mental status in six patients with OHS treated with nasal CPAP and supplemental oxygen use[144], BPAP is the recommended mode of initial therapy[145] as it augments ventilation with faster CO_2 clearance.

Generally, BPAP is commenced in the acute setting using the same criteria and protocols suggested for patients with acute exacerbations of COPD.[89, 145] However, significantly higher EPAP is usually

required compared to other causes of respiratory failure due to the presence of upper airway obstruction.[78] Sufficient inspiratory pressure support is then needed to achieve target tidal volumes of ~8 ml/kg of ideal body weight. As a consequence of reduced respiratory system compliance, a longer inspiratory time with a less sensitive cycle off criteria is used to maximise tidal volume. A rise time of 200-300ms is favoured for patient comfort. Consequently, a pressure control mode may provide more effective ventilation for some patients by preventing early switching from IPAP to EPAP due to restrictive chest wall mechanics. Volume-assured modes of BPAP may be more effective in providing high inflation pressures when needed to overcome the high chest wall impedance seen in this condition.[145] Likewise, employing automatic EPAP adjustment could improve the efficacy of therapy and patient comfort by allowing a variation in expiratory pressure depending on the patient's wake/sleep state and their body position.[146] Whether these modes provide additional benefits to fixed pressure BPAP requires further evaluation.

In a large observational study of patients with OHS and acute respiratory acidosis treated with BPAP, lower rates of late therapy failure, readmission to ICU and in-hospital mortality were seen compared to similarly severe and managed COPD patients.[89] The need for intubation and the length of ICU and hospital stay, however, were similar between groups.

Nevertheless, failure rates of BPAP therapy and mortality can be significant in this population. In a cohort of 61 OHS patients with hypercapnic respiratory failure and multi-organ failure admitted to an intensive care unit, Marik and Desai[78] reported a failure rate of almost 40%. A prospective, observational study looked at the determinants of BPAP failure in this patient group.[143] In this study, failure of BPAP occurred in 17% of patients, primarily those presenting with hypoxemic respiratory failure and pneumonia. In contrast, BPAP was consistently successful in reversing idiopathic hypercapnic acute respiratory failure. Notably, in more than half of the hypercapnic group, a delayed response to PAP therapy was observed, characterized by limited changes in pH and $PaCO_2$ during the first 6-12 hours of treatment. However, all patients ultimately improved clinically, with reversal of respiratory failure and avoidance of intubation. This may be explained by their altered chemoresponsiveness to hypoxia and hypercapnia. Aggressive loop diuretic therapy for peripheral oedema can also worsen hypercapnia by causing contraction alkalosis.[147] Similarly, acute hyperoxia-induced hypercapnia is well recognized in this population[141], so management should include targeting an oxygen saturation range of 88-92%[145].

Appropriate positioning of the patient is vital to optimize the chance of BPAP success. The upward displacement of the diaphragm in the supine position leads to increased intrathoracic pressure, lower lung volumes and small airway closure in the dependent parts of the lungs. This is exacerbated in morbid obesity, leading to expiratory flow limitation, auto-PEEP and worsening gas exchange. In addition, the supine position may increase the tendency for upper airway collapse, particularly if an oronasal mask is used.[148] Supine positioning also has detrimental hemodynamic effects due to a drop in cardiac preload and increase afterload seen in massive abdominal obesity.[143] The sitting position alleviates these effects by reducing the gravitational forces of the abdomen on the diaphragm and on the upper airway tissues, improving the efficacy of BPAP intervention.

At hospital discharge, it is not clear whether empirical PAP therapy should be continued or whether home therapy should be withheld until completion of an outpatient workup (sleep studies for diagnosis and PAP titration). No randomised controlled trials have addressed this issue. However, observational studies suggest high mortality rates in untreated OHS patients following hospital discharge.[66, 121, 149] If therapy is continued at discharge, this will often be BPAP therapy, without consideration of CPAP as a longer-term therapy[149]. A small prospective study demonstrated that a significant number of stable OHS patients could be transferred from BPAP to CPAP without adversely affecting gas exchange, quality of life or sleep quality.[150] Eighty percent of patients in this study had been commenced on BPAP during an acute hospital admission, suggesting there may be overuse of BPAP for long-term home therapy.

Perioperative Management

Many OHS patients presenting for surgery have not been diagnosed or have been misdiagnosed. Pre-operative recognition is essential as OHS poses a much higher perioperative morbidity and mortality risk than eucapnic OSA.[65]

The STOP-Bang questionnaire is used as a screening tool in pre-operative patients to identify those at high risk for OSA.[151] In obese or morbidly obese patients with an elevated STOP-Bang ($\geq$4), a high serum bicarbonate and low awake SpO_2, a diagnosis of OHS should be considered and a blood gas performed. Depending on the emergent nature of the surgery, further referral to sleep services (polysomnogram and PAP therapy titration) and pre-operative cardiopulmonary evaluation (such as an echocardiogram to assess RV function and pulmonary hypertension) may be required.[152]

Intraoperative considerations include anticipation and preparation for difficult intubation and mask ventilation, appropriate positioning, use of PEEP, protective ventilation and the use of intraoperative capnography.[153] Strategies to minimise opioid-related respiratory depression should be considered, including consideration for local and regional anaesthesia and a multimodal approach to analgesia.[152]

Post-operatively, OHS patients should be admitted to a monitored bed as they are at high risk of postoperative cardiopulmonary failure.[154] Early resumption of PAP therapy is essential to avoid postoperative atelectasis and has been found to decrease respiratory failure in severely obese patients in ICU after extubation.[155] Again, an opioid-sparing analgesic regimen should be considered.

2.2.6.2 Non-PAP therapy

Despite the effectiveness of PAP therapy in reversing respiratory failure, reducing symptoms and improving quality of life, mortality rates of treated OHS remains high, primarily related to cardiovascular and metabolic factors.[76, 90] In addition to PAP therapy, optimal long-term care of OHS requires an integrated management approach, including lifestyle modification, consideration of bariatric surgery to address weight loss, pharmacotherapy for cardiovascular and metabolic comorbidity and programs to support and encourage physical activity.

Weight Management

Weight loss is an integral part of OHS management as obesity is not only the main contributor to the development of OHS, but it also impacts cardiovascular and metabolic outcomes. The importance of weight loss is highlighted in the recent iteration of the American Thoracic Society practice guidelines, recommending weight loss interventions that produce a sustained weight loss of 25-30% of actual body weight to achieve resolution of hypoventilation[156].

The use of PAP has been shown to result in small but significant reductions in weight, possibly related to an increase in physical activity.[96, 116] In a randomised trial, the addition of a multidisciplinary weight-loss program resulted in more significant weight loss than BPAP alone at three months follow up, as well as significant improvements in blood pressure, exercise capacity and

quality of life.[157] Unfortunately, by 12 months, these effects were lost, in part due to difficulties retaining patients in the program over this length of time. Although intensive lifestyle intervention has been successful in achieving weight loss in obese patients, maintaining this loss is difficult, and studies have failed to show improved long-term cardiovascular outcomes[158].

Bariatric surgery is superior to conservative weight loss approaches in terms of achieving significant and sustained weight reduction.[159] There are several surgical techniques available, with gastric bypass, sleeve gastrectomy and laparoscopic adjustable gastric banding (LAGB, now out of favour due to higher complications rates and lower weight loss efficacy) being the most commonly used. Significant improvement in rates of diabetes, hypertension, dyslipidaemia and obstructive sleep apnoea were achieved with surgery,[160] with LAGB less effective at achieving weight loss compared to gastric bypass and sleeve gastrectomy[159].

Unfortunately, the majority of surgical trials have either not specifically identified those with OHS or excluded them. Observational studies have shown significant improvements in gas exchange, self-reported daytime hypersomnolence and hemodynamic function in OHS patients following bariatric surgery[161, 162], with improvements in gas exchange sustained at five years follow-up.[163] A randomised trial of 63 patients with obesity (BMI>35kg/m2) and severe OSA (AHI>30/hour) or OHS (25 patients) on PAP therapy showed that bariatric surgery (LAGB) achieved greater improvements in sleep disordered breathing and weight loss than intensive nutritional care.[164] However, the study did not report outcomes separately for the OHS group.

Bariatric surgery is associated with high cost and risk for postoperative morbidity and mortality.[160, 165] This may be even greater in the OHS population, given their high rates of cardiorespiratory comorbidity. When considering surgery, particularly for the super morbidly obese, the benefits of meaningful and sustained weight loss need to be weighed against the likely risks for the individual concerned.

Recent trials involving incretin receptor agonists have shown success in weight loss and reducing the burden of OSA[166]. Although no trials so far have examined its use specifically in the OHS population, this may serve as an important tool in addressing a key driver of its pathogenesis.

Pharmacotherapy

Respiratory stimulant medications have been explored as a potential treatment for OHS given the reduced sensitivity of respiratory chemoreceptors being a factor in the development of daytime hypoventilation.

Acetazolamide, a weak carbonic anhydrase inhibitor, and medroxyprogesterone, a central respiratory stimulant, have been reported to improve ventilatory response and blood gas measurements in OHS (Sutton 1975, Raurich 2010).[167, 168] However, there are limited long-term data on efficacy and tolerance. Medroxyprogesterone increases the risk of venous thromboembolism, which the OHS population is already at higher risk for. The potential risk of worsening acidemia and impaired respiratory muscle function makes acetazolamide undesirable in OHS.

Given the lack of data and safety concerns, routine pharmacotherapy cannot be recommended in OHS. However, in those who do not adequately respond to PAP therapy, the addition of pharmacotherapy may be considered in selected patients.

Management of Comorbidities

The majority of OHS patients have one or more cardiovascular risk factors in addition to obesity. The risk of cardiovascular disease is higher than in weight-matched obese patients. Death from cardiovascular causes outnumbers that of respiratory failure in the OHS population once PAP therapy is commenced.[76, 90] Attention to risk factor screening and guideline-directed pharmacotherapy, along with lifestyle modification, is important in reducing mortality rates.

2.2.7 Research Deficiencies

Research thus far has demonstrated the importance of understanding the pathophysiology of OHS, phenotyping OHS (with regard to one of the causative mechanisms - severe obstructive sleep apnoea) in determining the choice of PAP therapy. Unfortunately, OHS remains underdiagnosed and under-recognised. Potentially, a subset of OHS patients do not go through the recommended pathway of in-laboratory diagnostic and PAP titration study, but instead, are managed with auto-titrating CPAP, which is currently not recommended for OHS. However, given that auto-titrating

CPAP also addresses the underlying obstructive sleep apnoea, it remains to be seen whether it is an effective and safe alternative. Chapter 6 will look to address this in a direct comparison study with fixed CPAP.

While clinical outcomes have improved with addressing respiratory failure and sleep-disordered breathing in OHS patients, their mortality remains high, mostly due to cardiovascular disease. The association of cardiovascular disease and OHS will be further explored in Chapter 2.3. Potential mechanisms linking the high rates of cardiovascular morbidity and OHS will also be discussed. Chapter 4 will add to the existing cardiovascular outcomes data and look to answer some of the discrepancies, specifically atherosclerosis and coronary disease outcomes, in OHS.

2.3 Cardiovascular Consequences of OHS

The following has been published in Sleep Medicine Reviews:
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As briefly discussed in Chapter 2.2.4 (Clinical consequences of OHS), cardiovascular disease is common in patients with obesity hypoventilation syndrome (OHS) and accounts in part for their poor prognosis. This narrative review examines the epidemiology of cardiovascular disease in obesity hypoventilation syndrome, explores possible contributing factors and the effects of therapy. All studies that included cardiovascular outcomes and biomarkers were included. Overall, there is a higher burden of cardiovascular disease and cardiovascular risk factors among patients with obesity hypoventilation syndrome when compared to eucapnic obesity or OSA. In addition to obesity and sleep-disordered breathing, there are several other pathophysiological mechanisms that contribute to higher cardiovascular morbidity and mortality in OHS. There is evidence emerging that positive airway pressure therapy and weight loss have beneficial effects on the cardiovascular system in OHS patients, but further research is needed to clarify whether this translates to clinically important outcomes.

2.3.1 Introduction

Obesity imposes adverse effects on respiration, affecting upper airway function during sleep (manifesting as obstructive sleep apnoea [OSA]), work of breathing, respiratory muscle function and lung volumes. Despite this, the majority of obese people (even those with OSA) can compensate for the adverse effects on respiration to maintain eucapnia. Nevertheless, a small proportion (most with comorbid OSA) will develop OHS. OHS is characterised by obesity (body mass index >30kg/m^2) and CO_2 retention ($PaCO_2$ >45mmHg) related to nocturnal and daytime hypoventilation that is unexplained by other disorders[169]. All OHS patients have underlying sleep-disordered breathing with varying degrees of obstructive sleep apnoea and central hypoventilation [169].

The risk of developing OHS and other obesity-related diseases such as coronary heart disease and type 2 diabetes mellitus rises with increasing body mass index (BMI)[169, 170]. Patients with OHS have higher cardiovascular morbidity compared with OSA alone [171, 172]. While the development of cardiovascular disease is often attributed to obesity, conventional cardiac risk factors and underlying sleep apnoea, it is unclear whether additional factors play a role in the increase in cardiovascular morbidity seen in those with OHS. In addition, although treatment of OHS improves respiratory failure and symptoms, the impact on cardiovascular outcomes is less explored.

2.3.2 Cardiovascular disease in OHS

Despite the variability in cardiovascular disease between studies, the prevalence consistently appears to be inversely correlated with the increasing severity of OSA[173]. However OHS patients are more likely to have a cardiovascular event than those with OSAS [171]. They are also at a higher risk of developing cardiovascular morbidity some years before their OHS diagnosis[174]. Also, patients with hypercapnic OSA (majority with OHS) are more likely to have postoperative heart failure than eucapnic OSA [175]. Several studies [171, 175-178] report higher rates of congestive heart failure (CHF) and arrhythmia in OHS than OSA. The reported prevalence of CHF in OHS varies from 8-60% (Table 2), while the rate of arrhythmia in OHS vary from 0 to 36% between studies (Table 2). The most frequent arrhythmia documented was atrial fibrillation (AF), which accounted for around half of all arrhythmias or 18% [179]. In comparison, AF rates in OSA from The Sleep Heart Health Study were 4.8% [180]. History of arrhythmia and heart failure was associated with increased mortality in a retrospective cohort [171].

In contrast, it is less clear whether OHS is associated with higher rates of ischaemic heart disease (IHD) above that of OSA. Kaw et al. showed higher rates of IHD in its cohort of hypercapnic OSA versus non-hypercapnic OSA [175]. However, several other studies [171, 176, 177, 181] surprisingly reported similar or lower rates of IHD in OHS than OSA. Although the majority of the hypercapnic OSA was due to OHS (81/117), a sizeable proportion also had chronic obstructive pulmonary disease (COPD) (35/117) as their primary factor leading to hypercapnia. In this context, COPD-OSA overlap syndrome is well recognised to have higher coronary disease rates [182]. Overall, it remains unclear if the prevalence of IHD is lower in the OHS population than in OSA compared to other cardiovascular diseases. It is possible symptoms related to IHD may instead be attributed to deconditioning and

right ventricular failure related to OHS, resulting in delayed/missed diagnosis. However, in a small case series of autopsy results in those with a clinical diagnosis of OHS or suspected to have OHS, none of the ten patients had evidence of significant coronary artery disease [183]. Alternatively, patients at higher risk of IHD may succumb to cardiac complications or receive medical attention to address weight management before developing OHS due to progressive weight gain.

The reported rates of pulmonary hypertension (PH) are also higher among OHS populations compared to simple obesity (5%) [184] and obstructive sleep apnoea (10%) [185] cohorts. The PH rates based on right heart catheterisations and echocardiograms are higher than those reported from clinical records (8 to 30%) in OHS populations (Table 2.), highlighting possible under-diagnosis despite PH being a well-recognised haemodynamic comorbidity in OHS. This finding is reflected in the Pickwick Study, where the reported rates of pulmonary hypertension were 8.5% before enrolment. However, more than half the patients with OHS had echocardiographic findings of pulmonary hypertension [186].

2.3.3 Cardiovascular mortality in OHS

Studies also show that untreated OHS has a high five-year mortality rate of 23-30% [187, 188] and this rate is higher than simple obesity [178]. Importantly, cardiovascular disease is the leading cause of death in the OHS population [138, 171, 189]. Even with appropriate positive airway pressure (PAP) therapy, OHS patients are subject to higher mortality rates when compared to obese patients with OSAS (roughly 3-4 times higher 5-year mortality [171, 181]). Furthermore, being on a combination of cardiovascular agents, a reflection of underlying cardiovascular disease, was also predictive of increased mortality among obese hypercapnic patients [90]. However , there does not appear to be a gender difference in survival rate [190].

2.3.4 Underlying mechanisms linking cardiovascular disease to OHS

2.3.4.1 Obesity

As discussed in section 2.1.2, obesity is undoubtedly a critical risk factor for cardiovascular disease and death in all populations, including OHS, where the majority of patients have class 3 obesity (BMI>40kgm^2) [191]. Indeed, the American Heart Association and the American College of Cardiology list obesity as a major modifiable cardiovascular risk factor [192]. Obesity is associated with endothelial dysfunction, atherogenic dyslipidaemia, increased basal sympathetic tone, insulin resistance and hypertension [193, 194]. Overall, obesity is considered a pro-inflammatory and pro-thrombotic state [195] and is an independent risk factor for developing heart failure [196]. Morbidly obese patients can develop obesity cardiomyopathy (adipositas cardis) due to lipotoxicity and physical compression by pericardial fat deposition [197]. A rise in BMI leads to an exponential increase in the risk of developing heart failure [198] and atherosclerosis [199]. Men and women with BMI >35kgm^2 have a 3-fold and 2-fold increase in risk, respectively, of cardiovascular disease-related death, compared to those with normal BMI [200]. The majority of this is due to an increase in coronary artery disease.

Obesity also increases the risk of developing other well-recognised and modifiable cardio-metabolic risk factors associated with metabolic syndrome such as hypertension, type 2 diabetes mellitus and dyslipidaemia [201]. The prevalence of these risk factors among OHS studies is shown in Table 2. The reported prevalence is highly variable between studies despite similar mean age and BMI, likely reflecting different study locations and inclusion criteria. The rates of hypertension, dyslipidaemia and type 2 diabetes mellitus appear similar to data from an obesity study of those with BMI>40kg/m^2 [201]. Type2 diabetes mellitus appears to be a predictor of poor outcome in patients with OHS [181, 202] while hypertension is more commonly found in OHS patients with left ventricular diastolic dysfunction [203]. Overall, the high prevalence of traditional cardiovascular risk factors in OHS is in keeping with their degree of obesity and likely explains the high rates of cardiovascular disease seen in this group.

Regular moderate-intensity physical activity is an integral part of cardiovascular disease prevention and treatment[204]. In contrast, a sedentary lifestyle promotes weight gain and the development of obesity[204] and is a major risk factor for cardiovascular disease and mortality[205]. In two studies that assessed physical activity in OHS, the mean immobile time was around 200 minutes/day[157, 206]. In the latter study, there were inverse correlations between daytime activity and weight and waist

circumference in OHS[206]. However, there are no data directly linking cardiovascular outcomes to physical inactivity in OHS.

2.3.4.1 Obstructive sleep apnoea

Apart from obesity, there are several proposed mechanisms for the association between obstructive sleep apnoea and cardiovascular disease that will also apply in OHS populations. Repetitive obstructive events result in surges in sympathetic activity and intermittent hypoxia, leading to the formation of reactive oxidative species, vasoactive substances, increasing systemic inflammation and endothelial dysfunction. Furthermore, the intrathoracic pressure swings during frank apnoea contribute towards autonomic and haemodynamic instability [207]. Given the intermittent hypoxic episodes seen in OSA and its relationship to the development of reactive oxidative species and endothelial dysfunction, it could be extrapolated that OHS patients who have a more severe OSA phenotype would be at a higher risk of cardiovascular morbidity and mortality than OHS with milder or no OSA. Surprisingly, a cross-sectional analysis of 302 patients from the Pickwick project showed an inverse relationship between cardiovascular morbidity and severity of OSA [208]. Except for ischaemic heart disease, the most severe oxygen desaturation index (ODI) tertile (greater total sleep time with SpO_2<90% and lower mean SpO_2) had the lowest prevalence of pulmonary hypertension, stroke, arrhythmia, chronic heart failure and leg arteriopathy. Chronic heart failure had the strongest inverse relationship with ODI tertiles [208]. Patients in the most severe ODI group were younger, predominantly male, more obese, sleepier and with worse nocturnal and daytime gas exchange. They had a lower prevalence of hypertension, better exercise tolerance and fewer hospitalisation days than the lowest OSA severity group. However, even after adjusting for age and medical treatment, the inverse relationship was still apparent [208].

Lavie et al. hypothesised that cycles of apnoea and hypopnoea in OSA might resemble cycles of ischaemia reperfusion, which exert a cardioprotective effect from more severe ischaemic and cardiovascular events similar to ischemic preconditioning. This phenomenon has been shown to be protective in other organ systems [209]. Morbidly obese patients with more severe OSA are also likely to develop OHS at a younger age and access healthcare earlier due to their sleep symptoms. As a result, their duration of exposure to chronic hypoxia and hypercapnia and other cardiovascular risk factors may be shorter than OHS patients with a mild OSA phenotype. The disparity in patients' baseline characteristics from the two Pickwick project cohorts (OHS with and without severe OSA)

also suggests this. While the two cohorts had similar mean BMI and $PaCO_2$, the OHS patients without severe OSA had a higher mean age (68 years old versus 60 years old) and higher rates of cardiovascular comorbidities, including heart failure and pulmonary hypertension[210, 211].

Given sleep-related/nocturnal hypoventilation is much less common than OSA, data related to its impact on the cardiovascular system is sparse. Pulmonary hypertension is a recognised complication of chronic hypoxia seen in other primary or secondary sleep-related hypoventilation disorders. Autonomic dysfunction, assessed using heart rate variability (HRV) and a predictor of future cardiovascular disease, is found in various causes of sleep-related hypoventilation disorders (idiopathic, congenital central hypoventilation syndrome, chest wall deformities and neuromuscular disease [212-214]) as well as in OHS with or without sleep apnoea [213, 215]. The severity of oxygen desaturation appears to correlate with the degree of HRV abnormality. In keeping with this, a recent analysis of hypoxic burden (area under the desaturation curve from pre-event baseline) predicted cardiovascular mortality across large population cohorts [216]. The cardiovascular analysis on the Pickwick project cohort only used ODI to distinguish tertiles. It is possible that analysis of overall hypoxic burden, which accounts for effects of hypoventilation and duration of apnoea-related desaturation events, may show a different relationship with cardiovascular morbidity. In summary, as individual OHS patients have varying degrees of obstructive sleep apnoea and sleep-related hypoventilation, their detrimental effects on the cardiovascular system will also vary.

2.3.4.3 Hypercapnia

Chronic hypercapnia is a defining feature of obesity hypoventilation syndrome and a reflection of its severity. In addition, the acute effects of carbon dioxide on the cardiovascular system are well studied in animal models.

In humans with OHS, the repeated acute rises in $PaCO_2$ during sleep accompanying periodic apnoea and hypoventilation are particularly pronounced during REM sleep. As $PaCO_2$ rises, there is a rise in blood pressure, heart rate and cardiac output [217, 218]. In parallel, hypercapnia and acidosis directly depress cardiac myocyte function [219] and during periods of severe acidosis or when catecholamine stores are depleted as well as when sympathetic activity is inhibited (negative inotropic medications), acute hypercapnia leads to depression in cardiac function, vasodilation and hypotension. Respiratory acidosis also leads to pulmonary vasoconstriction, compounding the

effects of chronic hypoxia on the pulmonary circulation and the right ventricle [218, 220]. $PaCO_2$ may also act as a mediator of coronary blood flow. However, it is unclear whether this will contribute to regional ischaemia via the coronary steal phenomenon or whether it is actually protective by reducing vascular resistance [221]. In addition to the arrhythmogenic effects of increased catecholamines, hypercapnia also increases QT interval and dispersion [218].

The long-term effects of chronic hypercapnia on the cardiovascular system are unknown. In animal models, chronic hypercapnia appears to inhibit the development of hypoxic pulmonary vascular remodelling [222], suggesting that the development of pulmonary hypertension in chronic respiratory failure is due to other factors. However, another animal model showed that chronic hypoxia's cardioprotective effects are blunted by chronic hypercapnia [223].

2.3.4.1 Pulmonary hypertension

Pulmonary hypertension (PH) is defined by a mean pulmonary arterial pressure (mPAP) of ≥25mmHg at right heart catheterisation (RHC). Pulmonary hypertension is an indicator of poor prognosis in patients with left heart disease and chronic obstructive pulmonary disease.

Pulmonary hypertension is also a recognised feature in obesity, but there is limited prevalence data [224]. Retrospective data from a single centre showed that 5% of individuals with a BMI>30kg/m^2, who were otherwise healthy and with normal echocardiography parameters, had moderate or severe PH (pulmonary artery systolic pressure, PASP>40mmHg on transthoracic echocardiogram, TTE) [184]. This is likely related to the positive relationship between BMI and PASP[184] as well as right ventricular (RV) dysfunction [225].

In contrast to simple obesity, the rates of PH in OSA studies appear to be higher at around 15-20% [185]. Whilst OSA patients often have comorbid conditions that contribute to the development of PH, it appears that OSA itself is an independent cause of PH. This is based on studies showing improvement in pulmonary artery pressures with CPAP treatment [226]. However the rates of PH are even higher and more severe among OHS populations [227]. OHS patients are also more likely to suffer from cor pulmonale [172]. Several OHS studies have examined the rates of PH using echocardiograms and right heart catheterisation (RHC) (Table 3). The wide range of reported prevalence of PH among OHS (50-80%) is due to different measurement techniques, technical difficulties due to underlying

obesity, changing measurement guidelines and PH definitions over time. There are many contributing mechanisms to the development of PH in OHS. Several studies found evidence of post-capillary PH on RHC (elevated pulmonary capillary wedge pressure) or echocardiogram (left ventricular dysfunction). Diastolic dysfunction (~60%) [179, 203, 228] rather than systolic dysfunction (~20%) [176, 179] is the more common echocardiographic finding. Fat deposition in myocytes leads to apoptosis and fibrosis, thereby increasing ventricular stiffness. Other significant contributors to myocyte dysfunction include insulin resistance, elevated sympathetic tone and activation of the renin-angiotensin axis [229]. The intensive negative intrathoracic pressure experienced during obstructive apnoea in OHS leads to a leftward shift of the interventricular septum and further impediment of the left ventricular filling. Studies using RHC have demonstrated a raised transpulmonary vascular gradient or diastolic pulmonary pressure gradient [228, 230, 231] indicating pulmonary vascular changes. In OHS, there is a progression from transient pulmonary vasoconstriction (due to apnoea related oxygen desaturation) to pulmonary vascular remodelling (endothelial dysfunction, arterial wall thickening and fibrosis) with the development of chronic hypoxaemia [229]. It is likely at this point that even adequate treatment of their sleep-disordered breathing will not be sufficient to reverse the elevated pulmonary vascular resistance.

Despite mechanistic evidence linking PH with OHS, it is not clear whether the presence of pulmonary hypertension confers a worse prognosis in OHS. However, the need for supplemental oxygen (likely linked to underlying pulmonary hypertension) was independently associated with higher mortality [188]. This is in keeping with a worse prognosis with PH in other cardiopulmonary diseases; however, further research is needed to confirm this.

2.3.4.1 Other Biomarkers

Several studies compared various cardiovascular biomarkers between OHS, OSAS and eucapnic obese. When compared to eucapnic obese (age and BMI matched), OHS subjects had higher pro-inflammatory (high-sensitivity C-reactive Protein, RANTES and glycosylated haemoglobin A1c) and lower anti-inflammatory (adiponectin) markers [232]. There is also a reduction in insulin-like growth factor 1 (IGF-1) in OHS compared to obese controls [233]. IGF-I is a growth factor that is important in maintaining endothelial function. It is inversely related to $PaCO_2$ and diaphragmatic muscle function[233]. Its inverse correlation with triglyceridaemia may also be a link between respiratory failure and cardiovascular disease. Leptin, a protein produced by adipose tissue that controls satiety and energy expenditure, is also a respiratory stimulant. While leptin levels are elevated in obesity

and OHS, many organ systems in the body exhibit resistance to the effects of leptin. Patients with OHS may be characterised by greater leptin resistance, and leptin resistance has been proposed as a potential contributor to reduced central ventilatory drive and the development of chronic hypoventilation [234]. Leptin is also associated with sympathetic activation, endothelial dysfunction and linked to cardiovascular complications (coronary heart disease, cardiomyopathy) in obesity [235].

Patients with OHS also have greater inter-atrial and intra-atrial electromechanical delay and higher p wave duration and dispersion than gender-matched obese controls [236]. These echocardiography findings are predictors of the development of atrial fibrillation. In this context, OHS subjects (compared to similarly obese OSA subjects) had a reduced HRV [213, 215] and more impaired endothelial function measured by peripheral arterial tonometry compared to eucapnic obese [232]. Both these markers would suggest OHS patients are at greater risk of cardiovascular-related events and mortality.

2.3.5 Effects of therapy:

2.3.5.1 Positive Airway Pressure (PAP) Therapy

PAP therapy is essential in addressing sleep-related breathing abnormalities and reversing chronic respiratory failure in OHS. The two most commonly used modes in OHS are continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV, also known as bi-level positive airway pressure). PAP therapy effectively improves OSA and associated nocturnal hypoxia, respiratory failure, daytime sleepiness and sleep quality and reducing rates of hospitalisation [169]. PAP therapy also appears to have modest effects in improving physical activity and reducing weight [122, 124, 206].

PAP therapy appears to have a mortality benefit, and poor adherence is a predictor of mortality in OHS. Data from the long-term follow up of Pickwick study subjects (OHS with severe OSA) as well as other observational studies found that OHS patients with higher adherence had lower hospitalisation rates, emergency department visits, a reduced risk for ICU admission and mortality in addition to a lower risk of cardiovascular events than those with lower adherence [138, 181, 189]. When long-term outcomes of OHS patients without severe OSA phenotype are analysed in isolation, the addition of PAP therapy (NIV) did not improve mortality or reduce cardiovascular events [237] despite improvements in $PaCO_2$ and sleep parameters when compared to the control group (assessed during

the two months randomised clinical trial) [211]. It is not clear what accounts for the discrepancy in outcomes seen in the two OHS phenotypes. The OHS without severe OSA cohort had a low recruitment rate, and the study terminated early, so it may have been underpowered to detect a difference. Ultimately, cardiovascular disease may be more established among OHS without severe OSA, and PAP therapy may not significantly alter their cardiovascular profile beyond routine clinical care.

Analysis of serial transthoracic echocardiography (up to 3 years) of OHS patients with severe OSA from the Pickwick project demonstrated improved pulmonary hypertension and left ventricular diastolic function with PAP therapy [238]. Systolic pulmonary artery pressure reduced significantly with both NIV and CPAP treatment arms, but no significant change in the right ventricular function in either PAP group [238]. Markers of diastolic function also improved significantly with PAP therapy, but there was no significant change in left ventricular hypertrophy (LVH) and systolic function [238]. The initial two months echocardiographic analysis of the Pickwick project only showed systolic pulmonary artery pressure reduction with the NIV arm in addition to a decrease in LV mass index (although this was no longer apparent at later intervals) [186]. The pattern of haemodynamic improvement with NIV versus CPAP appears to mirror $PaCO_2$ – a more rapid improvement in the NIV arm initially, but equivalent to CPAP in the longer-term analysis in this cohort of patients (OHS with severe OSA). The long-term comparison of meaningful clinical outcomes also supports their equivalence with no differences in mortality and cardiovascular events between the two modes of PAP therapy [85, 138, 239]. Smaller studies before the Pickwick project showed conflicting results – no improvement in echocardiographic parameters (TAPSE, PASP) and a rise in NT-proBNP after three months of NIV in a study involving 14 patients [240]; while another demonstrated in OHS patients with RV overload at diagnosis, that NIV improved PASP on echocardiogram and six-minute walk distance [241].

There is limited RHC data available to elucidate the effects of PAP therapy on cardiac function with only one small study, which also included non-OHS related hypoventilation disorders [231, 240]. An analysis of 18 patients referred for pulmonary hypertension assessment attributed to being secondary to alveolar hypotension (12/18 had OHS) showed significant improvements in cardiac indices on RHC (PASP and pulmonary vascular resistance) between baseline and after three months of NIV therapy. There were also supportive echocardiographic improvements, a substantial reduction in NT-proBNP, and functional improvements post-PAP therapy [231].

Both systolic and diastolic BP improved with PAP therapy in OHS patients with severe OSA from the Pickwick project [210]. This was sustained across a 3-year follow-up in both NIV and CPAP treatment arms[138]. BP improvement was not demonstrated in OHS patients without significant OSA after three months of NIV treatment, as well as during longer-term follow-up[139, 211]. The addition of supplemental oxygen in hypoxaemic patients despite PAP therapy was associated with BP improvements [242]. In another smaller uncontrolled prospective trial, PAP therapy significantly reduced the number of nocturnal BP surges in OHS with underlying OSA. Furthermore, patients with better compliance had a more significant improvement in nocturnal BP regulation after six weeks [243, 244].

PAP therapy has also been shown to reduce atrial electromechanical delay on echocardiogram, which was associated with a reduction in the frequency of paroxysmal atrial fibrillation episodes detected by loop recorder at six months compared to baseline [236]. PAP therapy's effect on other biomarkers has either been negative or modest, with unclear clinical significance [244-247].

Overall, although there are established benefits of weight loss and PAP therapy in reversing respiratory failure, their positive effects on the cardiovascular system appear to be more modest. Most cardiovascular-oriented research has focused on the beneficial effects of treatment on pulmonary circulation, haemodynamics, and systemic blood pressure (which may not apply to OHS without a severe OSA phenotype). Benefits in reducing cardiovascular events and mortality are inferred from adherence data rather than directly measured as a clinical outcome in clinical trials.

2.3.5.2 Weight Loss

Weight loss is an integral part of OHS management. It not only addresses the contribution of obesity to the development of respiratory failure but its impact on cardiovascular and metabolic diseases. In OHS patients, the addition of a multidisciplinary weight loss program compared to NIV alone resulted in more weight loss and improved quality of life [248]. Weight loss intervention also led to a modest improvement in blood pressure and exercise capacity. However, it is not clear if the improved exercise capacity reflects higher cardiovascular fitness beyond reducing workload from weight loss [248].

Observational studies in OHS demonstrated improved gas exchange and reduced daytime hypersomnolence with bariatric surgery [228, 249]. Weight loss surgery also led to improvements in cardiovascular parameters, in addition to the reversal of respiratory failure. There was a reduction in pulmonary artery pressure and improved left ventricular function [228]. As there were no comparator groups, it is unclear if the haemodynamic improvements of weight loss surgery translated to clinical outcomes in reducing cardiovascular events and mortality.

Finally, a recent systematic review recommended targeting a weight loss of 25-30% of actual body weight, which may resolve OHS [250]. Weight loss of this magnitude is unlikely to be achieved and maintained by lifestyle measures alone, where the average weight change achieved from a comprehensive weight loss programme has only been 6-7% [250]. While weight loss is achievable by surgery, it will need to be balanced with a higher perioperative risk due to cardiopulmonary complications [175].

Cardio-metabolic risk factor and multi-modal approach: To date, research around improving outcomes in OHS has focused on PAP therapy and weight management. There are no trials or observational data on whether targeting other modifiable cardio-metabolic risk factors (such as blood pressure, blood sugar and lipid control) will improve cardiovascular outcomes and overall survival among OHS patients.

Various guidelines on cardiovascular disease prevention advocate using risk estimation scores to assist in the decision-making around early intervention (individuals with higher baseline risk will have greater absolute cardiovascular risk reduction) [251, 252]. However, these risk estimation systems do not consider the degree of obesity as a variable, although BMI and central obesity are recognised as factors that have risk reclassification potential [252]. Given that these scoring systems are based on the general population, they are unlikely to be valid for individuals with OHS, where the impact of extremes of obesity and sleep-disordered breathing is not factored in.

Nonetheless, most OHS patients are likely to fall in the very high-risk or high-risk category based on the presence of other cardiometabolic risk factors (Table 2) or prior diagnosis of cardiovascular disease (Table 1). Hence, intensive risk modification via lifestyle and pharmacotherapy is recommended. Although previous clinical trials and observational studies have acknowledged the prevalence of cardiovascular diseases, there appears to be a lack of further efforts to specifically target these comorbid risk factors beyond the provision of lifestyle modification recommendations (without objective data on whether patients follow the given advice).

The intervention targets for OHS patients, given their cardiovascular risk, are likely to fall in the range of <130/80mmHg for blood pressure, <1.8 or 2.6mmol/L (<70 or <100mg/dL) for low-density lipoprotein (LDL) and a glycosylated haemoglobin A1c (HbA1c) of < 7.0% (53 mmol/mol) [251, 252]. Given that the corresponding mean values (BP, LDL, HbA1c) measured from OHS cohorts are around or above this value, it suggests further optimisation of these risk factors may be of value.

A multi-modality approach (guided lifestyle modification and intensive targeting of comorbid cardio-metabolic risk factors) may be what is needed to further reduce cardiovascular mortality in OHS patients. However, data are lacking, and further research is needed to explore whether this intervention style is feasible, acceptable, and yields clinically meaningful outcomes. The recent advances in obesity pharmacology (glucagon-like peptide-1 receptor agonist (GLP-1 RA), GLP-1/glucose-dependent insulinotropic polypeptide receptor agonist (GLP-1/GIP RA)) may provide another therapeutic option in OHS, as it has been shown to lead to significant weight loss, improved cardiovascular biomarkers and reduce the burden of OSA[166]. However, as no studies have been performed in the OHS population, more data is desired to ascertain its safety and efficacy for OHS patients[253].

2.3.6 Limitations

There are several limitations in this review. There are limited numbers of high-quality clinical trials examining OHS treatment. Most of the population studies are descriptive and from a single centre. Most clinical trials and observational studies have small study numbers as OHS patients are hard to recruit. Also, the definition of OHS has not been consistent across studies.

Although OHS diagnosis requires excluding other disorders that may cause alveolar hypoventilation, this may not always be the case as various studies have different methods of achieving this. Some studies allowed comorbid COPD within their study population, while the majority tried to exclude them using different spirometry cut-offs. However, even with the use of spirometry exclusion criteria, it may not entirely exclude the presence of chronic airways disease and its contribution to cardiovascular disease. Although the effects of smoking and its link to cardiovascular disease has not been discussed among the OHS population, with smoking data often not available across OHS studies, it is nonetheless a potential confounder.

OHS patients' presentation and identification are also evolving, so there is significant heterogeneity in the sampled OHS patients across different studies over time. Recently, a staging system has been proposed for classifying OHS severity, ranging from I to IV[254]. Given that the OHS definition in most of our included studies was based on the third edition of the International Classification of Sleep Disorders, OHS stages III and IV (awake $PaCO_2$>45mmHg with or without OHS-related complications) are preferentially captured. Stages I and II may have been included in the obese eucapnic comparator groups among some case-control studies. There is a selection bias towards either sick patients who require hospitalisation or are symptomatic due to their sleep-disordered breathing. These limitations may explain some of the differences in cardiovascular outcomes across studies.

When comparing cardiovascular outcomes with non-OHS patients, such as eucapnic obese OSA or simple obesity, it is difficult to control for multiple confounding factors. Most of the rates of cardiovascular comorbidities come from medical records or self-reporting, and as indicated in the PH data, there may be considerable under-diagnosis. The focus of most treatment trials has been respiratory failure rather than cardiovascular disease, which tend to be secondary or exploratory outcomes. Besides addressing obesity, modifiable cardiovascular risk factors have not been explicitly addressed as a targetable treatment among the OHS population.

Large multicentre studies with standardised definitions and data collection methods focusing on cardiovascular disease (as a therapeutic target and a measured outcome) are required to address these limitations. Longer-term data is desired, given changes in clinically meaningful cardiovascular outcomes may not be as rapid as the improvement in respiratory failure and sleep parameters. Further phenotyping OHS patients is important to identify those most at risk for worse cardiovascular outcomes.

2.3.7 Conclusion

Treatment with PAP therapy has improved OHS outcomes. Despite PAP use, OHS mortality remains higher than eucapnic OSA, with a shift of cause of death from respiratory failure to cardiovascular events. Consequently, early recognition and intervention of OHS and any cardiovascular comorbidity may be vital in improving outcomes in this population. Although the association of cardiovascular diseases with OHS is expected given the presence of shared cardio-metabolic risk factors, obesity, sleep-disordered breathing, and impaired gas exchange, the mechanisms and interaction of various contributing factors are not well elucidated. Treatment of underlying respiratory failure with PAP

therapy and/or weight loss is likely to benefit cardiovascular morbidity and mortality, although treatment effects on cardiac biomarkers have been mixed, and further research is needed in this area.

Practice Points

1. There is a high burden of cardiovascular disease among OHS patients, greater than matched eucapnic OSA or simple obesity;
2. There is uncertainty in the rates of cardiovascular comorbidities and risk factors among OHS cohorts, reflecting study heterogeneity;
3. The causative factors of higher burden of disease appear to extend beyond obesity and sleep disordered breathing, but their exact role and their interaction are not well understood
4. The impact of OHS treatment with PAP therapy and weight loss has positive impacts on various cardiovascular biomarkers, but its impact on long term clinically important cardiovascular outcomes is unknown

Research Agenda

In the future, in order to further improve OHS outcome, greater emphasis needs to be placed on managing their cardiovascular risk

1. Achieve a better understanding of contributing factors and their interaction towards cardiovascular morbidity in OHS;
2. Collaboration among OHS research centres in the determination of cardiovascular burden using standardised definitions and data collection methods;
3. Focus on addressing cardiovascular disease as a therapeutic target and a measured outcome
4. Obtaining longer-term data of clinically meaningful cardiovascular outcomes in therapeutic trials;
5. Further phenotyping OHS patients is important to identify those most at risk for the worse cardiovascular outcomes;
6. Identifying early cardiovascular biomarkers that confer increased risk among OHS patients

2.4 Obesity in Chronic Obstructive Pulmonary Disease (COPD)

2.4.1 Epidemiology and Impact on Pathophysiology of COPD

The prevalence of obesity and COPD are both increasing, hence it is not surprising that the prevalence of combined COPD and obesity is also on the rise.[255] A number of studies report that the rates of obesity is higher in patients with COPD than those without, including a large Canadian National Health Survey (24.6% vs 17.1%).[256-258] However, the rate of obesity is highest in GOLD stages 1 and 2 (less degree of spirometry severity) and lowest in GOLD stage 4.[259] In patients with COPD, the distribution of obesity severity is similar to that of the general population (Class 1 21%, Class 2 9%, Class 3 5%) (COPDGene).[259] Hence, the variability in reported rates of obesity in COPD are due to differences in degree of airflow limitation, demographic differences and study method (self-reported versus objective measurements).[259]

Although there is increasing interest in exploring the link between obesity and COPD, so far, little is known about the underlying mechanism.[260] There is evidence that COPD patients may lead a more sedentary lifestyle, which predisposes the development of obesity.[261] As obesity may contribute to increased dyspnoea and exercise intolerance, COPD patients who are obese may also seek medical attention and be diagnosed with airways disease earlier than their non-obese counterparts. COPD exacerbations also lead to repeated exposures to systemic glucocorticoids, thus increasing the risk of developing truncal obesity. Systemic inflammation is a feature of both COPD and obesity. COPD patients who have persistent inflammation at baseline are more likely to be obese.[261, 262] Obesity, in the form of visceral adiposity and metabolic syndrome also increases the risk of airway exacerbation, which in turn contributes to progressive lung function decline in COPD patients.[262] [260]

2.4.2 Effect of Obesity on COPD Mortality

Being overweight or obese has been associated with better prognosis in subjects with chronic diseases, known as the obesity paradox. This is in opposition to the typical U-shaped pattern observed in the general population when plotting mortality against BMI. The protective effect of obesity on all-cause mortality is also apparent in COPD (reverse J-shaped), more evident in patients

with more severe obstruction, whereas the mortality pattern among patients with milder airflow obstruction is similar to the general populace.[263] Weight loss is also linked with higher mortality in COPD. Weight gain is associated with better survival in those with a BMI<25kg/m^2, while the best survival is weight maintenance in COPD patients with a BMI>25kg/m^2.[263]

The mechanism for the obesity paradox is uncertain. Due to unfavourable respiratory mechanics and poor ventilatory efficiency, more energy is consumed from respiratory work in COPD, particularly during acute exacerbations. Hence, obese individuals may have more metabolic reserve to counter the cachexic effect of COPD.[263, 264] As discussed earlier, BMI is a crude measure of obesity and will not differentiate adipose tissue from muscle mass. Sarcopenia (low fat-free mass) is associated with increased all-cause mortality in COPD, and a higher BMI may reflect larger muscle mass.[263, 264] Obese individuals are also proposed to have physiological advantages that improve survival, such as less hyperinflation and preserved fitness (healthy obese). Unintentional weight loss, which is common in advanced COPD, may be a more significant mortality risk than obesity itself.[264]

Nonetheless, not all studies have demonstrated the obesity paradox. One study showed this pattern was not apparent among non-smoking COPD (which accounts for 25-45% of total COPD).[265] Potentially, smoking is a confounding factor as it is associated with weight loss and numerous diseases associated with mortality (cancer, cardiovascular disease, diabetes). Other studies also demonstrated that the obesity paradox may no longer remain relevant at extreme obesity, where the cohort of COPD patients with a BMI>40kg/m^2 was significantly associated with increased respiratory disease mortality and cardiovascular mortality.[266, 267]

2.4.3 Effect of Obesity on Respiratory Function and Exercise Capacity in COPD

Although the physiological impact of obesity and COPD are studied extensively in isolation, their pathophysiological interaction and impact on the individual are less examined. Potential complicating factors include COPD being a heterogeneous disease with various physiological phenotypes, increased presence of comorbidities, and effects of ageing. In addition, the effects of obesity on respiratory function and exercise performance depend on the distribution and the extent of excess adipose tissue.

Physiological impairments compounded by obesity in patients with COPD are due to an interaction between various abnormalities in lung/chest wall mechanics, muscle function, pulmonary gas exchange, ventilatory control and cardiovascular system.

In COPD, FRC and ERV both decrease exponentially with increasing BMI. TLC and RV generally remain stable or are only slightly decreased with obesity. Consequently, resting inspiratory capacity (IC) increases in response to increasing BMI across all COPD severity. This increase in IC may be mechanically advantageous in obese COPD patients. However, this benefit is lost in extreme obesity, as TLC also reduces while the FRC reduction plateaus.[255]

Airway resistance is further increased with obesity in COPD. Reduced lung volumes lead to further loss of traction on the small airways which are already diseased in COPD.[255] Obesity also increases tracheal collapsibility (manifest as excessive dynamic airway collapse), which may exacerbate wheeze, breathlessness and sleep-disordered breathing in COPD.[268]

Previous research suggests that obesity and obstructive airways disease have additive rather than synergistic effects on spirometric indices.[269] The potential reduction in FVC may also mask the diagnosis of COPD and impact the sensitivity of spirometry to detect airflow obstruction. This is reflected in the increased prevalence of PRISm (preserved ratio, impaired spirometry) with obesity observed in the COPDGene study.[270]

The effect of obesity on respiratory muscle strength in COPD is not well studied. One study showed no difference in muscle strength between COPD patients with normal BMI and mild-moderate obesity. However, obesity increases intraabdominal pressure and static lung recoil.[271] The effect of obesity on gas exchange is difficult to predict. Decreases in FRC, observed with obesity, may worsen V-Q mismatch in COPD.

Similar to non-COPD patients, metabolic and ventilatory requirements are increased for a given measured power output during cycle exercise in obese compared to normal weight COPD.[271] Surprisingly, there was no difference in oxygen saturation, breathing pattern, dead space ventilation and symptom rating between obese and non-obese COPD subjects. In COPD, IC can progressively reduce with exercise due to dynamic hyperinflation. Obesity in COPD appears to be mechanically advantageous as there is less rise in end-expiratory lung volume with exercise.[255] Nonetheless, obese COPD patients have greater self-reported exercise intolerance and reduced 6-minute walk distance compared to nonobese patients with COPD.[272] This exercise limitation may be due to non-

respiratory mechanical factors, such as increased metabolic loading, musculoskeletal abnormalities and cardiocirculatory impairment.[255] However, at extremes of obesity, the mixed obstructive-restrictive ventilatory deficit and abnormal gas exchange is expected to play a major role in exercise intolerance.

2.4.4 Obesity Complicating Sleep in COPD – COPD-OSA Overlap Syndrome

The detrimental effects of sleep on the respiratory system are more apparent in disease states such as COPD. During sleep, there is a blunted ventilatory response to hypercapnia and hypoxia, and a reduced respiratory drive to skeletal muscle. The positional aspect of sleep (i.e. lying supine) is also disadvantageous to pulmonary mechanics, with cranial displacement of the diaphragm by the abdomen, imposing additional load and reducing respiratory muscle capacity.[273] In COPD, the combination of diminished ventilatory drive, unfavourable lung mechanics, upper airway obstruction, worsening VQ mismatch and loss of accessory muscle assistance, particularly in REM sleep, can result in significant hypoxaemia and hypercapnia. Sleep disturbance is a common symptom in COPD in the setting of sleep disordered breathing, compounded by respiratory symptoms (nocturnal cough, wheeze), common comorbidities (cardiac dysfunction, reflux) and side effects from potential pharmacotherapy in COPD (corticosteroids, diuretics, β-adrenergic). COPD patients have reduced sleep efficiency (increased sleep latency and reduced sleep maintenance), increased light sleep and fragmented sleep (sleep stage shifts and microarousals). Consequently, there are increased reports of chronic fatigue, insomnia, sleepiness and overall, reduced quality of life. The frequency of sleep-related symptoms and gas-exchange abnormalities during sleep correlates with the severity of airflow obstruction.[274, 275 273, 276]

Compounding the various factors leading to poor sleep in COPD patients is that they may also have comorbid obstructive sleep apnoea (OSA)—the coexistence of both COPD and OSA in the same patient is termed overlap syndrome (OVS). As COPD and OSA are common conditions, they often coexist, and there is debate about whether there is a causative relationship.[273] The prevalence of OSA in COPD varies between studies, with some showing no higher prevalence than in the general population.[276] The discrepancy in prevalence is likely a reflection of the fact that COPD is a heterogenous disease, whereby the presence of different phenotypes may either be promoting (visceral obesity driven by steroid use, rostral fluid shift from right heart failure, smoking related upper airway inflammation) or protective (lung hyperinflation, cachexia, reduced REM sleep) against overlap syndrome.[273, 276] The traditional ‘blue bloater’ phenotype would be at higher risk than the ‘pink puffer’ phenotype. In addition to anatomic factors, COPD may also impact non-anatomic

factors of OSA. While one study showed that patients with COPD had lower arousal threshold and higher loop gain, which correlated with the degree of gas trapping, a separate physiologic phenotyping study did not demonstrate significant differences between OSA and OVS.[277, 278]

In the Sleep Heart Health Study, once stratified by BMI quartile, the respiratory disturbance index between participants with and without obstructive airways disease was not significantly different between groups.[279] Hence, obesity might be the main determining factor in the presence and severity of OSA in COPD patients. It is estimated that for each additional 1kg/m^2 in BMI, the risk of OSA in COPD increases 2.55-fold.[280] In addition, a few studies showed that OVS patients have a greater burden of obesity than OSA alone.[281, 282] Contributing factors include being more sedentary and the impact of steroid exposure, which leads to truncal adipose tissue deposition.

The combination of obesity, OSA, and COPD shares synergistic pathogenic effects, such as systemic inflammation, endothelial dysfunction, haemodynamic stress and accelerated atherosclerosis. OVS patients are more likely to have cardiovascular disease, arrhythmias and pulmonary hypertension/ cor pulmonale (long-term consequences of abnormal gas exchange). Consequently, OVS have higher mortality than either condition alone.[281] OVS, when compared to COPD alone, also have higher rates of hospitalisation and mortality from COPD exacerbation. [283]

OVS is associated with greater burden of symptoms and lower quality of life compared to COPD patients without OSA. Various studies have shown that OVS (versus COPD alone) is associated with worse health-related quality of life (by St George's Respiratory Questionnaire), sleep quality (Pittsburgh Sleep Questionnaire Index), increased sleepiness, while more likely to experience daytime headaches, exertional dyspnoea, fatigue, global cognitive impairment, nocturia and erectile dysfunction.[284, 285]

OVS patients, particularly those with low awake oxygen saturation, will experience more profound oxygen desaturation at night. During REM sleep, the loss of mechanical assistance from accessory muscles may lead to further sustained oxygen desaturation, reflecting periods of alveolar hypoventilation. Other polysomnographic findings in OVS include lower sleep efficiency, lower sleep time in REM and Stage 3 sleep, higher arousal index, AHI, and ODI compared to COPD-only patients.[285]

As the combination of OSA (likely with associated obesity) and COPD contribute towards worse gas exchange, a proportion of overlap syndrome (OVS) will develop chronic hypercapnia. Hypercapnic

OVS, when compared to normocapnic OVS, have increased BMI, worse respiratory function, increased sleep hypoxia and daytime sleepiness.[286] AHI, TST<90% (total sleep time with SpO_2 below 90%), vital capacity and FEV_1/FVC ratio were the strongest predictors of hypercapnia among OVS patients. Generally, in patients with COPD alone, hypercapnia is not present until FEV_1 is below 50% of predicted, whereas patients with overlap syndrome can develop hypercapnia when FEV_1 is > 60% of predicted. The proportion of patients with overlap syndrome who have hypercapnia is unknown. However, one study showed that over one-third of their OVS study population had baseline hypercapnia with a mean $PaCO_2$ of 44.59 mmHg.[286]

2.4.5 Management of Overlap Syndrome

Therapy goals in overlap syndrome (OVS) are to improve quality of life and functional capacity, reduce mortality and morbidity (particularly cardiovascular), and normalise nocturnal gas exchange (preventing nocturnal hypoxaemia and hypoventilation). Treatment of overlap syndrome is based on the individual respective treatment guidelines for COPD and OSA, as there is limited OVS-specific therapeutic data.

Inhaler therapy (long-acting beta agonists and muscarinic antagonist, LABA/LAMA) can improve nocturnal oxygenation (2-3% for each vs. placebo) in addition to its benefits in exercise tolerance, dyspnoea, health-related quality of life, lung function and exacerbation frequency. Although theophylline improves nocturnal oxygenation and reduces AHI in OSA, its clinical utility is limited by side effects (cardiac and GI). Even in COPD populations, where theophylline is shown to reduce airway inflammation while improving gas exchange and lung function, there is diminishing use due to its side effect profile.

Supplemental oxygen therapy is recommended for resting hypoxaemia in COPD (PaO_2 <55mmHg, or <60mmHg if there is pulmonary hypertension, which is more common in overlap syndrome) as it improves survival. Oxygen therapy can improve nocturnal oxygen desaturation in both COPD and OSA, but does not improve sleep quality or nighttime arousals. There is limited evidence on whether long-term nocturnal oxygen has a long-term clinical benefit in OVS. A small study showed that while it improved nocturnal oxygen desaturation, there was an increase in the frequency of obstructive episodes, with associated hypercapnia and reduction in pH. [287, 288]

Positive airway therapy, usually CPAP, is well-established and often first-line therapy in OSA. For COPD patients, long-term non-invasive ventilation (NIV) is beneficial for a subgroup with stable chronic hypercapnia (specifically $PaCO_2$ > 52mmHg) with possible reduction in mortality, reduced hospitalisation, improved quality of life, reduced dyspnoea, improvements in gas exchange and functional capacity.[289] PAP therapy is also the mainstay management option in OVS. PAP therapy in this population is associated with reduced hospitalisation, COPD exacerbations, mortality and lower healthcare costs. Within the limits of available evidence (no RCTS comparing PAP with no PAP), PAP therapy is recommended over no treatment in the majority of OVS patients and screening for OSA symptoms is recommended in COPD patients.[287]

CPAP is recommended as first-line therapy for non-hypercapnic OVS with at least moderate OSA. An in-patient titration is generally recommended as auto-titrating CPAP event detection and algorithm is not designed to respond to hypoventilation that may be observed in COPD patients, particularly in REM sleep.[127, 290] CPAP adherence is important, as it is associated with reduced COPD exacerbation, fewer COPD-related symptoms and enhanced lung function. Failure of CPAP in overlap syndrome was reported in 23% of patients in one study, with those who were more obese and with worse lung function more likely to fail therapy.[291]

It is not well established when non-invasive ventilation (NIV) is preferred over CPAP. Nonetheless, NIV is utilised in OVS patients with daytime hypercapnia or signs of nocturnal hypoventilation, as hypercapnia and nocturnal hypoxemia were independent predictors of early CPAP failure in patients with OVS.[291] An inpatient titration is recommended (as opposed to pure COPD), to guide appropriate EPAP setting and allow sufficient pressure swing to achieve an appropriate tidal volume, while balancing required pressures against patient tolerance to therapy. Ultimately, hypercapnic OVS encompasses patients with varying degrees of COPD severity (FEV_1% predicted, or FEV_1 to FVC ratio), obesity (BMI or waist-hip ratio) and OSA. Hence, whether CPAP is sufficient in a subgroup of hypercapnic OVS (similar to what is observed in OHS) is unknown.

2.4.6 Impact of Obesity on Symptom Burden, Quality of Life and Neurocognitive Function in COPD

A multicentre prospective cohort study (COPDGene) demonstrated that increasing obesity was independently associated with worse respiratory-specific (St George's Respiratory Questionnaire)

and general quality of life (Short Form-36), increased dyspnoea (Modified Medical Research Council score) and increased risk of exacerbation.[272, 292] This association was found to be in a dose-dependent fashion. Even when adjusted to account for increased comorbidity count, the link between obesity in COPD and worse quality of life (SGRQ, but not SF-36), increase dyspnoea remained. There is also a gender discrepancy with regards to the impact of obesity, with women more likely to be impacted.[292]

Although there is evidence to link poor neurocognitive outcome in both obesity and COPD individually, little is known about the combination of both disorders. Even among the COPD cohort, the pattern of neurocognitive impairment and the mechanism of injury remains poorly understood. Some of the proposed mechanisms leading to brain dysfunction is expected to be exacerbated by the presence of obesity. Intermediatory factors include worsening gas exchange (hypoxia, hypercapnia), vascular disease, sleep disorder, mental health disorder, reduced physical activity, greater frequency of exacerbation, elevated oxidative stress and systemic inflammation.[293, 294]

2.4.7 Research Deficiencies

The impact of obesity on COPD outcomes is controversial. Previous research studies thus far have shown mixed results with regards to mortality and pulmonary physiology. Recent COPDGene results have highlighted some of the detrimental effects of obesity as it increases dyspnoea, reduces functional capacity, worsens quality of life, increases exacerbation risk and negatively impacts on COPD mortality. While extreme obesity with COPD is associated with high mortality, little is known regarding symptom-based and functional outcomes, in particular neurocognitive function.

While overlap syndrome is recognised as conveying worse outcomes than either COPD or OSA alone, the optimal PAP mode is unclear. There are no randomised clinical trials in this area. In particular, hypercapnic overlap syndrome is excluded from existing clinical trials in hypercapnic obese OSA patients (obesity hypoventilation) as well as hypercapnic COPD patients.

These research deficiencies will be further explored in Chapters 3 and 5.

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Chapter 3 Symptom Burden and Neurocognitive Consequences of Obesity-associated Hypoventilation Disorders

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3.1 Abstract

Study Objectives

Symptom burden and neurocognitive function have not been previous compared between patients with obesity-associated hypoventilation disorders (obesity hypoventilation syndrome, OHS) and hypoventilation in the setting of obesity and obstructive airways disease (OHAD). The aim of this study is to compare baseline sleep-related symptoms, health-related quality of life and neurocognitive function between OHS and OHAD and the impact of PAP therapy on these outcomes.

Methods

ESS, PSQI, SF36, and various neurocognitive tests, in addition to anthropometric, polysomnography, lung function and blood gas data from participants with OHS and participants with OHAD, were included in the analysis. This data was originally collected in their respective randomised clinical trials, comparing the efficacy of different PAP modes (bilevel PAP versus CPAP) in resolving hypercapnia. Between group (OHS vs OHAD), pre- and post-treatment (with 3 months of positive airway pressure) comparisons were made using linear mixed modelling.

Results

45 OHS participants (mean age 51yo, 33% female, BMI 52kg/m^2, FER 0.81, $PaCO_2$ 54mmHg, AHI 87/hr) and 32 OHAD participants (mean age 61yo, 31% female, BMI 43kg/m^2, FER 0.60, $PaCO_2$ 54mmHg, AHI 59/hr) were included in the analysis. Both OHS and OHAD had similar baseline ESS (14(5.6) vs. 12(5.4)), Global PSQI (10(3.2) vs 11(4.8)), SF36 and neurocognitive test performances

(other than OHAD had lower digit symbol substitution test performance). Treatment with PAP therapy resulted in similar ESS, Global PSQI, and SF36 improvements in both groups. Neurocognitive performance did not significantly improve after PAP therapy in either group.

Conclusion

The symptom burden between two separate hypoventilation disorders (OHS and OHAD), in terms of sleepiness, sleep quality, quality of life and cognitive function, were similar. OHS and OHAD had similar treatment responses in these parameters after 3 months of PAP therapy.

Keywords: chronic obstructive pulmonary disease, obstructive sleep apnoea, overlap syndrome, obesity, hypercapnic respiratory failure, positive airway pressure therapy, sleepiness, quality of life, neurocognitive function

STATEMENT OF SIGNIFICANCE

Hypoventilation syndromes in the setting of obesity, with and without airways disease, are associated with poor sleep quality, increased sleepiness, neurocognitive dysfunction and lower quality of life. This study compares these patient-centred outcomes between these groups (obesity hypoventilation syndrome and hypoventilation in the setting of obesity and obstructive airways disease) before and after positive airway pressure therapy, which has not been previously performed.

3.2 Introduction

Hypoventilation during sleep occurs in several disorders associated with obesity, lung disease or both. Obesity hypoventilation syndrome (OHS) is diagnosed based on obesity and sleep-disordered breathing in the presence of awake alveolar hypoventilation not attributable to other causes[2]. Patients with lung disease are excluded from this diagnosis. Consequently, patients with a combination of obesity/obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD), resulting in chronic hypoventilation, are generally excluded from clinical studies examining either COPD or OHS. Those with OSA and COPD will be classified as overlap syndrome, although neither obesity nor hypercapnia is necessary for this latter diagnosis.

Previous studies have documented poor sleep quality, increased sleepiness, and lower quality of life among patients with OHS[3-5]. These parameters have been compared to eucapnic controls, obese individuals and OSAS[3]. The characteristics of patients with hypoventilation in the setting of obesity and obstructive airways disease (OHAD) are less well known but have been described as also having low quality of life scores, reduced sleep quality and more daytime sleepiness[6]. These two hypoventilation cohorts (OHS and OHAD) have not been directly compared in previous research.

Adequate sleep quality is important for aspects of both memory and non-memory cognitive function[7], with poor sleep a risk factor for cognitive decline[8]. Obesity-related hypoventilation disorders represent the extreme of sleep-disordered breathing and are expected to have a high burden of sleep fragmentation and hypoxemia – two factors proposed to be predictors of cognitive dysfunction in OSA[9]. Likewise, cognitive deficits are also seen in COPD[10], a comorbid condition in OHAD. The degree of cognitive impairment appears to correlate with the severity of COPD, reflected by an increase in dynamic lung volumes, degree of hypoxia and the presence of hypercapnia[11].

Treatment of sleep-disordered breathing, often OSA, is associated with improved neurocognitive performance in several domains[9, 12]. PAP therapy is expected to improve gas exchange and reduce

sleep fragmentation [13] in hypoventilation disorders. However, the resolution of hypercapnia appears more mode-dependent (CPAP vs Bilevel PAP) in OHAD than in OHS [5, 6, 14, 15]. Sleepiness and sleep quality also improve with PAP therapy[6, 13], but it is not clear if one cohort is more responsive to PAP treatment or a particular mode of PAP with respect to symptoms or neurocognitive function.

The aim of this study was to compare baseline symptom burden and neurocognitive function between participants with OHS and those with OHAD, and determine the impact of PAP therapy on these outcomes.

3.3 Methods

Data Source and Study Design

This retrospective cross-sectional study aimed at exploring and comparing symptom burden and neurocognitive function between two different groups of patients with obesity-related hypoventilation disorders. We obtained data from two separate clinical trials, one involving participants who met the diagnostic criteria for obesity hypoventilation syndrome (OHS, recruited from 2003-2006)[5] and the second involving participants with awake hypoventilation in the setting of obesity and obstructive airways disease (OHAD, recruited from 2003 to 2012)[6].

Both studies enrolled patients with obesity (BMI>30kg/m^2) and stable daytime hypercapnia ($PaCO_2$ >45mmHg) at presentation to the Sleep Disorders Centre, Royal Prince Alfred Hospital. Patients without significant respiratory or neuromuscular disorders were diagnosed as obesity hypoventilation syndrome (OHS). Patients in whom an obstructive ventilatory defect on spirometry was found (ratio of forced expiratory volume in 1s/forced vital capacity or FER <0.7) or clinician

diagnosed COPD were included in the OHAD group. Other inclusion criteria included (1) no neuromuscular or chest wall skeletal disorders; (2) not currently being treated with positive airway pressure therapy; (3) no major psychiatric illness or unstable medical conditions that would affect the participant's ability to participate in the trial. Participants did not need to have symptoms of sleep disordered breathing to be included in this trial.[5, 6]

The original randomised clinical trials compared the efficacy of different PAP modes (1:1 randomised to either bilevel positive airway pressure therapy, BPAP, or continuous positive airway pressure therapy, CPAP) in reducing hypercapnia as the primary endpoints. The clinical trials also included sleep and neurocognitive data pre- and post-PAP intervention. Additional analysis was performed looking at the effects of PAP therapy. Three out of 32 OHAD participants and two out of 45 OHS participants dropped out at 3 months post-PAP therapy follow-up. See attached supplemental information regarding PAP-related protocol.

The Human Research Ethics Committees at The Royal Prince Alfred Hospital approved this cross-sectional study. The original clinical studies were registered at anzctr.org as part of ACTRN12605000096651.

Study Assessments

Participants were evaluated on two occasions: at baseline (prior to PAP treatment) and at three months (following the initiation of PAP treatment). Polysomnography data, arterial blood gases, anthropometric data, spirometry indices, Epworth Sleepiness Scale (ESS)[16], sleep quality using the Pittsburgh Sleepiness Quality Index (PSQI)[17] and health-related quality of life using the Medical Outcomes Survey Short Form 36 (SF 36)[18] were collected at both occasions. Adherence to therapy was recorded at follow-up. Neurocognitive evaluations included: psychomotor vigilance test (sustained attention, reaction time), digit span task (working memory), trail-making test (executive functioning) and digit symbol substitution test (cognitive dysfunction). Procedural details are included in the supplementary material.

Statistical Analysis

Baseline characteristics were expressed as mean and SD or percentages with 95% CIs and compared using Student's t-test and chi-squared analysis, respectively. Analysis of sleepiness, sleep quality, quality of life measures and neurocognitive outcomes was done using a linear mixed model for repeated measures. The model included fixed effects for disease group (OHS or OHAD), treatment arm (BPAP or CPAP), time (baseline and 3 months) and their interaction, age, and a participant-level random intercept. There was no imputation for missing data. The differences were reported as a mean with 95% confidence interval and p-value, with the significance test based on a two-sided α of 0.05. Multiple linear regression was used to assess whether arousal index and $PaCO_2$ were associated with sleepiness and sleep quality. Data management was performed using SPSS software (IBM SPSS Statistics).

3.4 Results

Participant Baseline Characteristics

A total of 32 participants with obesity-related hypoventilation with airways disease (OHAD) and 45 participants with obesity hypoventilation syndrome (OHS) were included in the analysis.

Table 3.1. summarises the baseline demographic data, lung function, blood gas measurements and sleep study parameters. The OHS group was younger than the OHAD group, had a greater degree of obesity and were less likely to be a current or ex-smoker. The OHAD group had lower FEV_1 and FER but similar FVC on spirometry. Arterial blood gas measurements were similar between groups. The OHS group had a higher AHI, but the hypoxic burden (total sleep time oxygen saturation spent less than 80% and 90%) was similar (both groups had 7 patients each, requiring supplemental oxygen

during their initial diagnostic study). No other statistically significant differences were noted in the other sleep study parameters.

Comparison of Sleepiness and Sleep Quality

No difference in baseline (pre-PAP therapy) sleepiness (ESS) or sleep quality (Global PSQI) was seen between the two disorders (Table 2). Both OHS and OHAD groups had improved sleep quality and reduced sleepiness after 3 months of PAP therapy compared to their respective baselines (Table 3). There were no intergroup differences to suggest either group responded better to PAP therapy (Table 3). The mode of PAP therapy allocated (CPAP or Bilevel PAP) did not appear to influence an outcome difference in either disorder (supplemental data).

Comparison of Quality of Life

There were no statistically significant differences in combined mental component or physical component of quality-of-life measures (based on SF36 questionnaire) at baseline between the two groups, shown in Table 2. There were statistically significant improvements in both physical and mental components in the OHS group while only the mental component significantly improved in the OHAD group post 3 months of allocated PAP therapy (Table 3). However, the intergroup differences were not statistically significant, indicating that the underlying hypoventilation disease did not influence responsiveness to PAP therapy (Table 3).

Comparison of Neurocognitive Testing Outcomes

The OHAD group had lower baseline digit symbol substitution performance compared to the OHS group. There were no other significant between-group differences in neurocognitive tests at baseline (Table 4). Post-PAP therapy, only one of three measures of the Psychomotor Vigilance Test improved within group, seen in the OHAD arm. As shown in Table 5, there were no intergroup differences in neurocognitive testing outcomes between disorders post-PAP therapy.

Correlation of Sleepiness and Sleep Quality to Arousal Index and $PaCO_2$

Multiple linear regression was used to test if arousal index and $PaCO_2$ significantly predicted change in ESS and Global PSQI. The overall regression was statistically significant for independent parameters: ESS in OHAD (R^2 0.317) and OHS (R^2 0.346); and for Global PSQI in OHAD (R^2 0.391) and OHS (R^2 0.271). Table 6 displays the change in arousal index and $PaCO_2$ post-PAP therapy.

Table 3.1. Baseline characteristics

	OHS (N=45)	OHAD (N=32)	P value
Age (years)	51 (14)	61 (11)	0.002
Gender (% female)	33	31	0.85
BMI (kg/m^2)	52 (8.5)	43 (7.2)	<0.001
Neck circumference (cm)	50 (4.7)	48 (4.5)	0.17
Waist circumference (cm)	145 (14)	133 (10)	<0.001
Hip circumference (cm)	149 (18)	134 (15)	0.001
Smoking status (% smoker) ^	51	97	<0.001
Spirometry			
FEV1 (L)	1.9 (0.77)	1.4 (0.58)	N/A
FEV_1 (% predicted)	60 (19)	48 (19)	N/A
FVC (L)	2.4 (0.97)	2.3 (0.84)	0.19
FVC (% predicted)	62 (18)	64 (22)	0.57
FER (%)	81 (5.9)	60 (9.7)	N/A
ABG			
$PaCO_2$ (mmHg)	54 (8.2)	54 (7.4)	0.86
PaO_2 (mmHg)	64 (15)	59 (10)	0.09
Bicarbonate (mmol)	32 (6.4)	32 (4.6)	0.75
Base Excess (mmol)	6 (3.9)	6 (4.0)	0.88
pH	7.39 (0.03)	7.39 (0.03)	0.46
PSG			
AHI (events/hour)	87 (34)	59 (35)	<0.001
Arousal (events/hour)	63 (38)	51 (32)	0.22
%TST <90%	76 (29)	78 (25)	0.77
%TST <80%	39 (30)	26 (22)	0.08
%NREM Sleep	89 (7.7)	89 (8.8)	0.68
%SWS	14 (18)	14 (15)	0.99
%REM Sleep	11 (7.7)	11 (8.8)	0.66

Displayed as mean (standard deviation), except for %TST <90% and %TST <80%, which are displayed as median (interquartile range).

^Smokers included ex-smokers (OHAD=17, OHS=13) and current smokers (OHAD = 14, OHS=10)

N/A – not applicable

Table 3.2 Baseline Measurements and Changes with Treatment Related to Quality of Life, Quality of Sleep and Sleepiness Scores

	OHS [Mean (SD)] Baseline	OHAD [Mean (SD)] Baseline	Baseline Intergroup Differences~	
			Mean (CI)	P Value
ESS	14 (5.6)	12 (5.4)	-1.1 (-4.0, 1.1)	0.27
Global PSQI	10 (3.2)	11 (4.8)	0.66 (-1.3, 2.6)	0.50
SF36				
Physical Component	29 (9)	32 (11)	2.6 (-2.3, 7.5)	0.30
Mental Component	33 (18)	27 (17)	-5.7 (-14, 2.9)	0.19

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburg Sleep Quality Index; SF36 = Medical Outcome Survey Short Form 36

~Adjusted for baseline values of the variables analysed and age

Table 3.3 Comparison of Impact of PAP therapy on Quality of Life, Quality of Sleep and Sleepiness Scores in OHS and OHAD

	OHS [Mean (SD)]		OHAD [Mean (SD)]		Intergroup Differences~	
	Baseline	Post-PAP (3m)	Baseline	Post-PAP (3m)	Mean (CI)	P Value
ESS	14 (5.6)	6.3 (5.2)**	12 (5.4)	6.4 (5.4)**	1.5 (-2.1, 5.1)	0.42
Global PSQI	10 (3.2)	6.3 (4.2)**	11 (4.8)	7.2 (3.4)**	0.19 (-2.6, 3.0)	0.90
SF36						
Physical Component	29 (9)	35 (13)*	32 (11)	34 (11)	-4.2 (-12, 3.6)	0.28
Mental Component	33 (18)	41 (19)*	27 (17)	41 (16)**	4.4 (-7.9, 16)	0.48

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburg Sleep Quality Index; SF36 = Medical Outcome Survey Short Form 36

~Adjusted for baseline values of the variables analysed and age

* $p<0.05$ intragroup difference (Post-PAP (3m) – baseline)

** $p<0.01$ intragroup difference (Post-PAP (3m) – baseline)

BPAP adherence in OHS: 6.1 ($\pm$2.1) hours

CPAP adherence in OHS: 5.8 ($\pm$2.4) hours

BPAP adherence in OHAD: 4.1 ($\pm$2.5) hours

CPAP adherence in OHAD: 5.6 ($\pm$2.3) hours

Table 3.4 Baseline Neurocognitive Outcomes in OHS and OHAD

	OHS [Mean (SD)] Baseline	OHAD [Mean (SD)] Baseline	Baseline Intergroup Differences~ Mean (CI)	P Value
PVT				
Lapses	9.2 (12)	8.9 (11)	-0.3 (-6.0, 5.4)	0.92
Median: RT (ms)	338 (96)	338 (82)	0.2 (-44, 44)	0.99
Mean Slowest 10% 1/RT (s)	1.9 (0.89)	1.9 (0.63)	0.002 (-0.38, 0.39)	0.99
Digit Span Forward	7.3 (2.8)	7.2 (2.0)	-0.03 (-1.3, 1.2)	0.96
Digit Span Backward	5.2 (2.5)	5.2 (2.0)	-0.03 (-1.2, 1.1)	0.96
Trail Making Test	116 (54)	132 (51)	15 (-14, 44)	0.30
Digit Symbol Substitution	43 (13)	36 (11)	-7.7 (-14, -1.4)	0.02

Abbreviations: PVT = psychomotor vigilance test; RT = reaction time

~Adjusted for baseline values of the variables analysed and age

* p<0.05 intragroup difference (3m – baseline)

Table 3.5 Impact of PAP therapy on Outcomes of Neurocognitive Tests in OHS and OHAD

	OHS [Mean (SD)]		OHAD [Mean (SD)]		Baseline Intergroup Differences~	
	Baseline	Post-PAP (3m)	Mean (CI)	Post-PAP (3m)	Mean (CI)	P Value
PVT						
Lapses	9.2 (12)	5.5 (12)	8.9 (11)	6.0 (11)	0.8 (-7.5, 9.1)	0.85
Median: RT (ms)	338 (96)	310 (89)	338 (82)	306 (67)	-4.6 (-64, 56)	0.88
Mean Slowest 10% RT (s)	1.9 (0.89)	2.2 (0.74)	1.9 (0.63)	2.2 (0.59)*	-0.02 (-0.54, 0.50)	0.95
Digit Span Forward	7.3 (2.8)	7.6 (2.9)	7.2 (2.0)	8.2 (2.0)	0.65 (-1.25, 2.5)	0.49
Digit Span Backward	5.2 (2.5)	5.7 (2.5)	5.2 (2.0)	5.4 (1.9)	-0.24 (-1.9, 1.4)	0.77
Trail Making Test	116 (54)	96 (36)	132 (51)	116 (43)	4.2 (-32, 40)	0.82
Digit Symbol Substitution	43 (13)	47 (11)	36 (11)	40 (13)	0.6 (-8.3, 9.5)	0.89

Abbreviations: PVT = psychomotor vigilance test; RT = reaction time

~Adjusted for baseline values of the variables analysed and age

* p<0.05 intragroup difference (Post-PAP (3m) – baseline)

BPAP adherence in OHS: 6.1 (±2.1) hours

CPAP adherence in OHS: 5.8 (±2.4) hours

BPAP adherence in OHAD: 4.1 (±2.5) hours

CPAP adherence in OHAD: 5.6 (±2.3) hours

3.5 Discussion

This is the first study to compare two different obesity-related hypoventilation disorders with respect to their impact on sleep quality, sleepiness, quality of life and neurocognitive function. Although there were expected differences in participant characteristics such as their degree of obesity, lung function abnormality and severity of comorbid obstructive sleep apnoea, the symptom burden and neurocognitive performance appears similar between OHS and OHAD participants.

Both studies recruited participants with similar severity of hypercapnic respiratory failure at baseline. The contribution of lower lung function in the development of daytime respiratory failure in the OHAD group appears to be balanced by the greater degree of obesity and burden of sleep apnoea seen in the OHS group. Although the exact mechanism of the development of hypercapnia is poorly understood in both disorders, some of the proposed factors include changes in respiratory mechanics, diaphragmatic dysfunction, sleep apnoea syndrome and altered respiratory drive[19] – all likely to feature to varying degrees between the two groups, but also between individuals within the same disorder.

Our study demonstrated that although the OHAD participants had a lower average awake arterial partial pressure of oxygen, the nocturnal hypoxic burden tended to be greater in the OHS group, reflected in the proportion of total sleep time with an oxygen saturation lower than 80%. This is

surprising as the combination of parenchymal disease and V/Q mismatch in COPD was expected to compound the effects of sleep disordered breathing seen in overlap syndrome[20]. However, awake oxygen saturation is not the only factor affecting nocturnal hypoxemia, and previous studies have shown BMI[21], expiratory reserve volume [22, 23] and ventilatory sensitivity to hypercapnia[24] are also important determinants of nocturnal oxygen desaturation. VQ mismatch is also apparent in OHS populations due to higher closing volume to functional residual capacity (FRC) ratio[25], which is further exacerbated in the supine position[26]. In addition, morbid obesity is associated with reduced FRC and thereby lung oxygen reserve. Greater obesity also increases whole-body oxygen demand[27].

In our study, despite the differences in AHI between and OHAD groups, the proportion of slow wave sleep and REM sleep were similar. Participants in both our obesity-related hypoventilation groups also reported similar levels of daytime sleepiness, sleep quality and quality of life. Both groups were more sleepy and experienced lower health-related quality of life than previous reports of these measures in non-hypercapnic OSA participants and healthy controls[28, 29].

CPAP therapy reduces daytime sleepiness and improves quality of life in patients with OSA [30, 31], but this is influenced by disease severity[32]. In the current study, both hypoventilation groups showed an equally impressive reduction in ESS and PSQI. Only the mental component of SF36 improved in the OHAD group with therapy, whereas both mental and physical components improved in the OHS group. It is possible that the improvement in hypercapnia and sleep-related symptoms is sufficient to improve the physical function of participants with OHS, but among participants with OHAD, they are still limited by their airways disease.

In our OHS and OHAD participants, daytime sleepiness and self-reported sleep quality correlated with improvements in hypercapnia and sleep fragmentation (arousal index). Carbon dioxide narcosis is a known complication of hypercapnic respiratory failure[33] and has an anaesthetic effect in animal models [34]. Slowing of electroencephalographic activity on spectral analysis is a proposed link between hypercapnia and daytime sleepiness[35]. Arousal index appears to be a predictor of excessive daytime sleepiness in patients with OSA in several studies[36-38], but this has not been a consistent

finding[39]. The underlying mechanism and sleep study characteristics that influences sleepiness and sleep quality is yet to be fully defined. Similarly, hypercapnia and arousal index only appeared to make a small overall contribution in our study. Although not explored, some of the other potential factors among our studied population include comorbid medical disease, physical inactivity, psychological factors, and mental health illness. Obesity and the associated proinflammatory state have also been proposed as causes of excessive daytime sleepiness[37].

Interest in the neurocognitive impact of sleep disordered breathing has been increasing, however only a few studies have investigated neurocognitive function in OHS and OHAD. Both conditions share similar features of hypoxia, hypercapnia and sleep fragmentation [11]. In addition, both conditions are also associated with higher rates of vascular disease. Despite this, baseline results from our cohorts did not differ significantly from previous reports of neuropsychological function in ?eucapnic OSAS and COPD samples [40, 41].

At baseline, both groups did not differ significantly in neurocognitive performance, except for digit symbol substitution test (DSST) where the OHS group averaged a better performance. This test assesses the integration of multiple cognitive domains, including motor speed, attention and visuo-perceptual functions[42]. Age has a major influence on DSST performance, accounting for 86% of the variance[43]. Even after adjustment for age as a covariate, OHAD participants performed worse than OHS participants in DSST at baseline.

PAP therapy over three months did not appear to significantly improve neurocognitive test performances, a finding similar to a previous study of OHS participants undergoing PAP therapy over the same treatment period [44]. Several factors likely explain this lack of improvement. Firstly, and rather surprisingly, the baseline digit span tests (forward assessing verbal working memory and attention, while backward also tests cognitive control and executive function[45]) were not different to previously reported results from population studies [45, 46], so significant improvements may not have been possible. It is also unclear whether further improvements could occur beyond that of the three-month therapy period. Overall, there was a trend towards improvement in all the

neurocognitive tests in both study groups compared to their baseline values, suggesting that correction of the respiratory failure and sleep disordered breathing improves neurocognitive function, irrespective of the underlying disorder. In OSA, CPAP therapy is associated with improvements in sustained attention, recall and some of the components of executive function[47]. Although statistically significant improvements were not demonstrated across a 3-month treatment period, we postulate long term PAP therapy is likely to be neuroprotective and may improve neurocognitive performance in several domains among the obese hypercapnic cohort. However, it is also possible that neurocognitive function may not revert to normal despite resolution or improvement of hypercapnia/sleep-disordered breathing due to permanence of injury or other contributing factors.

There are several limitations to this study. The study data comes from a single centre in stable participants with chronic respiratory failure presenting to a sleep laboratory. The data analysis was performed retrospectively and the data of interest were not the original outcomes of the trials. There may have been a selection bias towards enrolling patients with more symptoms or alternatively less severe respiratory failure. Both original studies had a small number of recruited participants and therefore likely lacked sufficient power to detect meaningful differences, as seen in the neurocognitive data. The OHAD group also took longer to recruit and 2 of its participants were lost to follow up due to death unrelated to respiratory failure.

Questionnaires were used to assess sleepiness and sleep quality rather than objective measures of sleepiness such as Maintenance of Wakefulness Test, driving simulation or daytime EEG quantification. Other potential factors, outside of participant age, were not adjusted for with respect to neurocognitive performance – such as education status, socio-economic status, underlying neurodegenerative/neurovascular disease, obesity and psychiatric illness.

Both bilevel PAP and CPAP were used in the post-PAP comparisons. At least in the OHAD population, there may be differences in treatment efficacy in the two PAP modalities [6]. Nonetheless, we did further compare the data of interest between bilevel PAP and CPAP without finding any significant

influence related to the mode of PAP therapy in either disorder. During the time the original trials were conducted, the PAP models used were also older to what is currently available.

Larger population data with longer periods of data collection are required to confirm and address some of the issues raised in this study. Future research should involve the collection of data from multicentre sleep registries and aim to further phenotype these patient groups based on sleep study measurements, patient characteristics, comorbidities, and other biomarkers. The impact of PAP therapy needs to be assessed in relation to participants' baseline symptomatology, as well as followed for a longer period. The various features of newer PAP devices, including different modes and pressure settings, should also be explored.

3.6 Conclusion

In this single centre cross-sectional study, symptom severity between two separate hypoventilation disorders (OHS and OHAD), in terms of sleepiness, sleep quality, quality of life and cognitive function were similar, despite differences in baseline lung function, anthropometric and PSG characteristics. Both OHS and OHAD were similarly responsive to 3 months of PAP therapy, resulting in reduced symptoms. Greater attention and research into neurocognitive function and quality of life in patients with obesity-related hypoventilation is needed.

Compliance with Ethical standards:

The Human Research Ethics Committees at The Royal Prince Alfred Hospital approved this cross-sectional study. All procedures performed in this study involving human participants were in accordance with the ethical standard of the Human Research Ethics Committees at The Royal Prince Alfred Hospital and with the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest:

Yizhong Zheng, Brendon J Yee, Keith Wong certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Trial Registration: ACTRN12605000096651

http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12605000096651

Nocturnal ventilatory support in obesity hypoventilation syndrome.

Number of Tables: 5

Number of Figures: 0

Supplementary Material

3.7 References

1. Zheng Y, Yee BJ, Wong K, Grunstein RR, Piper AJ. A comparison of two obesity-related hypoventilation disorders: Impact on sleep, quality of life and neurocognitive outcomes and the effects of positive airway pressure therapy. *Sleep Advances*. 2024;5(1):zpae016.
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Chapter 4 Cardiovascular Consequences of Obesity Hypoventilation Syndrome

Results and discussion from this chapter have been accepted for publication (Respirology).

Zheng, Y., Piper, A., Wong, K., Gauthier, G., Phillips, C.L., Grunstein, R. and Yee, B.J., 2025. A pilot randomised non-inferiority trial of auto-titrating versus fixed continuous positive airway pressure for obesity hypoventilation syndrome with severe obstructive sleep apnoea. (pending publication)

4.1 Abstract

Study Objectives

Cardiovascular disease is the leading cause of death in people diagnosed with OHS. While it might be expected that people with OHS would have a higher rate of cardiovascular risk factors, there is an under-recognition and diagnosis of cardiovascular diseases in this population. While treatment of OHS with PAP therapy improves respiratory failure, its impact on cardiovascular outcomes is less clear. The aims of this study are to assess measures of arterial stiffness and serum cardiovascular biomarkers at baseline and after short-term PAP therapy.

Methods

Pulse wave analysis (augmentation index, central pressures), pulse wave velocity, troponin, NT-proBNP, among other serum biomarkers were measured at baseline and after 3 months of PAP therapy. This is a sub-study from a randomised clinical trial, comparing the efficacy of different PAP modes (auto-titrating CPAP versus fixed-pressure CPAP) in resolving hypercapnia.

Results

28 OHS participants (Mean±SD: Age 55±12.5 years, BMI 54±9.9kg/m^2, $PaCO_2$ 49±2.6mmHg, AHI 88±31 events/hour) were included in the analysis. The prevalence of known hypertension, diabetes mellitus, dyslipidaemia and history of smoking was 46%, 32%, 21% and 54% respectively. The

augmentation index was 14.5 (SD 13.9)% and the pulse wave velocity was 7.25 (SD 0.92)m/s; both measures of arterial stiffness were within the normal population range. The OHS participant had high central pressures based on their pulse wave analysis. Serum cardiovascular biomarkers were elevated, and there were higher rates of cardiovascular risk factors than indicated based on medical records. There was no significant change in cardiovascular biomarkers following short-term PAP therapy.

Conclusion

Arterial stiffness does not appear elevated in our OHS participants and did not significantly change post-PAP therapy. However, serum biomarkers and central pressure measurements indicate an unfavourable cardiovascular profile, with under-diagnosis and under-treatment of cardiovascular risk factors.

4.2 Introduction

Cardiovascular disease has surpassed respiratory failure as the leading cause of death in PAP-treated OHS patients[1-3]. Although OHS is associated with high rates of cardiovascular risk factors, it is less clear whether OHS is also associated with higher rates of atherosclerosis (reflected in a diagnosis of ischaemic heart disease and cerebrovascular disease) above that of simple eucapnic OSA[4] (shown and discussed in Chapter 2.3). This lack of clinical clarity may be due to under- or misdiagnosis, similar to what has been observed concerning structural heart disease and pulmonary hypertension in this population[5].

The measurement of arterial stiffness using a non-invasive method of determining pulse wave velocity and aortic pressure augmentation may offer further insights into detecting subclinical atherosclerosis[6] in people with OHS. In particular, pulse wave velocity is a strong independent risk factor for cardiovascular disease and mortality[7-9]. Carotid femoral pulse wave velocity (cfPWV) is considered the gold standard for the assessment of arterial stiffness. There is also mounting evidence indicating that central blood pressure, more so than peripheral blood pressure, is associated with target organ damage and cardiovascular risk[10]. Cardiovascular blood biomarkers might be underutilised in the OHS population in terms of risk profiling (e.g. AST/ALT ratio[11, 12], HbA1c[13], lipid profile[14]) and detecting myocardial injury/strain (NT-proBNP[15] and troponin[16]).

As highlighted in Chapter 2.3, the data on cardiovascular outcomes with positive airway pressure (PAP) therapy has been mixed, with the more recent larger Pickwick trial indicating improvements in echocardiographic measurements post therapy in OHS with severe OSA, while there appears to be no improvement in cardiovascular events and mortality in OHS patients without significant OSA. Most pre- and post-interventional studies examined outcomes in peripheral blood pressure and haemodynamic outcomes, with less focus on the effects of therapy on blood biomarkers. The outcomes on arterial stiffness and central blood pressure measurements with PAP therapy have not been performed in the OHS population.

This study aims to assess arterial stiffness using various non-invasive methods, central pulse pressure, and cardiovascular blood biomarkers in OHS participants at baseline and after 3 months of CPAP therapy.

4.3 Methods

Study Participants

Participants with obesity hypoventilation syndrome, stable daytime mild-moderate hypercapnia ($PaCO_2$ 45-60mmHg and normal pH), concurrent severe obstructive sleep apnoea (AHI$\geq$ 30/h), who are naïve of long-term positive airway pressure therapy, presenting to Sleep-Disorder Centre, Royal Prince Alfred were screened for trial recruitment (July 2018 – December 2023). The study population was equivalent to the participants who were recruited for the auto-titrating vs fixed CPAP clinical trial and also consented to be enrolled in this sub-trial (Chapter 6). Exclusion criteria included the presence of any other condition that was more likely contributing to daytime hypoventilation, including neuromuscular disease, chest wall abnormalities, respiratory depressant medications, COPD or an FEV1/FVC ratio of less than 0.7. Participants who had uncontrolled medical or psychiatric conditions including those with decompensated right heart failure and reduced ejection heart failure were also excluded from the study. Participants had to be proficient in English and able to sign an informed consent.

Study Design and Intervention

This was a prospective interventional (pre-post) study conducted at Royal Prince Alfred Hospital, Camperdown, Sydney Australia. Data was collected at baseline and at 3 months post PAP therapy (either APAP or fixed CPAP, see Chapter 6 Methods for further details). Data collected at baseline included cardiovascular history and risk factors. Data collected pre and post PAP therapy included blood pathology (troponin T, NT-proBNP, fasting glucose, HbA1c, fasting lipid profile, CRP, AST, ALT, Creatinine), pulse wave analysis and pulse wave velocity.

Pulse Wave Analysis (PWA) and Pulse Wave Velocity (PWV) Collection:

Both PWA and PWV measurements were performed using the SphygomCor XCEL (Atcor Medical; Sydney, NSW, Australia), conducted in a temperature-controlled room in the afternoon (between 2-5 pm)[17].

PWA: Peripheral blood pressure was measured using an appropriately sized cuff around the upper arm, centred around the brachial artery. The central aortic pressure waveform is derived from cuff

pulsations recorded at the brachial artery using the PWA software. The PWA software determined the augmentation index (AIx and AIx@75). The augmentation index (AIx) is the ratio of the augmentation pressure to pulse pressure, expressed as a percentage. The AIx@75 is the heart-rate-corrected augmentation index to a standard heart rate of 75 beats per minute (to allow for consistent comparison between individuals with different heart rates). At least three valid measurements were performed and recorded in the sitting position.

PWV: An appropriately-sized femoral cuff was placed around the participant's right thigh, as high as possible. The carotid pulse on the same side was manually palpated. The PWV distance was determined using the direct method with a tape measure between the carotid artery and the top of the femoral cuff. The pulse transit time and calculated PWV were determined using the PWV software. Three valid measurements were performed and recorded with the participant in the supine position.

Statistical Analysis

Baseline characteristics were expressed as mean and SD or percentages with 95% CIs. Comparisons of cardiovascular biomarkers between OHS participants with and without cardiovascular risk factors or diagnosis were performed using an unpaired t-test. Comparisons between pre-PAP (baseline) and post-PAP cardiovascular measures were performed using a paired t-test. The significance test was based on a two-sided α of 0.05. Data analyses were performed using SPSS software (IBM SPSS Statistics).

4.4 Results

Participant Baseline Characteristics

Between July 2018 and December 2023, a total of 84 patients were assessed for eligibility criteria. At study termination, a total of 28 patients with obesity hypoventilation syndrome (OHS) and concurrent severe OSA (sOSA) were included in the trial. Twenty-one out of 28 patients completed the post-PAP therapy assessments. The prevalence of known hypertension, diabetes mellitus, dyslipidaemia and history of smoking were 46%, 32%, 21% and 54% respectively (see Table 4.1). The documented rates of ischaemic heart disease/coronary artery disease, atrial fibrillation, and structural heart disease were 14%, 18% and 18% respectively.

Baseline Arterial Stiffness and Central Pressures (PWA and PWV)

The markers of arterial stiffness, including augmentation index (AIx/AIx@75 from PWA) and PWV, central and peripheral blood pressures, are displayed in Table 4.2. The mean AIx was 31.5 (SD 13.9)% and the mean AIx@75 was 33.1 (SD 13.6)%. The PWV mean was 7.25 (SD 0.92)m/s. The mean (SD) systolic blood pressure, diastolic blood pressure and pulse pressure at baseline (pre-PAP therapy) were 136.9 (SD 12.4)mmHg, 78.7 (SD 12.3)mmHg and 58.2 (9.4)mmHg, respectively. Mean baseline (SD) central systolic blood pressure, diastolic blood pressure and pulse pressure were 124.4 (SD 10.7)mmHg, 81.3 (SD 12.0)mmHg and 43.0 (8.6)mmHg, respectively. Two separate columns display the mean and standard deviations of participants, grouped by whether they have a known diagnosis of hypertension or cardiovascular disease at baseline. Except for AIx being significantly higher in the known hypertension/cardiovascular disease group ($p = 0.04$), no other parameters were statistically significant between the two groups.

Baseline Cardiovascular Blood Biomarkers

The glucose and lipid profiles, as well as other cardiovascular biomarkers (hs-Troponin, NT-proBNP, AST/ALT ratio, and CRP), are displayed in Table 4.3. Two separate columns displayed the mean and standard deviations of participants, grouped by whether they had a relevant diagnosis (diabetes, dyslipidaemia, or cardiovascular disease) known at baseline. 100% and 67% of OHS participants without a known diagnosis of hypertension had high peripheral systolic and diastolic blood pressure, respectively. All OHS participants with known comorbid hypertension had their peripheral blood pressure measurements above the recommended target. 33% (based on fasting glucose) and 22% (based on HbA1c) of OHS participants without a known diagnosis of diabetes were diabetic, and another 44% were prediabetic. 20% (based on HbA1c) and 33% (based on fasting glucose) of OHS participants with known diabetes had suboptimal glucose control. 44% of OHS participants without known dyslipidaemia had high fasting LDL cholesterol. 60%, 43%, 64% and 93% of OHS participants had unfavourable cardiovascular biomarkers, based on elevated troponin, NT-proBNP, AST to ALT ratio and CRP, respectively.

Effects of PAP Therapy

The effects of PAP therapy (13 fixed-pressure CPAP and 15 auto-titrating PAP) on PWA and PWV are displayed in Table 4.4. There were no significant changes in any of the measured cardiovascular endpoints of interest post-PAP therapy. Further post-hoc analysis, including only subjects who had PAP adherence >4h average daily use, also did not show a significant change in any of the cardiovascular biomarkers pre- compared to post-PAP therapy.

Table 4.1. Baseline characteristics

	Recruited OHS Participants (N=28)
Age – yr	55 ± 12.5
Female sex – no. (%)	13 (46)
Race or ethnic group – no. (%)	
- White	21 (75)
- Polynesian	4 (14)
- Other	3 (11)
BMI – kg/m^2	54 ± 9.9
Weight – kg	152 ± 31.3
Smoking status	
- Non-smokers – no. (%)	13 (46)
- Ex-smokers – no. (%)	10 (36)
- Current smoker	5 (18)
Cardiovascular History	
- Hypertension – no. (%)	13 (46)
- Diabetes mellitus – no. (%)	9 (32)
- Dyslipidaemia – no. (%)	6 (21)
- Ischaemic heart disease – no. (%)	4 (14)
- Arrhythmia – no. (%)	5 (18)
- Echo abnormality – no. (%)	5 (18)
Spirometry	
- FEV1 – L	2.07 ± 0.68
- FEV_1 % predicted	67 ± 16.7
- FVC – L	2.60 ± 0.87
- FVC % predicted	65 ± 14.1
- FER – %	80 ± 5.7
ABG	
- $PaCO_2$ – mmHg	49 ± 2.6
- PaO_2 – mmHg	64 ± 7.9
- Bicarbonate – mmol	31 ± 1.7
PSG	
- AHI – events/hour	88 ± 31
- %TST<90% – %	72 ± 29
- SpO2 average – %	83 ± 6

Displayed as mean ± standard deviation or number of participants (percentage of total).

Table 4.2 Baseline Measurements of Pulse Wave Analysis and Pulse Wave Velocity

	Baseline Measurements Mean ± SD (% outside of recommended target)			**P value**
	All OHS Participants	**No CV Diagnosis**	**Known HTN/CV Diagnosis**	
PWA				
PSBP (mmHg)	137 ± 12	137 ± 12 *(>130 = 22%, >120 = 100%)*	136 ± 13 *(>120 = 100%)*	0.96
PDBP (mmHg)	79 ± 12	84 ± 8 *(>90 = 33%, >80 = 67%)*	76 ± 13 *(>90 = 78%)*	0.17
PPP (mmHg)	58 ± 9	53 ± 8	61 ± 9	0.08
CSBP (mmHg)	124 ± 11	124 ± 11 *(>110 = 100%)*	124 ± 11 *(>110 = 91%)*	0.95
CDBP (mmHg)	81 ± 12	86 ± 8 *(>80 = 55%)*	79 ± 13 *(>80 = 64%)*	0.21
CPP (mmHg)	43 ± 9	39 ± 7	45 ± 8	0.09
PPP:CPP (ratio)	1.35 ± 0.15	1.39 ± 0.10	1.33 ± 0.17	0.44
AP (mmHg)	14.5 ± 8.2	9.5 ± 5.1	17.5 ± 8.3	0.03
Aix (%)	31.5 ± 13.9	23.4 ± 9.8 *(>33% = 27%)*	36.2 ± 13.8 *(>33% = 45%)*	0.04
AIx@75 (%)	33.1 ± 13.6	25.7 ± 9.2	37.3 ± 13.8	0.06
PWV				
cfPWV (m/s)	7.25 ± 0.92	7.25 ± 0.93 *(>10 = 0%)*	7.25 ± 0.92 *(>10 = 0%)*	0.99
cfPTT (ms)	80 ± 14	77 ± 8	81 ± 16	0.53

Abbreviations: PWA = pulse wave analysis, PSBP = peripheral systolic blood pressure, PDBP = peripheral diastolic blood pressure, PPP = peripheral pulse pressure, CSBP = central systolic blood pressure, CDBP = central diastolic blood pressure, PPP = central pulse pressure, PPP:CPP = ratio of peripheral to central pulse pressure, AP = central augmentation pressure, AIx = augmentation index, AIx@75 = augmentation index corrected to a heart rate of 75bpm

Recommended targets:

PSBP: <120mmHg normal; 120-130 mmHg stage 1; 130-140mmHg stage 2; >140mmHg stage 3

PDBP: <80mmHg normal; 80-90mmHg stage 1; >90mmHg stage 2

CSBP: <110mmHg normal; 110-130mmHg stage 1; >130mmHg stage 2

CDBP: <80mmHg normal; 80-90mmHg Stage1; >90mmHg Stage 2

Aix: <33%

Aix@75: <40%

PWV: <10m/s

p-value based on two-tailed non-paired t-test.

Table 4.3 Baseline Serum Cardiovascular Biomarkers

	Baseline Measurements Mean ± SD (% outside of recommended target)		
	All OHS Participants	**No DM Diagnosis**	**Known DM Diagnosis**
Glucose Profile			
Fasting Glucose (mmol/L)	7.00 ± 2.11	8.17 ± 2.69 *(>5.6 = 78%, >7 = 33%)*	6.23 ± 1.1 *(>7 = 33%)*
HbA1c (%)	6.7 ± 1.77	8.1 ± 2.08 *(>5.7 = 56%, >6.5 = 22%)*	5.9 ± 0.87 *(>7 = 20%)*
	All OHS Participants	**No Dyslipidaemia Diagnosis**	**Known Dyslipidaemia Diagnosis**
Lipid Profile (mmol/L)			
Total Cholesterol	4.35 ± 1.48	4.43 ± 1.50 *(>5.2 = 15%)*	3.87 ± 1.28 *(>5.2 = 33%)*
HDL Cholesterol	1.18 ± 0.27 *(<1^{M}, <1.3^{F} = 36%)*	1.17 ± 0.289	1.22 ± 0.12
LDL Cholesterol	2.33 ± 0.90	2.29 ± 0.98 *(>2.6 = 44%)*	2.50 ± 0.40 *(>2.6 = 50%)*
Triglyceride	1.69 ± 0.70 *(>2 = 31%)*	1.62 ± 0.75	2.00 ± 0.24
	All OHS Participants	**No CV Diagnosis**	**Known CV Diagnosis**
Cardiovascular Biomarkers			
Troponin (ng/L)	20 ± 17 *(>14 = 60%)*	12 ± 7	32 ± 21
NT-proBNP (ng/L)	109 ± 95 *(>125 = 43%)*	74 ± 81	171 ± 85
AST/ALT ratio	1.20 ± 0.40 *(>1 = 64%)*	1.17 ± 0.32	1.23 ± 0.48
CRP (mg/L)	19 ± 14 *(>3 = 93%)*	23 ± 17	20 ± 13

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-proBNP = NT pro-B-Natriuretic peptide; AST/ALT ratio = Aspartate Aminotransferase to Alanine Aminotransferase ratio; CRP = C-reactive protein; OHS = obesity hypoventilation syndrome; DM = type 2 diabetes mellitus; CV = cardiovascular

Recommended targets:

Fasting glucose (mmol/L): <5.6 = normal fasting glucose, 5.6-7 = impaired fasting glucose, >7 = diabetic range; target 4-7 in known diabetics [18, 19]

HbA1c (%): <5.7 normal, 5.7-6.5 prediabetes, >6.5 diabetes; target <7% in known diabetics [18, 19]

Total cholesterol: <5.2 mmol/L[20]

HDL: >1.3 mmol/L in females, >1 mmol/L in males[20]

LDL: <2.6 mmol/L[20]

Triglyceride: <2 mmol/L[20]

Troponin (ng/L) : Risk stratification, <6 = low; 6-12 = intermediate; >12 = high [21]

NT-proBNP: >125 ng/L abnormal[22]

AST/ALT ratio: >1 conveys higher cardiovascular risk [23]

CRP: >3mg/L conveys higher cardiovascular risk [24]

Table 4.4 Pulse Wave Analysis and Pulse Wave Velocity Pre- and Post-PAP Therapy

	Baseline Measurements Mean ± SD	**Post-PAP Measurements** Mean ± SD	**p-value**
PWA			
PSBP (mmHg)	137 ± 12	140 ± 19	0.65
PDBP (mmHg)	79 ± 12	80 ± 11	0.88
PPP (mmHg)	58 ± 9	60 ± 15	0.43
CSBP (mmHg)	124 ± 11	126 ± 16	0.89
CDBP (mmHg)	81 ± 12	81 ± 12	0.68
CPP (mmHg)	43 ± 9	45 ± 13	0.25
PPP:CPP (ratio)	1.35 ± 0.15	1.35 ± 0.14	0.79
AP (mmHg)	14.5 ± 8.2	11.9 ± 6.9	0.16
Aix (%)	31.5 ± 13.9	26.0 ± 12.0	0.08
AIx@75 (%)	33.1 ± 13.6	26.4 ± 12.6	0.10
PWV			
cfPWV (m/s)	7.25 ± 0.92	6.94 ± 1.02	0.57
cfPTT (ms)	80 ± 14	90 ± 21	0.13

Abbreviations: PWA = pulse wave analysis, PSBP = peripheral systolic blood pressure, PDBP = peripheral diastolic blood pressure, PPP = peripheral pulse pressure, CSBP = central systolic blood pressure, CDBP = central diastolic blood pressure, PPP = central pulse pressure, PPP:CPP = ratio of peripheral to central pulse

pressure, AP = central augmentation pressure, AIx = augmentation index, AIx@75 = augmentation index corrected to a heart rate of 75bpm

p-value based on two-tailed paired t-test.

4.5 Discussion

This is the first study to investigate the outcomes of pulse wave analysis (PWA) and pulse wave velocity (PWV) in the obesity-hypoventilation population. In this study, we found that while our OHS participants had higher blood pressure measurements, both peripheral and central, and were more likely to have abnormal cardiovascular biomarkers compared to those reported in a large multinational European population sample (free from overt cardiovascular disease or risk factors), their markers of arterial stiffness fell within normal reference values[25]. The augmentation index (AIx and AIx@75) in our participants was above the mean reported in large unselected populations but below the 95% prediction limits[26, 27]. They would, however, fall in the highest tertile of HeartScore (a cardiovascular risk prediction tool)[27]. The AIx/AIx@75 in our OHS participants also appears higher than that observed in the OSA study subjects[17]. The PWV of our OHS participants fell well below the level (cfPWV >10m/s) indicative of higher cardiovascular risk[6, 28].

One previous study found that OHS, when compared to eucapnic obese patients matched for BMI, had significantly more impaired endothelial function using peripheral arterial tonometry[29]. While the use of PWA and PWV has not been examined in the OHS population previously, there are meta-analysis data from obstructive sleep apnoea and obesity[30, 31]. However, it can be challenging to distinguish the impact of individual conditions on arterial stiffness from other confounders. One meta-analysis found that PWV, in univariate analysis, strongly correlated with age, gender, SBP, T2DM and dyslipidaemia, but does not appear to be related to obesity, severe-range AHI or hypoxic burden (TST<90%)[30]. Severe OSA was not significantly associated with PWV in their multivariable analysis[30]. Another analysis, using pooled data from six studies, found that OSA severity and hypoxia were correlated with the augmentation index (AIx) and central arterial pressure (CAP), but these associations were weak[32]. The effects of obesity on arterial stiffness have also been mixed. While many studies indicated a positive association of PWV with obesity[33-35], several other studies reported a lack of association[36, 37]. The discrepancies in outcomes identified in these studies may be partly explained by the different methods used to assess obesity, as aortic stiffness is more related to visceral adiposity (waist circumference, truncal fat) than overall BMI[38]. Based on the existing evidence, we

anticipated that markers of arterial stiffness would be elevated in our study population, given that OHS represents extremes of obesity and sleep-disordered breathing and is associated with high rates of cardiovascular risk factors. The reason for this discrepancy in findings is unclear, with potential explanations including significant obesity impacting PWV accuracy (obesity is a well-known factor of technical operator bias[39]) and an underpowered study.

The higher central pulse pressure found in our OHS participants, compared with the general population[40] and OSA subjects[17], indicates a higher left ventricular afterload, which may, in turn, contribute to higher rates of diastolic dysfunction observed in echocardiography among the OHS population. This is also reflected in higher levels of NT-proBNP and troponin detected in our study participants, both markers of myocardial strain and injury.

Another interesting finding from this study is the discrepancy between rates of measured versus reported cardiometabolic disorders and risk factors. 100%, 33% and 44% of our OHS participants without a known history of hypertension, type 2 diabetes, and dyslipidaemia, respectively, had elevated blood pressure using the AtCor pulse wave analyser, raised HbA1c/glucose and lipid profile at baseline assessment. Similarly, the rates of cardiac strain and myocardial injury based on blood pathology (NT-proBNP and troponin T) are higher than the reported rates of cardiac disease. Our study findings align with those previously reported in published studies, where the rates of structural abnormalities detected on transthoracic echocardiography or elevated filling pressures/pulmonary arterial pressures were significantly higher than the self-reported/medical record-based prevalence of left ventricular dysfunction or pulmonary hypertension[4]. This may reflect the fact that this group of patients may not seek medical assessment and treatment, delaying detection of cardiometabolic risk factors and disorders. The lower-than-expected rates of reported ischaemic heart disease in the OHS literature may also be explained by reduced medical attendance and a lower likelihood of undergoing diagnostic evaluation. For the participants with one or more known cardiovascular risk factors/disorder diagnoses, many were not achieving the targeted therapeutic goals for cardiovascular risk optimisation.

In previous studies involving OSA patients, CPAP therapy was associated with improvements in augmentation index[41], central pulse pressure[41, 42] and pulse wave velocity[42, 43]. The improvement with PAP therapy in AIx was also observed in a study that recruited patients with severe obesity (BMI > 35 kg/m²)[44]. However, CPAP did not modify PWA levels back to those observed in non-OSA patients, highlighting the need for a multifaceted approach when optimising cardiovascular risk in patients with severe obesity and OSA[44]. The benefits of PAP therapy in reducing arterial stiffness were not replicated in our study. Around half of our participants were randomised to auto-titrating CPAP. Prior

studies examining the effects of APAP on arterial stiffness found that although APAP also reduces arterial stiffness, it may not be as effective as CPAP[45] and that there are a group of non-responders[46]. However, given that the arterial stiffness measurements in our participants were not significantly elevated at baseline, it would be difficult for therapy to achieve further significant improvements. Our study also did not demonstrate significant changes in cardiac biomarkers (specifically NT-proBNP and troponin) post PAP therapy. A previous RCT study in OHS did not demonstrate a significant improvement in echocardiographic features (systolic pulmonary arterial pressure or SPAP and markers of LVH) after CPAP therapy[47]. A small non-controlled study, using volume-targeted BPAP over a longer recruitment period involving OHS participants, showed a reduction in NT-proBNP, but not troponin at 12 months[48]. Our pre- and post-PAP therapy treatment comparison period was also only 3 months, and may be too short to detect significant cardiovascular improvements. Whether BPAP is more effective than CPAP in the short-term in improving cardiovascular biomarkers among OHS patients, as suggested by Corral et al.[47], will require further research.

There are several limitations with our study. First, it is a small exploratory study with the main goal of testing a device to assess arterial stiffness in OHS patients non-invasively. Hence, the study is underpowered to detect meaningful changes after PAP-therapy and may not be representative of the general OHS population (only included OHS with severe OSA phenotype, with mostly mild degrees of hypercapnia). We used two modes of CPAP, with no comparison control group or bilevel PAP therapy. There was also a high number of follow-up losses. Some of the previous OHS studies exploring cardiovascular outcomes also had echocardiographic or right heart catheterisation data. Cardiac imaging and pressure measurements would have been useful to complement blood biomarkers.

The measurement of pulse wave velocity and pulse wave analysis has not been previously standardised for patients with obesity hypoventilation syndrome. Our participants found it difficult to lie supine for the duration of the PWV measurement and 5 minutes before, as recommended by the standard protocol, due to the upward pressure on the diaphragm from increased abdominal adipose tissue. The protocol had to be adjusted to allow a 15 ° elevation of the head of the bed and a reduction in the duration of the pre-measurement rest phase. In addition, tachypnoea and the use of accessory muscles impacted the AtCor device's ability to identify carotid pulsation, potentially affecting the accuracy of cfPWV. The body habitus also impacted the quality of waveforms from the brachial and femoral cuffs. Other laboratories also experienced problems using applanation tonometry equipment in carotid and femoral arteries, with the depth of vessels and surrounding subcutaneous fat tissue impacting the ability to provide clear readings in significantly obese subjects[45, 49, 50].

The calculation of PWV depends on the measured travelled distance, which can be overestimated when measured over the body surface in patients with wider waist circumference[51]. As our study cohort is likely to have significantly increased waist circumference compared to previous studies using AtCor for the calculation of cfPWV, there may be measurement bias when using travelled distance measured over the body surface compared to linear distances taken from radiological images. We did apply the 0.8 correction factor according to the method consensus documents to account for the overestimation of distance measured over the body surface[25], but this correction factor may not be appropriate in an OHS population. Nonetheless, this is likely to overestimate the calculated cfPWV, which is unlikely to affect the conclusion that arterial stiffness, as measured by cfPWV, was not elevated in our OHS cohort.

Ultimately, this was an exploratory study involving a small number of participants. A future study with adequate power, more diverse OHS representation, and the use of different alternative methods to assess arterial stiffness at baseline and after a longer period of optimal PAP therapy (with the addition of a weight loss intervention) is desired to answer some of the questions raised in our study. Realistically, registries of patients with obesity hypoventilation, which collect data on cardiovascular biomarkers and risk factor profiling, may be more practical. OHS patients represent an extreme form of sleep disordered breathing and hence provide a good opportunity to assess the cardiovascular impact of PAP therapy.

4.6 Conclusion

Our exploratory cardiovascular profiling study did not identify increased arterial stiffness in our OHS participants, nor did it significantly change post-PAP therapy. However, the study participants did have high serum biomarkers and elevated central pressure measurements, which predict poor cardiovascular prognosis. There appears to be under-diagnosis of cardiovascular risk factors, with detection of hypertension, hyperglycaemia and abnormal lipid profile in the subgroup of OHS participants not known to have these risk factors. The subgroup with known hypertension, diabetes, and dyslipidaemia was not reaching the recommended goals of risk factor optimisation.

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Chapter 5 Comparison of CPAP vs Bilevel PAP in Obesity Hypoventilation with Airways Disease

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5.1 Abstract

Background Both obesity and airways disease can lead to chronic hypercapnic respiratory failure, which can be managed with positive airway pressure (PAP) therapy. The efficacy of PAP has been studied in obesity hypoventilation syndrome as well as in chronic hypercapnic COPD patients, but not in patients where both obesity and airway obstruction coexist. This pilot study aims to compare the efficacy of continuous positive airway pressure (CPAP) versus bi-level positive airway pressure spontaneous mode (BPAP S mode) in the treatment of hypoventilation disorder with obesity and obstructive airways disease.

Methods We sequentially screened PAP naïve patients with stable chronic hypercapnic respiratory failure ($PaCO_2$>45mmHg), obesity (BMI>30kg/m^2) and obstructive airways disease. Participants were randomised to CPAP or BPAP S mode treatment for 3 months. Participants were blinded to their PAP allocation. Change in awake $PaCO_2$ was the primary endpoint. Secondary endpoints included change in lung function, daytime sleepiness, sleep quality, quality of life, PAP adherence and neurocognitive function.

Results A total of 32 participants were randomised (Mean±SD: Age 61±11 years, BMI 43±7 kg/m^2, $PaCO_2$ 54±7mmHg, FEV_1 1.4±0.6L, AHI 59±35 events/hour). Sixteen participants in each PAP group were analysed. BPAP yielded a greater improvement in $PaCO_2$ compared to CPAP (difference 9.4mmHg, 95% CI 4.3 to 15mmHg). There were no significant differences in PAP adherence, sleepiness, sleep quality or neurocognitive function between the two therapies.

Conclusions Although both PAP modalities improved hypercapnic respiratory failure in this group of participants, BPAP S mode showed greater efficacy in reducing $PaCO_2$.

5.2 Introduction

Obesity and chronic obstructive pulmonary disease (COPD) are both common conditions with increasing prevalence worldwide. The reported proportion of patients with coexisting COPD and obesity varies between different cohorts and is likely influenced by COPD phenotype and the severity of the airflow limitation.[1] Available data suggests that obesity is more prevalent in patients with COPD than the general population.[1]

Both COPD and obesity place significant strain on the respiratory system. Altered lung mechanics, increased burden of respiration and reduced respiratory muscle efficiency are some of the shared physiological derangements.[2-4] Although most patients with COPD or obesity can compensate, maintain ventilation and remain eucapnic, a minority will develop chronic hypoventilation (hypercapnic COPD or obesity hypoventilation syndrome). Sleep can further exacerbate the dysfunction as it leads to reduced respiratory motor neuron output, increased upper airway resistance (i.e. obstructive sleep apnoea) and diminished chemoreceptor sensitivity.[5] The pathophysiological effects of both COPD and obesity are not well studied, but their coexistence likely increases the risk of developing chronic hypercapnia.

The treatment of chronic respiratory failure has been examined in randomised clinical trials for both obesity hypoventilation syndrome and chronic hypercapnic COPD. Continuous positive airway pressure (CPAP) therapy is equivalent to bi-level positive airway pressure (BPAP) therapy in stable OHS with concurrent severe OSA,[6-9] while BPAP is the preferred option in OHS without severe OSA.[10] In COPD with concurrent OSA (overlap syndrome), CPAP is the therapy of choice, including those with awake hypercapnia, with studies showing improvements in $PaCO_2$.[11-13] CPAP has also been associated with reduced hospitalisation and mortality,[14] but has not been directly compared to BPAP in this cohort. Patients who have both obesity and obstructive airways disease contributing to their hypoventilation are often excluded from clinical trials – patients with forced expiratory ratio (FER) <0.7 are excluded from OHS trials,[7-9] while the presence of obesity or OSA often results in exclusion in long-term BPAP trials in pure COPD.[15] A randomised clinical trial has not been previously conducted to directly compare different PAP modalities in this particular cohort of patients.

In this pilot clinical trial, the primary goal was to compare the efficacy of CPAP and BPAP S mode in reversing ventilatory failure (reduction in $PaCO_2$) over a 3-month treatment period among obese patients with hypoventilation disorder and concurrent obstructive airways disease. Secondary outcomes included changes in spirometry indices, weight, health-related quality of life, quality of sleep and sleepiness.

5.3 Methods

Participants

Participants with obesity (BMI>30kg/m^2) and stable daytime hypercapnia ($PaCO_2$ >45mmHg) presenting to the Sleep Disorders Centre, Royal Prince Alfred Hospital were screened for suitability for trial enrolment. Those without significant respiratory or neuromuscular disorders were diagnosed as obesity hypoventilation syndrome (OHS) and recruited for other studies. Participants in whom an obstructive ventilatory defect on spirometry was found (ratio of forced expiratory volume in 1s/forced vital capacity or FER <0.7) or clinician diagnosed COPD were invited to participate in the current study. Other inclusion criteria included (1) no neuromuscular or chest wall skeletal disorders; (2) not currently being treated with positive airway pressure therapy; (3) no major psychiatric illness or unstable medical conditions that would affect the individual's ability to participate in the trial. Participants did not need to have symptoms of sleep disordered breathing to be included in this trial.

Study Design

This study was designed as a single-blinded randomised control trial with two parallel groups, comparing CPAP with Bi-level PAP (S mode) over 3 months. The CPAP group used a fixed pressure CPAP mode. The Bilevel PAP group received non-invasive ventilation using a spontaneous mode of ventilatory support. The protocol included a planned change to Bi-level PAP in the event of treatment failure in the CPAP group. Treatment failure was defined by (1) oxygen saturation

remaining below 80% continuously for 10 minutes; (2) a rise in transcutaneous CO_2 >10mmHg during REM sleep; or (3) an increase in awake CO_2 of 10mmHg despite PAP use. Polysomnography was used to titrate PAP settings at randomisation. The Human Research Ethics Committees at The Royal Prince Alfred Hospital approved the project, and all participants were provided written informed consent. This study was registered at anzctr.org as part of ACTRN12605000096651.

Randomisation and Masking

Demographic information, anthropomorphic data, medical history and medications were collected at recruitment. Spirometry, baseline diagnostic sleep study and daytime seated arterial blood gases were measured to assess eligibility criteria. Following baseline data collection, participants were randomly assigned (1:1) using block randomisation and computer-generated sequence. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes. Participants were blinded to their allocated treatment arm.

Interventions

All participants had laboratory based (type 1) diagnostic and PAP titration studies using commercially available digital sleep systems following recognised guidelines and scored according to Rechtschaffen and Kales scoring classification by experienced sleep scientists unaware of the patient's involvement in the trial. Additional monitoring of transcutaneous carbon dioxide ($TcCO_2$) was performed. Further details are included in the supplemental material.

Following randomisation and on a separate night to the diagnostic study, all participants underwent a conventional in laboratory titration study using the PAP mode corresponding to their allocated arm (either fixed CPAP or Bi-level S mode). For CPAP titration, pressure was manually increased in 1cmH_2O increments with the aim of preventing obstruction, flow limitation, desaturation and arousal. For BPAP titration, EPAP was increased in 1cmH_2O increments with the aim of abolishing obstructive events and if inspiratory efforts did not consistently trigger IPAP; while the IPAP was initially set 4cmH_2O higher than EPAP and then increased to eliminate hypopneas and improve saturation. Supplemental oxygen was added at 1-2L/min to maintain SpO2>90% if SpO_2 remained

below 88% in sleep during the patient's allocated treatment study despite optimisation of ventilation or at maximum pressure that eliminated obstructive apnoeic or hypopneic events.

Participants were prescribed the titrated settings as determined by their PAP titration studies. In addition to the usual standard of care (management of their airways disease, instructions on lifestyle modification), participants were instructed to use their allocated PAP device nightly and received education as per usual clinical care. Participants were contacted at 2 weeks following initiation of therapy and encouraged to call the clinical service at any time if problems or queries arose.

Instrumentation and Measurements

Participants were evaluated on two occasions, at baseline and after three months from initiating PAP treatment. The primary outcome $PaCO_2$ was assessed by daytime arterial blood gas (ABG) analysis. Secondary outcomes assessed included: other ABG parameters; anthropometric data; spirometry indices; compliance; Epworth Sleepiness Scale (ESS)[16], sleep quality using the Pittsburgh Sleepiness Quality Index (PSQI)[17] and health-related quality of life using the Medical Outcomes Survey Short Form 36 (SF 36)[18]. Neurocognitive evaluations included: psychomotor vigilance test (sustained attention, reaction time), digit span task (working memory), trail-making test (executive functioning) and digit symbol substitution test (cognitive dysfunction). Procedural details are included in the supplementary material.

Statistical Analysis

An a priori power calculation suggested that a sample size of 13 in each group would be needed to detect a difference in the mean change in arterial CO_2 of 7mmHg with a power of 80% and a $p<0.05$. Additional patients were recruited to allow for dropouts.

Baseline characteristics were expressed as mean and SD or percentages with 95% Cis and compared using Student's t-test and X2 analysis respectively. Intention-to-treat analysis was performed. Analysis of primary, secondary endpoints and exploratory neurocognitive tests were done using a linear mixed model for repeated measures. The model included fixed categorical effects for treatment arm (CPAP or BPAP), time (baseline and 3 months) and their interaction and a random intercept, adjusted for covariates (baseline values of age, BMI, absolute FEV_1 and AHI). Post-hoc

analysis using linear mixed model was also performed with additional covariates (baseline $PaCO_2$ and PAP adherence) for the primary outcome. These covariates were selected as they were known or anticipated important prognostic variables that that can affect outcome comparisons. There was no imputation for missing data as a mixed effects model was used for analysis. The differences in mean, 95% confidence interval and p-value were reported with the significance test based on a two-sided α of 0.05. An additional analysis of covariance was performed for the primary outcome with adjustment for PAP adherence. PAP adherence was compared using unpaired t-test. Data management was performed using SPSS software (IBM SPSS Statistics).

5.4 Results

Participant Characteristics

Between December 2003 and February 2012, a total of 237 participants were assessed for inclusion criteria. A total of 32 participants met eligibility criteria and were enrolled to the study (Figure 1.).

Table 1 summarises the baseline demographic data. The mean age across both groups were 61 ($\pm$ 11) years. All but one patient had moderate or severe OSA, with a mean AHI of 59 ($\pm$35) events per hour. The mean BMI was 43 ($\pm$7) kg/m^2 with the majority of patients having class III obesity (20/32 had BMI>40kg/m^2). The mean FEV_1 was 1.4 ($\pm$0.6) L. Baseline age and FVC were lower in the BPAP arm. There were more males in the CPAP arm, whereas gender distribution was even in the BPAP arm. There were no significant differences in baseline $PaCO_2$, FEV_1 and BMI between groups. The mean titrated settings were IPAP 15.8cmH_2O and EPAP 9.7cmH_2O for BPAP arm; 12.7cmH_2O for CPAP arm. Table 2 compares polysomnography data from the diagnostic study with titration studies (at recruitment and trial exit). During the initial titration study, five participants of the CPAP arm (mean = 1.4L/min) and six participants of the BPAP arm (mean = 1.7/min) required and were prescribed supplemental oxygen in addition to their PAP therapy.

Primary Outcome

There was a significant improvement in $PaCO_2$ in both the CPAP arm ($p<0.05$) and BPAP arm ($p<0.01$) and (Figures 24). However, the intergroup analysis indicated that BPAP S mode was superior to CPAP in reducing $PaCO_2$ (9.4mmHg, CI = 4.3 – 15mmHg, p=0.001, see Table 3). The BPAP advantage persisted with additional adjustment for baseline $PaCO_2$ and PAP adherence (9.6mmHg, CI = 2.1 – 17mmHg, p=0.01). Two patients in the CPAP arm were switched to BPAP due to safety concerns based on their CPAP titration study (details in supplementary material) but were analysed as per their allocated arm as per randomisation. Inclusion of these two patients within the BPAP arm during analysis did not alter the intergroup comparison. Ten participants in the BPAP arm and eight participants in the CPAP arm had a $PaCO_2$ within the normal range at the end of 3 months.

Secondary Outcomes

There were no significant intergroup differences in other secondary outcomes as summarised in Table 3, 4 and 5. There was a numerically greater improvement in both FEV_1 and FVC in the BPAP arm compared to the CPAP arm (0.3L and 0.5L respectively), but this was not statistically significant. Compared to baseline, BPAP was also associated with a significant improvement in the mental component of SF36.

The mean weight did not change in either group with therapy. Both BPAP and CPAP reduced daytime sleepiness measured by the ESS ($p<0.01$) at 3 months compared to baseline. The BPAP arm also showed improvements in sleep quality using PSQI ($p<0.05$) and mental component of SF36 in the BPAP arm ($p<0.01$) at 3 months compared to baseline.

Exploratory neurocognitive testing did not identify significant intergroup differences in performance. BPAP improved the mean of the slowest 10% reaction times on the psychomotor vigilance test when compared to pre-PAP baseline.

The mean adherence calculated at the end of 3 months therapy period was 4.1($\pm$2.5) hours (BPAP) and 5.6($\pm$2.3) hours (CPAP) (p=0.10). Eight out of 14 patients in the BPAP arm, and 10 out of 15 patients in the CPAP arm had average use ≥4 hours at end of trial download. No major therapy related adverse effect was reported.

Table 5.1 Baseline characteristics

	BPAP (N=16)	CPAP (N=16)	All (N=32)
Age (years)	57 (9.7)	65 (10.7)	61 (10.9)
Gender (% female)	50	13	31
BMI (kg/m^2)	45 (7.8)	40 (5.8)	43 (7.2)
Neck circumference (cm)	46 (4.9)	49 (3.5)	47 (4.4)
Waist circumference (cm)	132 (10.2)	133 (10.7)	133 (10.3)
Hip circumference (cm)	137 (14.1)	131 (14.8)	134 (14.5)
Spirometry			
FEV1 (L)	1.3 (0.6)	1.5 (0.5)	1.4 (0.6)
FEV_1 (% predicted)	45 (19.8)	51 (17.5)	48 (18)
FVC (L)	2.0 (0.9)	2.6 (0.7)	2.3 (0.8)
FVC (% predicted)	58 (23)	68 (20)	64 (22)
FER (%)	62 (8)	59 (11)	60 (10)
ABG			
$PaCO_2$ (mmHg)	57 (8)	52 (5.6)	54 (7.4)
PaO_2 (mmHg)	60 (11)	57 (9)	59 (10)
Bicarbonate (mmol)	33 (5)	31 (3.8)	32 (4.6)
Base Excess (mmol)	6.5 (4.5)	5.5 (3.4)	6 (4.0)
pH	7.39 (0.03)	7.39 (0.03)	7.39 (0.03)
PSG			
AHI (events/hour)	57 (34)	61 (37)	59 (35)
%TST <90%	93 (70-99)	84 (58-96)	85 (68-98)
%TST <80%	28 (17-47)	17 (5-37)	23 (7-43)
%NREM Sleep	90 (9)	87 (9)	89 (9)
%REM Sleep	10 (9)	13 (9)	11 (9)
$TcCO_2$ mean (mmHg)	57 (13)	50 (6)	54 (11)
$TcCO_2$ peak (mmHg)	69 (15)	65 (9)	67 (12)

Displayed as mean (standard deviation), except for %TST <90% and %TST <80%, which are displayed as median (interquartile range). Please note $TcCO_2$ data was only available for 7 of the BPAP arm and 5 of the CPAP arm.

Table 5.2 Baseline Measurements and Changes with Treatment Related to the Primary and Secondary Outcomes of Pulmonary Function and Weight

	BPAP [Mean (SD)]	CPAP [Mean (SD)]	Intergroup Differences: P value

	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
ABG						
PaCO2 (mmHg)	57 (8)	44 (8)* 0.000	52 (6)	47 (6)^ 0.03	0.06	0.02
Bicarbonate (mmol/L)	33 (5)	27 (3)* 0.000	31 (3)	28 (3)^ 0.02	0.2	0.03
Spirometry						
FEV1 (L)	1.3 (0.6)	1.6 (0.7) 0.17	1.5 (0.5)	1.6 (0.5) 0.85	0.39	0.33
FVC (L)	2.0 (0.9)	2.3 (0.9) 0.22	2.6 (0.7)	2.5 (0.6) 0.85	0.31	0.25
Weight (kg)	125 (28)	124 (28) 0.93	120 (19)	120 (19) 0.98	0.96	0.78

~Adjusted for baseline values of the variables analysed and age, gender, BMI, AHI and FEV1

* p<0.01 intragroup difference (3m – baseline) ^ p<0.05 intragroup difference (3m – baseline)

Table 5.3 Baseline Measurements and Changes with Treatment Related to Secondary Outcomes of Quality of Life, Sleep and Sleepiness

	BPAP [Mean (SD)]		CPAP [Mean (SD)]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
ESS	12 (6)	4 (3)* 0.000	13 (5)	8 (6)* 0.01	NS 0.28	NS 0.2
Global PSQI	12 (4)	6 (3)* 0.002	10 (5)	8 (4) 0.12	NS 0.17	NS 0.2
SF36						
Physical Component	32 (12)	35 (12) 0.45	32 (11)	32 (11) 0.88	NS 0.65	NS 0.67
Mental Component	19 (13)	39 (17)* 0.002	34 (17)	41 (15) 0.22	NS 0.12	NS 0.1

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburg Sleep Quality Index; SF36 = Medical Outcome Survey Short Form 36

~Adjusted for baseline values of the variables analysed and age, gender, BMI, AHI and FEV1

* p<0.01 intragroup difference (3m – baseline) ^ p<0.05 intragroup difference (3m – baseline)

Table 5.4 Baseline Measurements and Changes with Treatment Related to the Secondary Outcomes of Neurocognitive Tests

	BPAP [Mean (SD)]		CPAP [Mean (SD)]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
PVT						
Lapses	13 (13)	8 (13) 0.2	5 (7)	5 (9) 0.95	NS 0.36	NS
Median: RT (ms)	361 (97)	315 (80) 0.12	316 (60)	297 (54) 0.49	NS 0.52	NS
Mean Slowest 10% RT (s)	1.6 (0.7)	2.1 (0.6)^ 0.03	2.1 (0.5)	2.3 (0.6) 0.44	NS 0.3	NS
Digit Span Forward	7 (2)	8 (2) 0.47	7 (2)	8 (2) 0.14	NS 0.64	NS
Digit Span Backward	5 (2)	5 (2) 0.98	5 (1)	6 (2) 0.58	NS 0.72	NS
Digit Span Task	12 (4)	13 (3) 0.65	13 (3)	14 (3) 0.22	NS 0.63	NS
Trail Making Test	129 (39)	116 (42) 0.57	134 (61)	116 (45) 0.34	NS 0.83	NS
Digit Symbol Substitution	36 (12)	39 (16) 0.54	35 (10)	40 (11) 0.3	NS 0.84	NS

Abbreviations: PVT = psychomotor vigilance test; RT = reaction time

~Adjusted for baseline values of the variables analysed and age, gender, BMI, AHI and FEV1

* p<0.01 intragroup difference (3m – baseline)

^ p<0.05 intragroup difference (3m – baseline)

PAP compliance

BPAP – 4.1 (2.5)

CPAP – 5.6 (2.3)

Significance = 0.096

5.5 Discussion

To our knowledge, this is the first randomised controlled trial that compares PAP therapies in patients with chronic hypercapnic respiratory failure in the setting of concurrent obesity and COPD.

Compared to baseline, 3 months of PAP therapy resulted in significant decreases in $PaCO_2$ in both BPAP and CPAP arms, with BPAP S mode superior to CPAP in reducing $PaCO_2$ in our study population. BPAP allocation was also associated with a greater improvement in FEV_1, FVC and mental component of SF36 when compared to CPAP. There were no significant differences between the two arms in other secondary outcomes or PAP adherence.

In clinical trials involving OHS patients with severe OSA and without airways disease (FER >0.7), BPAP and CPAP had similar efficacy in improving ventilatory failure.[7-9] As sleep apnoea plays an important role in the development of hypercapnia in this OHS phenotype, CPAP is effective in resolving upper airway obstruction. CPAP also has a volume-inflation effect, which improves VQ mismatch due to small airway closure[2] and over time, improves central ventilatory drive.[19] In contrast, the addition of nocturnal BPAP in addition to usual care is recommended in chronic stable hypercapnic COPD patients,[15,20] where BPAP is thought to provide improved minute ventilation, resting of fatigued respiratory muscle and better VQ matching.[3,21] Studies of OHS patients exclude those with concurrent lung disease,[7-9] while studies of hypercapnic COPD do not include patients with obstructive sleep apnoea.[15] As a consequence, few studies have reported outcomes of PAP therapy in patients with hypercapnic OSA and moderate to severe lung disease. In OHS and in overlap syndrome, predictors of CPAP failure include less severe OSA, reduced lung function and more sleep time spent in SpO_2 <90%.[2,21] Although the majority of our study participants (26/32) had severe OSA (a mean baseline AHI 59 events/h), they also had severe impairment in their lung function and a large portion of their total sleep time was spent with SpO_2 <90% during their diagnostic study. It appears that while CPAP is an effective alternative to BPAP in the majority of obese hypercapnic patients, the added burden of airways disease favours treatment with BPAP in reducing awake $PaCO_2$ in our participants, even though compliance with therapy was lower.

When comparing study population characteristics of this study to that of OHS or hypercapnic COPD, the additive effects of obesity-driven sleep apnoea and lung disease are apparent. At a similar baseline $PaCO_2$, our study population had a lower baseline BMI compared to OHS clinical trials,[8,9] but better lung function (FEV_1) compared to hypercapnic COPD trials.[22] As expected, nearly all our participants (31/32) would fit the definition of overlap syndrome (presence of both COPD and OSA).

Although PAP therapy, in particular BPAP, has been associated with improved lung function [7,11,12,20,23] and reduction in weight [7-9,12] in some of the COPD and OHS trials, no significant change in spirometry indices or weight were observed in our study. Participants in the BPAP arm did have a more significant change in spirometry indices than the CPAP arm, however it's not clear if this is related to having lower baseline values and whether their airways disease was optimally controlled at the time of enrolment.

Our data suggest that this cohort of patients is subject to a high burden of symptoms. They have increased daytime sleepiness, poor quality of sleep and low health-related quality of life. Baseline daytime sleepiness, as assessed by the Epworth Sleepiness Scale, was comparable to OHS populations[7-9] as well as nonhypercapnic overlap syndrome[24] with similar improvements with treatment. Our cohort had worse mental health status (mental component of Short Form-36 Health Survey) than that reported in non-hypercapnic overlap syndrome and pure COPD.[25] BPAP, but not CPAP, therapy was associated with improvement in mental health, although it is not clear if this was due to a lower baseline mental component SF-36 scores in the BPAP arm.

Prevalence of cognitive impairment is higher in patients with COPD than healthy controls and appears to correlate with the severity of disease.[26] Although less explored, neurocognitive impairment is also seen in OHS and is more common than in healthy and obese controls.[27] The underlying mechanism is not well understood, but contributing factors include hypoxia, hypercapnia and sleep fragmentation.[28] Results from our cohort did not differ significantly from previous reports of neuropsychological function in OSAS and COPD groups.[29,30] PAP therapy over three months did not appear to improve neurocognitive test performances significantly, a similar finding to an OHS cohort over the same treatment period.[31]

Benefits from PAP therapy are dependent on good adherence. PAP adherence is an independent predictor of mortality in both overlap syndrome and OHS[32,33] The average adherence to PAP was similar to other clinical trials in hypoventilation disorders.[7-9,22] Although the expectation is that BPAP would be better tolerated given a lower exhalation pressure, adherence was not significantly different between the two arms, with participants on CPAP showing a slightly higher average hours

of use. This is despite patients in the BPAP arm reporting better within-group improvements in sleep quality compared to the CPAP group.

There are several limitations to this trial. This study specifically recruited a population with hypercapnia; thus the results of the data apply only to this subset of obese patients with concurrent COPD. Although nearly our entire cohort had by definition overlap syndrome, the study conclusion cannot be applied to the general overlap syndrome population, where the majority of patients are not hypercapnic or morbidly obese, and CPAP is likely to be sufficient. The severity of airway obstruction and therefore contribution of co-exist airways disease to hypoventilation would have varied between recruited individuals. A subgroup of patients with mild airways disease and severe sleep obstructive sleep apnoea may do equally well on either PAP therapy. The recruited participants are from a single site and may lack applicability to other population centres. While patients were blinded to their allocated therapy, investigators were not, and this could have introduced biases.

Many of the treatment effects found were within-group analysis. These findings are not conclusive and will need to be replicated in larger studies. The study population was small and may not be powered to detect treatment effect several secondary endpoints. As the studied population has a high burden of disease and other medical comorbidities, they are challenging to recruit and retain – two participants were lost to follow up due to death unrelated to respiratory failure/PAP treatment. A control (non-PAP) arm was not included in the study design as the majority of patients likely to be recruited were expected to be symptomatic from their sleep disordered breathing and to have ventilatory failure, so withholding therapy could not be justified.

Recruitment for the study was slower than anticipated, with many patients presenting with acute respiratory decompensation or referred for review after already being established on either CPAP or BPAP therapy by other centres.

A spontaneous mode of BPAP was used in this study, and other modes using a backup rate or volume-assured pressure support may have been even more effective. During the time when the trial was conducted, the PAP devices were not able to provide data on residual AHI on treatment.

Despite randomisation, there were intergroup differences in baseline measurements (age, gender and BMI). Statistical analysis was able to adjust for differences in these covariates. Although not statistically significant, the relatively higher baseline $PaCO_2$ would favour BPAP's overall treatment effect. Although the participants were not informed of their PAP treatment allocation, the PAP devices are not re masked, in theory participants still have the ability to unblind themselves as the PAP machines in the two treatment arms were not physically identical.

Future studies will need a larger sample size through multi-centre trials and be powered to measure clinically meaningful outcomes such as hospitalisations, cardiovascular outcomes and mortality over more extended periods. Further phenotyping studies are required to help determine biomarkers that will predict optimal initial PAP modality. The optimal pressure targets are unclear in this group of patients. Recent COPD trials suggest a benefit of larger driving pressure, while a higher EPAP is required to offset the OSA, both which need to be balanced with patient acceptance and adherence to therapy along with the possible impact of higher leak on the effectiveness of therapy.

5.6 Conclusion

In this single centre pilot randomised control trial, BPAP was more effective in improving $PaCO_2$ than CPAP in people with a hypoventilation disorder, in the setting of obesity and concurrent obstructive airways disease. BPAP also resulted in a greater change in lung function (FEV_1 and FVC) and quality of life (mental component of SF36) when compared to CPAP. There were no significant differences between groups in weight loss, daytime sleepiness, sleep quality, neurocognitive testing or adherence over 3 months.

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Chapter 6 Comparison of Auto-titrating versus Fixed CPAP in Obesity Hypoventilation Syndrome with Concurrent Severe Obstructive Sleep Apnoea

This chapter has been accepted for publication (Respirology).

Zheng, Y., Piper, A., Wong, K., Gauthier, G., Phillips, C.L., Grunstein, R. and Yee, B.J., 2025. A pilot randomised non-inferiority trial of auto-titrating versus fixed continuous positive airway pressure for obesity hypoventilation syndrome with severe obstructive sleep apnoea. (pending publication)

6.1 Abstract

Background and objective

Fixed CPAP (fCPAP) is the preferred first-line ventilatory therapy in patients with obesity hypoventilation syndrome with severe obstructive sleep apnoea (OHS+sOSA). Auto-titrating CPAP (APAP) is not recommended but has not been systematically evaluated in this population. Our pilot study aimed to provide feasibility data for a larger comparative effectiveness trial to determine whether APAP is non-inferior to fCPAP for improving hypercapnic respiratory failure.

Methods

Participants with OHS+sOSA were randomised to either APAP or fCPAP for 3 months. The primary outcome was the change in $PaCO_2$. Secondary outcomes included changes in quality of life and cardiovascular biomarkers. A sample size of 82 was needed to demonstrate non-inferiority of APAP compared to fCPAP (assuming a non-inferiority margin of -2.5mmHg). To assess feasibility (recruitment, treatment adherence, dropouts) we aimed to recruit up to 44 participants in this pilot trial.

Results

Twenty-eight of 84 screened participants were randomised (Mean±SD: Age 55±12.5 years, BMI 54±9.9kg.m^{-2}, $PaCO_2$ 49±2.6mmHg, AHI 88±31 events/hour) to APAP (n=15) or fCPAP (n=13). Mean adherence exceeded 4 hours in both groups, however 25% of randomised participants did not complete the trial. Both treatments reduced $PaCO_2$ (fCPAP: -5.7±1.6mmHg, APAP: -4.1±2.8mmHg). Test of non-inferiority for APAP versus fCPAP was inconclusive (mean $\Delta PaCO_2$ difference = -1.7mmHg (95% CI -5.0 to 1.6mmHg)). Adherence favoured fCPAP. fCPAP significantly improved sleep quality compared to APAP. No intergroup differences were identified in sleepiness, quality of life or cardiovascular biomarkers.

Conclusion

The pilot study highlighted important challenges with recruitment and retention. While the study was not powered to confirm the non-inferiority of APAP compared to fCPAP, some patient-relevant outcomes may favour fCPAP. A larger study with protocol modifications is required to confirm these preliminary findings. Using APAP to manage OHS+sOSA should be approached with caution.

Keywords: obesity, hypercapnic respiratory failure, positive airway pressure therapy, sleepiness, quality of life, cardiovascular disease

Brief Summary:

Fixed-mode CPAP is recommended as first-line therapy in obesity hypoventilation syndrome (OHS) with concurrent severe obstructive sleep apnoea (sOSA). Auto-titrating CPAP is not recommended in OHS but has not been previously studied in this population. This is the first randomised trial to compare auto-titrating with fixed CPAP mode in OHS+sOSA. While our study showed that both modes of CPAP improved respiratory failure, we could not conclude that APAP is non-inferior to fCPAP in this population.

6.2 Introduction

Obesity hypoventilation syndrome (OHS) is diagnosed based on obesity, sleep-disordered breathing in the presence of awake alveolar hypoventilation not attributable to other causes[1]. Although the pathogenesis of obesity hypoventilation syndrome is not fully elucidated, carbon dioxide accumulation during repeated periods of prolonged apnoea is thought to be one of the main contributors to the development of respiratory failure in the subset of patients with concurrent severe obstructive sleep apnoea (sOSA)[2]. Consequently, alleviating obstructive apnoeas during sleep with positive airway pressure therapy can improve and resolve respiratory failure. Randomised control trials and meta-analysis of OHS subjects with the sOSA phenotype have demonstrated equivalence of continuous positive airway pressure (CPAP) in the fixed-mode and bilevel positive airway pressure (BPAP) in improving hypercapnia and symptoms[3-5], and CPAP is recommended as the first line PAP option in ATS practice guidelines for OHS with sOSA[6].

Auto-titrating (or APAP), with the ability to automatically adjust the level of pressure delivery to eliminate upper airway obstruction, has been used for OSA since the mid-1990s[7]. Proprietary algorithms modify pressure based on sensed parameters such as flow profile, airflow change and vibratory snore[8]. APAP has potential advantages over a fixed-CPAP (fCPAP) as it caters to dynamic changes in upper airway collapsibility, which can be observed due to alterations in body position, transition to different sleep stages, weight gain/loss, factors that are relevant to the OHS population. Meta-analysis data comparing APAP to fCPAP in eucapnic OSA suggests APAP is better accepted by patients and has a small advantage in adherence and improvement in sleepiness[9], while outcomes in minimum oxygen saturation and blood pressure favour fCPAP[10, 11]. In addition, APAP's ability to determine pressure requirements bypasses the need for in-laboratory titration studies and associated

issues of cost, inconvenience, and limited access. There is an increased reliance on APAP to initiate treatment and provide long-term therapy among patients with OSA.

As OHS is under-recognised and can be misdiagnosed as simple OSA, APAP may be inadvertently used in this population for unattended pressure titration or long-term therapy. There has also been reported use of APAP devices in OHS observational studies[12]. However, there are several theoretical problems with APAP use in OHS patients. The rate of pressure increase in existing APAP algorithms may also be too slow to respond to upper airway obstruction in OHS, where the burden of visceral adiposity is likely higher than in typical OSA. With hypoventilation disorders, arterial oxygen desaturation can still occur with intact airflow, particularly in REM sleep[13]. Consequently, most studies evaluating APAP efficacy and safety exclude patients with significant comorbidities such as OHS. Hence, APAP is neither recommended for therapy nor unattended titration in OHS based on consensus, AASM guidelines and the manufacturer's product manual[14-16].

As there has been no supporting evidence against the use of APAP in stable OHS with concurrent sOSA, the purpose of this pilot study was to assess the feasibility of conducting an randomised controlled trial comparing auto-titrating CPAP with standard of care, fixed-mode CPAP with respect to recruitment rates, participant retention, PAP adherence and safety. This pilot non-inferiority study sought to gather preliminary data on the efficacy of APAP compared to fCPAP in reversing chronic respiratory failure, improving sleep quality and sleepiness, and improving overall quality of life. As cardiovascular disease has surpassed respiratory failure as the main factor in determining mortality, additional cardiovascular assessment and biomarkers were also included as additional exploratory outcomes.

6.3 Methods

Study Participants

Subjects with obesity hypoventilation syndrome (BMI>30kgm^{-2}), stable daytime hypercapnia ($PaCO_2$>45mmHg and normal pH), concurrent severe obstructive sleep apnoea (AHI$\geq$ 30/h) and naïve of long-term positive airway pressure therapy, presenting to the Sleep-Disorder Centre, Royal Prince Alfred were screened for trial recruitment (July 2018 – December 2023). Exclusion criteria included the presence of any condition that may contribute to hypoventilation, including neuromuscular disease, chest wall abnormalities, respiratory depressant medications, COPD or an FEV1/FVC ratio of less than 0.7. Subjects who had uncontrolled medical or psychiatric conditions, decompensated right heart failure, pre-existing cerebrovascular disease, or reduced ejection heart failure were also excluded from the study. Subjects had to be proficient in English and able to sign an informed consent. Subjects with $PaCO_2$>60mmHg were also excluded as subgroup data analysis from previous clinical trials shows that the severely hypercapnic subjects are more likely to fail CPAP therapy and require escalation to bilevel PAP therapy[5].

Study Design and Intervention

This parallel, double-blinded, randomised, non-inferiority trial was conducted at Royal Prince Alfred Hospital, Camperdown, Sydney, Australia. Participants were randomised 1:1 to auto-titrating CPAP or fixed CPAP. Data was collected at baseline and at 3 months post PAP therapy to compare changes in arterialised CO_2 (primary endpoint), sleepiness, quality of life, functional status, and cardiovascular biomarkers. Feasibility objectives (eligibility rate from screened participants, recruitment rate, drop-out rate, study assessment and treatment acceptability) were collected.

A computer-generated randomisation list using random block sizes (2, 4 or 6) with stratification based on the severity of hypercapnia ($PaCO_2$ 45-52mmHg or $PaCO_2$ 52-60mmHg). The treatment allocation was concealed in sequentially numbered, sealed opaque envelopes by a researcher, not involved in data collection or clinical care of the participant. A senior sleep nurse, experienced in CPAP therapy and education, was responsible for setting up the CPAP devices for the enrolled participants. Participants were blinded to which device mode they were allocated, as was the researcher involved in the data collection and analysis. Markings indicating the mode of therapy were not identifiable on their allocated machine (either Philips Dreamstation or ResMed Airsense 10).

All participants had an in-laboratory CPAP titration study (full-night titration, protocol as per AASM clinical guidelines for the manual titration of positive airway pressure with obstructive sleep apnea[17]) and had a group education session on mask fitting and PAP device operation.

For the three-month trial period, participants were instructed to use their allocated device (CPAP or APAP) every night at home during the entire sleep period. Participants allocated to CPAP were on a fixed pressure based on their CPAP titration study. Participants allocated to APAP were on an auto-titrating pressure with a range set between 8-20cmH2O. At the end of the trial, based on the optimal settings from their titration study, APAP participants were switched to fixed CPAP mode.

The Human Research Ethics Committees at The Royal Prince Alfred Hospital approved this randomised control study. The study was registered at anzctr.org (ACTRN12618000379213, UTN U1111-1207-3374).

Study Assessments

Participants were evaluated on two occasions, at baseline (before PAP treatment) and at three months after initiating PAP treatment. Demographics, polysomnography data, and spirometry indices were collected at trial enrolment. Arterialised blood gas, Epworth Sleepiness Scale (ESS)[18], Functional

Outcomes of Sleep Questionnaire (FOSQ)[19] and Severe Respiratory Insufficiency Questionnaire (SRI)[20] were collected on both occasions.

Adherence to therapy based on CPAP download for the trial period was included in the 3-month follow-up. Procedural details are included in the supplementary material.

Sample-Size Estimation

The sample size was calculated based on the standard deviation of $PaCO_2$ change with PAP (4.5mmHg) documented in previous studies' [4, 5]. We estimated the sample size required to detect a non-inferiority margin of -2.5mmHg (based on previous OHS RCT power calculation[4] and what is considered clinically significant), with a power of 0.8, one-sided significance level of 0.05 will be 82. However, as this was a proof-of-concept pilot study, assessing capacity to recruit, a sample size of 44 was targeted. This was based on a conservative proportion of 0.5, 95% confidence level and margin of error of 15%.

Statistical Analysis

An intention-to-treat analysis was performed. Baseline characteristics were expressed as mean and SD or percentages with 95% CIs and compared using Student's t-test and chi-squared analysis, respectively. Analysis of arterial blood gas, sleepiness, quality of life, functional status was performed using a linear mixed model with repeated measures. The model included fixed effects for the treatment arm (APAP or fCPAP), time (baseline and three months), and their interaction, age, and a subject-level random intercept. The differences were reported as a mean with a 95% confidence interval and p-value, with the significance test based on a two-sided α of 0.05. Data analyses were performed using SPSS software (IBM SPSS Statistics).

6.4 Results

Feasibility Outcomes

Between July 2018 and December 2023, a total of 84 patients were assessed for eligibility criteria (figure 1. and figure 2.). Due to lower-than-anticipated recruitment rates, the study was terminated

before the targeted sample size of 44 was achieved. Across 66 months, 70 participants completed screening, and 28 participants with OHS and concurrent severe OSA (sOSA) were enrolled in the study, 15 randomised to APAP and 13 randomised to fCPAP. Recruitment rate (4.3 participants per year) was lower than the anticipated 12 participants per year. Recruitment significantly declined post COVID-19 pandemic (15 participants enrolled in first 18 months, 1 participant during 2020 and 12 participants from 2021 – 2023). Three out of 15 in the APAP and 4 out of 13 in the fCPAP arm did not complete the trial (drop-out rate 25%). Most declined to travel to the study site for end of trial study assessments as they were from regions outside of Sydney. While most study assessments, including the primary endpoint ($PaCO_2$) were acceptable to participants, pulse wave velocity measures were difficult to tolerate for participants. Both modes of CPAP were accepted by participants with only 1 (fCPAP) allocated participant being intolerant to therapy.

Participant Baseline Characteristics

Table 1 summarises the demographic data and baseline characteristics. The participants were middle aged (55 ±12.5 years), slightly more were male and most were Caucasian. Rates of diagnosed cardiovascular comorbidities were elevated. On average, participants in the fCPAP arm were younger and had lower rates of diagnosed cardiovascular disease. Participants in the APAP arm had a slightly higher baseline $PaCO_2$ than the fCPAP arm (50$\pm$2.8mmHg versus 48$\pm$1.9mmHg). Both groups had similar sleep study characteristics and spirometry indices. The mean fixed pressure setting in the fCPAP arm was 16.7$\pm$2.4cmH_2O. The median, 90^{th}/95^{th} centile and maximum pressure in the APAP arm were 10.8$\pm$3.1, 13.1$\pm$3.5 and 14.1$\pm$3.4cmH_2O. The mean recommended pressure based on their in-laboratory CPAP titration study was 17.4$\pm$1.1cmH_2O and 17.4$\pm$1.0cmH_2O in the CPAP and APAP arm, respectively.

Primary Outcome - Reversal of Respiratory Failure

The estimate of the difference in effect (APAP-fCPAP in $PaCO_2$ improvement) was -1.70mmHg (95% CI: -5.01 to 1.61mmHg). As the 95% CI spanned the pre-specified non-inferiority margin (-2.5 mmHg) and 0 mmHg, non-inferiority of APAP versus fCPAP was determined to be inconclusive[21] (Figure 1.). Post-hoc multivariate analysis, adjusting for differences in baseline age, sex, cardiovascular risk factors and disease, also did not show a statistically significant difference in $PaCO_2$ improvement (-0.29mmHg; 95% CI: -4.99 to 4.31mmHg; p-value = 0.90). To address the missing data from loss to follow up, multiple imputations were performed during post-hoc analysis. Assuming data were missing at random and using 20 imputations, the pooled APAP vs CPAP effect on $PaCO_2$ change was -0.74mmHg (95% CI -5.44 to 3.96mmHg), which will reach a similar conclusion when using complete-case analysis (n=21). Results were robust when the number of imputations was increased to 50. Sensitivity analyses using a tipping point approach demonstrated that the overall conclusion of no clear difference would only change if the imputed APAP outcomes differed systemically by more than $\pm$2mmHg. There were no significant differences in between-group comparisons in changes in PaCO2, PaO2 or bicarbonate (Table 2). 89% of participants in the fCPAP arm experienced normalisation of their $PaCO_2$ (<45mmHg) compared to 50% of the APAP arm (p-value 0.06). In a within-group pre- and post-PAP therapy comparison, both PAP arms showed significant improvements in $PaCO_2$ and reductions in bicarbonate. With the exception of one participant in the APAP arm, all participants experienced a reduction in their $PaCO_2$ with PAP therapy. PaO_2 also significantly improved in the APAP arm post-therapy.

Secondary Outcomes

Comparison of Symptom Improvement

Both fCPAP and APAP significantly improved ESS, by a similar amount (Table 3.). fCPAP therapy was associated with a greater improvement in FOSQ Total than APAP therapy. There were significant improvements in sleep quality (FOSQ Total) and health-related quality (SRI) of life in the fCPAP arm post-therapy. No improvement was observed in sleep quality, health-related quality of life or any of their subscales in the APAP arm.

Comparison of Cardiovascular Biomarkers

There were no significant changes in any of the measured cardiovascular endpoints of interest in within- or between-group comparisons post-PAP therapy (Table 4).

Treatment Adherence and Side Effects

The average PAP hours of use were 6.7±1.7h per night in the fCPAP arm compared to 4.9±2.4h in the APAP arm (p-value 0.06). PAP use over 4 hours occurred in 88% of days recorded in the fCPAP arm, compared to 65% in the APAP arm (p-value <0.03). Post-hoc analysis showed adherence did not significant influence the primary endpoint outcome. Further, post-hoc analysis suggested that pressure and leak impacted on PAP adherence (see supplementary material). Reported side effects included aerophagia (1), noise disruption (1) and mask interface irritation (2). All participants continued PAP therapy within their treatment arm without further adjustment of mode/settings. One participant who did not return for follow-up measurements cited issues with their PAP therapy due to pressure intolerance (APAP arm). One participant was hospitalised during the trial period, unrelated to the PAP therapy (lower limb cellulitis). No other serious adverse events were recorded during the trial.

Table 6.1. Baseline characteristics.

	fCPAP (N=13)	APAP (N=15)	All (N=28)
Age – yr	48 ± 9.0	60 ± 12.4	55 ± 12.5
Female sex – no. (%)	7 (54)	6 (40)	13 (46)
Race or ethnic group – no. (%)			
- White	10 (77)	11 (73)	21 (75)
- Polynesian	3 (23)	1 (7)	4 (14)
- Other	0 (0)	3 (20)	3 (11)
BMI – kg/m^2	54 ± 10.3	53 ± 9.9	54 ± 9.9
Weight – kg	149 ± 25.5	154 ± 36.3	152 ± 31.3
Smoking status			
- Non-smokers – no. (%)	5 (39)	8 (53)	13 (46)
- Ex-smokers – no. (%)	4 (31)	6 (40)	10 (36)
- Current smoker	4 (31)	1 (7)	5 (18)
Cardiovascular History			
- Hypertension – no. (%)	4 (31)	9 (60)	13 (46)
- Diabetes mellitus – no. (%)	3 (23)	6 (40)	9 (32)
- Dyslipidaemia – no. (%)	2 (15)	4 (27)	6 (21)
- Ischaemic heart disease – no. (%)	1 (8)	3 (20)	4 (14)
- Arrhythmia – no. (%)	1 (8)	4 (27)	5 (18)
- Echo abnormality – no. (%)	1 (8)	4 (27)	5 (18)
Spirometry			
- FEV1 – L	2.03 ± 0.75	2.11 ± 0.64	2.07 ± 0.68
- FEV_1 % predicted	63 ± 15.8	70 ± 17.5	67 ± 16.7
- FVC – L	2.56 ± 0.99	2.63 ± 0.78	2.60 ± 0.87
- FVC % predicted	63 ± 13.7	67 ± 14.9	65 ± 14.1
- FER – %	79 ± 5.7	80 ± 5.8	80 ± 5.7
ABG			
- $PaCO_2$ – mmHg	48 ± 1.9	50 ± 2.8	49 ± 2.6
- PaO_2 – mmHg	70 ± 6.7	60 ± 6.8	64 ± 7.9
- Bicarbonate – mmol	30 ± 1.4	31 ± 1.8	31 ± 1.7
PSG			
- AHI – events/hour	88 ± 28	89 ± 32	88 ± 31
- %TST<90% – %	72 ± 30	73 ± 30	72 ± 29
- SpO2 average – %	80 ± 8	86 ± 2	83 ± 6

Baseline characteristics displayed as mean ± standard deviation or number of participants (percentage of total).

Table 6.2 Baseline Measurements and Changes with Treatment (Respiratory Failure)

	fCPAP [Mean ± SD]			APAP [Mean ± SD]			P Value of Intergroup Differences
	Baseline	3 Months	Intragroup	Baseline	3 Months	Intragroup	
ABG							
$PaCO_2$ – mmHg	48.2 ± 1.9	42.5 ± 1.6	-5.7 ± 1.2***	50.0 ± 2.8	45.9 ± 5.4	-4.1 ± 2.8**	0.30
PaO_2 – mmHg	69.5 ± 6.7	75.6 ± 11.7	5.8 ± 7.7	59.9 ± 6.9	68.4 ± 6.7	8.5 ± 5.4**	0.56
Bicarbonate – mmol/L	30 ± 1.4	28 ± 2.4**	-2.2 ± 1.4**	31 ± 1.8	29 ± 3.4	-2.1 ± 1.9*	0.94

intragroup difference (3m – baseline): * p<0.05 ** p<0.01 *** p<0.001

Table 6.3 Baseline Measurements and Changes with Treatment Related to Quality of Life, Quality of Sleep and Sleepiness Scores

	fCPAP [Mean ± SD]		APAP [Mean ± SD]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted ~
ESS	12.3 ± 6.8	7.5 ± 4.9*	11.1 ± 5.1	7.5 ± 5.6*	0.434	0.428
FOSQ Total	64.5 ± 17.0	88.6 ± 11.0**	69.9 ± 14.5	75.4 ± 17.7	0.025	0.021
SRI Summary	54.2 ± 16.7	72.1 ± 19.6**	56.1 ± 17.6	60.8 ± 22.9	0.072	0.070

Abbreviations: ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcome Sleep Questionnaire; SRI = Severe Respiratory Insufficiency Questionnaire

~Adjusted for age

* p<0.05 intragroup difference (3m – baseline)

** p<0.01 intragroup difference (3m – baseline)

6.5 Discussion

This pilot study is the first study to examine the practicality of conducting a randomised controlled trial comparing auto-titrating CPAP with fixed CPAP for treatment of obesity hypoventilation syndrome with severe obstructive sleep apnoea. Although the recruitment target was not met and the drop-out rate was higher than anticipated (25%), valuable insights were gained in designing a future study. Recruitment was close to the anticipated rate prior to 2020/COVID-19. Public health restrictions, patient reluctance, reduced research and sleep laboratory activity all contributed to a

decline in recruitment after the first 18 months. The main barrier to participant retention was non-attendance at the end of trial visit due to the burden of travel. Both fCPAP and APAP treatment acceptance was high, well tolerated and with no major treatment side effects reported.

Using the observed standard deviation of the primary outcome (4.24mmHg) and drop-out rate from our pilot data, a two-arm parallel trial (powered at 0.8 and one-side significance of 0.05) to detect a between-group difference of 2.5mmHg will require approximately 62 participants per arm (124 total). Strategies to improve recruitment and reduce drop-outs will be required. These may include satellite recruiting clinics and use of telehealth to improve identification and enrolment of rural OHS patients. In addition, the lingering impact of COVID-19 on research and recruitment may diminish with time. Ultimately, the increased sample size for a definitive study will require a multicentre trial.

While our study was not powered for the primary endpoint and our test of non-inferiority was inconclusive, there were some interesting study findings around treatment efficacy. Our study suggests that both arms of PAP therapy may improve hypercapnia during the first three months of treatment. The absolute improvement in awake hypercapnia and the proportion of participants achieving normocapnia post-therapy were numerically greater in the fCPAP arm. While the relative improvements with both therapies were not statistically different, CPAP adherence and usage appeared to favour fCPAP.

Although our dataset could not conclude that APAP was non-inferior to fCPAP, APAP therapy did not result in significant harm/side effects, and on average, there was a significant reduction in $PaCO_2$. No previous trials have specifically examined the effects of APAP therapy in OHS. One observational study examining the impact of PAP adherence on OHS outcomes did include a significant portion of long-

term APAP use (69/84 CPAP users, 69/225 of total – i.e. most were on bilevel PAP) among its study population[12]. The study showed significant improvements in gas exchange, sleepiness, and quality of life with long-term PAP therapy, particularly in those with better adherence, but the study did not separate results based on PAP mode. The study population presented with a similar degree of chronic hypercapnia but lower BMI and better lung function than our study participants. The mean pressure of CPAP users was only 10.5±2.5 cmH2O, and it was unclear how the APAP pressure range was set[12].

In our pilot study, adherence tended to be lower in the APAP arm than in the fCPAP arm. This may be a clinically significant finding as previous trials have shown that a higher level of adherence in OHS was associated with improved gas exchange and quality of life, lower hospitalisation days, reduced healthcare resource utilisation and improved cardiovascular morbidity and mortality[12, 22]. The difference in adherence between APAP and fCPAP is not clear, but PAP adherence appears to have a positive correlation with median/set pressure delivered, and negative correlation with machine reported leak(see supplementary information). While potential pressure changes may also impact on PAP tolerance and adherence, our participants in the APAP arm did not have a wide range of pressure variations despite being set between 8-20cmH2O (see supplementary table 3). Compared to the recommended pressure during their titration study, pressure ranges during home use in the APAP group were generally lower, although the machine reported residual 'AHI' still indicated adequate control (<5 events/hr). Manual CPAP titration is the standard method of determining effective CPAP pressure for OHS with sOSA. Although unattended APAP is accepted as an alternative method to determine fixed CPAP treatment pressure in uncomplicated OSA [14, 16, 23], there is a lack of pressure agreement between different APAP models, as well as to the pressure suggested in a manual CPAP titration.[24, 25]In addition, APAP's proprietary algorithms have not been tested in OHS populations. APAP will not respond to persistent oxy-haemoglobin desaturation when the airflow is intact. Although OSA and upper airway obstruction play an important role in the pathophysiology of OHS,

there will still be periods of pure hypoventilation where APAP algorithms will not respond, as airway vibration, dynamic airflow reduction/limitation may not be present. The absence of these triggers of upper airway obstruction over a pre-determined time duration may even prompt a gradual pressure decrease[26]. The lower optimal pressure suggested by APAP may be undertreating our study population – whether over longer term will equate to lower efficacy is unclear.

Our study participants had similar degrees of improvement in sleepiness as those reported in previous CPAP trials in OHS with sOSA[3-5]. There was no difference in the improvement between the two arms in ESS—both returned to normal population levels after starting from a baseline similar to that previously reported in OSAS.[18] The CPAP arm experienced significant improvements in sleep quality and quality of life, which were also reported in previous trials[4, 5]. These improvements were not observed in the APAP arm.

There are several study limitations. The trial was terminated earlier than the original intended recruitment target (n=44) due to lower-than-anticipated recruitment rates and the impact of COVID-19. There was also a higher-than-anticipated number of follow-up losses (25%). While the trial lacks the power to truly detect non-inferiority in clinical outcomes between the two modes of CPAP therapy, the data on recruitment and drop-out rates is useful to guide future clinical trial design and power calculations. The trial also highlights the difficulty in capturing this group of patients and their potentially lower healthcare engagement.

The study was only conducted at a single centre in stable patients presenting to a sleep laboratory. We only included patients with mild to moderate degrees of hypercapnia, and the recruitment rate of moderate degrees was lower than expected (mean baseline $paCO_2$ of 49 mmHg). Hence, the outcome

may only apply to OHS with mild hypercapnia. There may also be a selection bias towards participants with more symptoms and less severe respiratory failure. Furthermore, only two brands of auto-titrating devices were used in the trial and although these two manufacturers are the largest CPAP producers, recently, there are other APAP devices on the market. Finally, although block randomisation was used to assign participants, there were differential baseline characteristics (age, cardiovascular disease, $PaCO_2$) between the two PAP arms.

Ultimately, this pilot study did not support the non-inferiority of APAP in improving gas exchange among our study population. However, some of the study findings, such as lower adherence and lower pressure settings, suggest that APAP may not be an effective alternative to fCPAP in some patients with OHS and sOSA. APAP also appears less effective in some of the patient-centred outcomes, such as sleep quality. Based on these preliminary findings, APAP does not replace the need for a CPAP titration study, nor is it recommended as the long-term PAP option over fCPAP for this population group. However, APAP may offer a temporary treatment option while awaiting a formal pressure determination study.

This pilot study serves to guide the design of a larger adequately powered study to account for the difficulties with participant recruitment and retention. Ideally, a multi-centre trial, over a greater duration may address some of the uncertainties raised in this current study. Alternatively, data could be collected from sleep registries where APAP are already in use for OHS patients. Further phenotyping of OHS patients and optimising pressure ranges may see greater applicability of APAP or in a multimodal approach (such as positional and weight loss therapy using incretins mimetics[27]). Further research is also required to identify potential barriers to healthcare engagement and to develop strategies to address this in order to improve outcomes in OHS management.

6.6 Conclusion

This single-centre pilot study identified several important challenges related to participant recruitment and retention. Strategies to address the decline in recruitment during post-COVID period and higher drop-out among participants residing in rural areas will need to be in place before a full-size trial. Owing to its limited sample size, our pilot randomised controlled trial was unable to conclude that APAP is non-inferior to fCPAP for reducing hypercapnic respiratory failure among participants with obesity hypoventilation syndrome and concurrent severe obstructive sleep apnoea. Nevertheless, several patient-relevant trends, including sleep quality, treatment adherence, favoured fCPAP. A larger, adequately powered, multi-centre study is needed to confirm these observations and provide more precise estimates of comparative efficacy between APAP and fCPAP for treatment of OHS+sOSA.

6.7 References

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Chapter 7 General Discussion and Future Directions

7.1 Clinical Impact of Obesity-associated Hypoventilation Disorders

Chapters 3 and 4 explored the consequences of obesity hypoventilation disorders. The majority of research so far in this field has focused on aspects of respiratory failure. Although the overall mortality has improved with long-term positive airway pressure therapy, this group of patients still has worse survival when compared to non-hypercapnic obese, mainly due to cardiovascular disease. As this group of patients represent the extreme end of sleep disordered breathing, they are anticipated to have a high burden of symptoms, beyond that of what is observed in simple OSA. This in turn, translates to potential negative neurocognitive outcomes.

In Chapter 3, we compared two groups of obesity-associated hypoventilation disorders, OHS patients with severe OSA and those with comorbid airways disease in addition to OSA, evaluating symptom burden and neurocognitive function. While some studies suggest COPD-OSA overlap syndrome experience less daytime sleepiness[1] compared to OSAS, other studies have reported more sleep fragmentation and worse quality of sleep than either condition occurring alone[2]. Overall, the clinical features of hypercapnic overlap syndrome are not well defined. Our study did not find significant differences in sleepiness, sleep quality or quality of life between the two study groups. The two groups also had similar neurocognitive function at baseline.

Sleep (intermittent) hypoxia and sleep fragmentation are proposed intermediary links between cognitive dysfunction and sleep-disordered breathing, with most of the research interest stemming from OSA study populations. In our study populations, the AHI (a reflection of ODI and arousal index) was higher in the OHS-OSA group, which in theory should account for worse symptom burden and neurocognitive function. This is potentially offset by the fact that the two groups had similar hypoxic burden and other sleep parameters during their diagnostic sleep study, as well similar degrees of daytime hypercapnic respiratory failure.

Both groups improved with positive airway pressure therapy (PAP) in terms of sleepiness, sleep quality and quality of life, with no between-group differences in response, indicating that the underlying hypoventilation disorder did not influence PAP responsiveness. The sleepiness and quality of life responses correlated with improvements in $PaCO_2$ and arousal index. Although this is not an

unexpected finding, it may be useful to phenotype traits to better predict PAP responsiveness and adherence. However, this will need to be further explored in larger studies involving patients with obesity hypoventilation, and ideally with longitudinal follow-up to fully assess the impact of PAP therapy that may not be apparent in short term studies.

In our study, outcomes of neurocognitive function did not significantly change with PAP therapy. This is even though our study population represented an extreme form of sleep disordered breathing (in terms of nocturnal hypoxia, hypercapnia and sleep fragmentation) with significant baseline symptom burden. Several potential possibilities could contribute to this negative finding. Our study duration was too short, and the study numbers were underpowered to detect meaningful change. The benefits of PAP therapy in improving neurocognitive function are not as positive as expected – even in the well-studied OSA population, improvements in cognitive function have been mixed[3]. As our group of patients are likely to have had exposure to severe sleep-disordered breathing over a longer period of time, potentially some of the cognitive deficits are established and no longer reversible even with improvements in gas exchange. These uncertainties will need to be addressed in a different study design. While it may be difficult to conduct an adequately powered study over a longer study period, advancements in biomarkers (neurodegenerative blood biomarkers, mean wakefulness test, neuroimaging, HD-EEG) and improvements in understanding of neural mechanisms may offer alternative pathways to further our appreciation of pathways leading to cognitive impairment, and which domains are responsive to PAP therapy.

In chapter 4, we explore the use of pulse wave velocity and aortic pressure augmentation to characterise the cardiovascular risk in obesity hypoventilation syndrome. We identified that although the measures of aortic stiffness are within the normal reference range, the augmentation index fell in the highest tertile of risk in the HeartScore prediction tool and was higher than that of OSA subjects. Our obesity hypoventilation cohort also had higher central pulse pressure, suggesting higher left ventricular afterload. We did not identify a significant improvement in any of the cardiovascular biomarkers with positive-airway pressure therapy. The effects of PAP therapy on cardiovascular outcomes will require more clarification involving a larger study population and over a longer period of follow up. Future studies can also look to incorporate more dynamic blood pressure measurements such as ambulatory blood pressure monitoring at home, wearables (which may overcome the technical limitations, such as cuff availability and arm shape mismatch) and finger cuff beat-to-beat blood pressure monitoring to assess the burden of hypertension in relation to the development of

structural heart disease in OHS, the relationship with sleep-related respiratory events as well as the impact of PAP therapy and weight loss, particularly during sleep.

There have been mixed research outcomes with respect to cardiovascular benefits of sleep disordered breathing. Longitudinal and biomarker studies indicate that patients treated for sleep-disordered breathing have better cardiovascular outcomes. These positive findings are not replicated in randomised clinical trials[4-6]. Potential explanation for the discrepancy in findings includes patient selection, as patients with more severe disease (greater hypoxic burden) and sleepier were excluded, while overall adherence was poor. Our study population is unlikely to fall in that category, as adherence from previous PAP trials in OHS was higher than OSA/CSA RCTs, while they are also sleepier and have greater hypoxic burden among patients with sleep-disordered breathing. Nonetheless, future cardiovascular-focused RCTs comparing PAP therapy to a control group are unlikely to be conducted, as it will be unethical to withhold PAP treatment from OHS patients due to their symptom burden and the data indicating worse outcomes overall in untreated OHS. The available longer-term cardiovascular data indicate that there was no difference between CPAP and NIV in improvement in pulmonary pressures, LV diastolic function, blood pressure and cardiovascular events in OHS-sOSA[7]. Over half of the mortality was due to cardiovascular causes. While no control group existed for this group, it does suggest that although PAP therapy improves respiratory mortality outcomes, it has less of an effect on cardiovascular mortality. In addition, a separate study in OHS without OSA showed no long-term benefit in cardiovascular events or blood pressure with NIV compared to control[8]. Given that the cardiovascular event rate remains high despite adherence to PAP therapy, a holistic approach to OHS treatment is required.

Addressing their underlying obesity, a critical risk factor in the development of OHS, may improve not only their respiratory failure, but also one of the main drivers via direct and indirect effects of cardiovascular morbidity and mortality. Addressing obesity via conventional diet and exercise have not been proven effective with respect to sustained weight loss, while bariatric surgery carries immediate peri-operative risks (potentially higher in OHS, due to the presence of respiratory failure and cardiovascular comorbidities) and long-term risk of nutritional deficiencies.

Recently, there have been exciting developments in the field of pharmacotherapy in the treatment of obesity. Randomised clinical trials showed that various incretin mimetics provided substantial and sustained weight reductions[9, 10]. In addition, the use of incretin mimetics has also demonstrated a reduction in cardiovascular death, worsening heart failure, myocardial infarction, stroke, steatohepatitis, prevention of diabetes and chronic kidney disease progression, while improving physical function in a variety of study populations. In the field of sleep medicine, tirzepatide, a long-

acting glucose-dependent insulinotropic polypeptide GIP) receptor and glucagon-like peptide-1 receptor agonist, is shown to improve sleep parameters (AHI and hypoxic burden), sleep-related patient-reported outcomes and cardiovascular biomarkers (systolic blood pressure, hsCRP) in moderate to severe obstructive sleep apnoea[11].

Unfortunately, participants with obesity hypoventilation were actively excluded in the Surmount-OSA trial. Given the positive cardiovascular outcomes in several studies thus far, a future trial exploring the benefits of incretin mimetics in obesity hypoventilation is also warranted. A potential study design could randomise OHS patients to tirzepatide or placebo while assessing outcomes of short-term cardiovascular biomarkers (blood pressure, pulse wave analysis and velocity, CRP, lipid profile, HbA1c, TTE parameters), respiratory failure parameters (PaCO2/hypoxic burden in those who decline PAP therapy; $TcCO_2$/hypoxic burden off PAP therapy or re-titration study in those who are PAP-adherent; lung function assessments) and symptoms (6MWT, dyspnoea and sleep questionnaires). Further studies can also look to integrate different approaches of weight loss (the use of pharmacotherapy for pre-bariatric surgery optimisation or post-bariatric surgery weight loss maintenance). More data is desired in determining the most effective, acceptable and cost-effective approach in addressing weight loss and finally reversing OHS.

7.2 Phenotyping Hypoventilation Disorders to Assist with Choosing PAP Modality

Chapter 5 compared two modes of positive airway pressure therapy in improving respiratory failure with both obesity and COPD. In real-world clinical practice, hypercapnic patients who present to the hospital often have mixed pathologies or multiple contributing factors towards the development of respiratory failure, in particular a combination of obesity and airways disease. As these patients are often excluded from clinical trials due to the presence of another comorbidity (airway obstruction from OHS trials and obesity or OSA from COPD trials), our study is important in it addresses an area of research void.

In our pilot RCT, we demonstrated that bilevel PAP therapy was superior to fixed CPAP therapy in reversing respiratory failure during the three-month treatment period. It is interesting to note that the arm that was treated with fixed CPAP also had reduced PaCO2 (some even normalised) at the end of the three-month trial. The mechanism for this is not clear but could be due to several factors. It highlights that addressing their underlying upper airway obstruction during sleep will reduce the OSA contribution towards the development of hypoventilation. During each obstructive event, there is an accumulation of CO2. While this is normally adequately cleared in most patients with OSA during inter-

apnoeic hyperventilation, this is not the case in patients with severe obesity and significant lung disease. Another benefit of CPAP in this group of patients is countering intrinsic PEEP. COPD patients have increased small airway resistance and impaired elastic recoil. Obesity also increases small airway resistance and can lead to gas trapping. The exogenous PEEP provided by PAP devices will help splint the lower airways, thereby improving alveolar ventilation and reducing VQ mismatch. CPAP also has a volume inflation effect and depending on where the patient is lying on the lung compliance curve may also reduce their work of breathing. These various factors that improve nocturnal ventilation may over time reset the central ventilatory drive. However, as hypothesised, bilevel PAP was superior to CPAP in resolving respiratory failure as the pressure support will further augment ventilation and allow resting of respiratory muscles. Unlike in pure OHS, where the two modes of PAP therapy are equivalent, in obese hypercapnic COPD patients, bilevel PAP therapy should be used as first line. Our pilot RCT supports the current standard of care, where hypercapnic overlap syndrome should be placed on nocturnal bilevel PAP therapy (compared to non-hypercapnic overlap syndrome being treated with CPAP therapy).

As our trial had a small sample size, future trials with a larger study population with adequate power to detect other clinically important outcomes (such as hospitalisation, cost, cardiovascular, neurocognitive, and exercise tolerance). As this group of patients is heterogeneous in terms of sleep disordered breathing (AHI, hypoxic burden), obesity (BMI and adipose distribution), lung function (severity of obstruction, degree of gas trapping and lung volume pattern) and gas exchange abnormalities (PaO2 and PaCO2), our small study will not be able to phenotype patients further – whether certain features are more likely to fail CPAP than others. Our bilevel arm only utilised S mode. Other bilevel modes and optimal bilevel settings were not explored. Future studies could assess whether a targeted volume (volume-assured pressure support to provide more consistent ventilation) and variable EPAP (AE mode to counteract variable upper airway obstruction) has better efficacy or acceptance.

Our patients are recruited from a combination of post-inpatients admission for acute exacerbation or directly from sleep laboratories. The timing of commencing PAP therapy is also not addressed in our studies. Current recommendations whether inpatients should be discharged on bilevel therapy is different between hypercapnic COPD patients and OHS patients. Hypercapnic COPD following acute exacerbation are trialled off bilevel therapy with an early follow up and repeat blood gas to determine whether these patients should be commenced on long-term NIV. Does the presence of OSA or significant obesity, as observed in our study population, change that decision and favour a similar approach to that of OHS (discharged on bilevel)?

As large clinical trials are difficult to conduct in this group of population, the alternative to answer some of these research questions could come from multi-centre respiratory failure registries, which is better positioned to capture real world patients who present to sleep clinics or post-hospitals admissions.

Chapter 6 compared two modes of CPAP, fixed (fCPAP) and auto-titrating (APAP), in the treatment of obesity hypoventilation syndrome with severe OSA phenotype (OHS-sOSA). While APAP is extensively used in treating OSA, it is not recommended to replace the need for in-laboratory CPAP titration for pressure determination or as the long-term PAP mode in OHS. Nonetheless, it is likely a proportion of real-world OHS patients are treated with APAP. Our study sought to assess whether APAP is a safe and effective alternative to fCPAP in treatment of OHS-sOSA.

While the primary outcome in resolving respiratory failure in our study was inconclusive, there were findings that caution against the use of APAP in OHS-sOSA. The absolute improvement in hypercapnia and the proportion of participants who are normocapnic at the end of the three-month PAP treatment period favoured the fCPAP arm. Treatment adherence was lower in the APAP arm – a concerning finding as PAP adherence has been associated with clinically important outcomes in prior OHS literature. The pressure range APAP was operating in during the treatment period was also lower than what was recommended in the formal titration study, suggesting the APAP algorithm may be undertreating participants with OHS-sOSA. In addition, the improvements in sleep quality and quality of life were only observed in the fCPAP arm.

We suspect that an adequately powered study is likely to confirm the inferiority of APAP in the treatment of OHS-sOSA, and our pilot study will assist in the design of a larger RCT. Given that a portion of participants in the APAP arm reached normocapnia, highlighting the importance of OSA and nocturnal CO2 accumulation in the pathogenesis of OHS, future research can also look to assess whether APAP set with an appropriate pressure range based on an in-laboratory pressure determination study in select patients is effective. Given the potential benefits of incretin mimetics in reversing obesity and thereby reducing the burden of sleep-disordered breathing, future trials could also assess whether APAP can be utilised in a multi-modal approach.

Our trial also highlighted the difficulties of recruitment of patients with OHS. Future research could look to expand patient recruitment and engage in other respiratory failure centres (ideally across multiple international sites) to diversify OHS patient population and improve statistical power or the development of large registries. This group of patients is also hard to capture, and better methods are

required to improve healthcare engagement. Earlier identification of patients at risk and intervention may also prevent the development of OHS and OHS-related complications.

7.3 References

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Appendix

Tables

Table 2.1. Frequency of comorbid cardiovascular conditions in OHS study populations.

Pub. Year	Authors	Location	Study Design	Size	Age	BMI	IHD/ CAD	CHF	Arr	CVA	PVD	PHT
2001	Berg et al.[1]	Canada	Retrospective	20	53	47	30%	60%	-	-	-	30%
2004	Nowbar et al.[2]	USA	Prospective	47	55	45	28%	32%	-	-	-	11%
2007	Budweiser et al.[3]	Germany	Prospective	69*	60	42	29% has heart disease					
2010	Trakada et al.[4]	Greece	Prospective	38	57	40	8%	13%	0%	0%	-	-
2013	Alzaabi et al.[5]	UAE	Retrospective	18	55	45	22%	-	-	-	-	33%
2013	Kauppert et al.[6]	Germany	Prospective	64	64	45	15%	-	-	-	-	-

2013	Salord et al.[7]	Spain	Prospective	29	59	44	**7%**	-	-	**14%**	-	-
2015	Alawami et al.[8]	New Zealand	Retrospective	47	60	49	-	-	**36%**	-	-	-
2015	Castro-anon et al.[9]	Spain	Retrospective	110	64	42	**13%**	**11%**	**18%**	**3%**	**4%**	-
2015	Masa et al.[10]	Spain	Prospective	221	60	48	**10%**	**15%**	**8%**	**8%**	**6%**	**9%**
2016	BaHammam et al.[11]	Saudi Arabia	Prospective	48M 49F	49M 62F	44	**15%M 13%F**	**8%M 14%F**	-	-	-	-
2016	Cortese et al.[12]	USA	Prospective	15	51	49	-	**40%**	-	-	-	-
2016	Kaw et al. [13]	USA	Retrospective	194	63	41	**46%**	**43%**	**22%**	**13%**	-	**8%**
2016	Marik et al.[14]	USA	Retrospective	600	58	48	**39% admitted with heart failure**					
2016	Masa et al.[15]	Spain	Prospective	86'	68	40	**10%**	**24%**	**11%**	**9%**	**15%**	**14%**

2016	Carter et al.[16]	USA	Prospective	17	50	49	-	**35%**	-	-	-	-
2017	Almeneessier et al.[17]	Saudi Arabia	Prospective	77	61	43	**12%**	**13%**	-	-	-	-
2017	Lacedonia et al.[18]	Italy	Retrospective	145	58	42	**34% has heart disease**					
2018	Al Khadra et al.[19]	Saudi Arabia	Retrospective	104	60	47	**37%**	**74%**	**22%**	**3%**	-	-
2018	Al Otair et al.[20]	Saudi Arabia	Prospective	113	58	43	**12%**	-	-	-	-	-
2018	Bhattacharjee et al. [21]	USA	Prospective	12	51	49		**33%**				
2018	Bouloukaki et al.[22]	Greece	Prospective	252	63	43	**11%**	**14%**	**8%**	**5%**	-	-
2020	Kreivi et al. [23]	Finland	Prospective	206	52	46	**14%**	-	**21%**	**4%**	-	-

Age is in years. BMI is in kg/m^2. BMI = body mass index; IHD/CAD = ischaemic heart disease or coronary artery disease; CHF = congestive heart failure; Arr = cardiac arrhythmia; CVA = cerebral vascular accident; PVD = peripheral vascular disease; PHT = pulmonary hypertension.

Table 2.2. Reported rates (%) of hypertension, dyslipidaemia, type 2 diabetes mellitus and smoking history in OHS study populations.

Pub. Year	Author	Study Location	Study Design	Size	Age	BMI	Hypertension	Dyslipidaemia	Diabetes Mellitus	Smoking History
2001	Berg et al.[1]	Canada	Retrospective	20	53	47	55%	NA	50%	NA
2004	Nowbar et al.[2]	USA	Prospective	47	55	45	50%	NA	NA	NA
2007	Budweiser et al.[3]	Germany	Prospective	69*	60	42	73%	12%	22%	NA
2009	Borel et al.[24]	France	Prospective	14	57	41	86%	43%	54%	NA
2010	Monneret et al. [25]	France	Prospective	15	56	41	53%	47%	33%	20%
2010	Trakada et al.[4]	Greece	Prospective	38	57	40	53%	8%	24%	NA
2013	Salord et al.[7]	Spain	Prospective	29	59	44	76%	35%	35%	55%
2013	Kauppert et al.[6]	Germany	Prospective	64	64	45	100%	62%	67%	67%
2013	Alzaabi et al.[5]	UAE	Retrospective	18	55	46	56%	NA	44%	NA

2015	Castro-anon et al.[9]	Spain	Retrospective	110	64	42	**75%**	**26%**	**27%**	**NA**
2015	Masa et al.[10]	Spain	Prospective	221	60	44	**68%**	**43%**	**37%**	**24%***
2015	Alawami et al.[8]	New Zealand	Retrospective	47	60	49	**66%**	**NA**	**43%**	**NA**
2016	Masa et al.[15]	Spain	Prospective	86'	68	40	**80%**	**43%**	**38%**	**12%***
2016	Marik et al.[14]	USA	Retrospective	600	58	48	**28%**	**NA**	**38%**	**NA**
2016	Carter et al.[16]	USA	Prospective	17	50	49	**94%**	**NA**	**35%**	**NA**
2016	Kaw et al.[13]	USA	Retrospective	194	63	41	**83%**	**NA**	**53%**	**52%**
2016	Cortese et al.[12]	USA	Prospective	15	51	49	**87%**	**27%**	**33%**	**40%**
2016	BaHammam et al.[11]	Saudi Arabia	Prospective	144 48M 96F	57 49M 62F	45	**71%** **54% M** **83% W**	**29%** **27% M** **45% W**	**51%** **29% M** **64% W**	**NA**
2017	Lacedonia et al.[18]	Italy	Retrospective	145	58	42	**74%**	**26%**	**40%**	**49%**

2017	Almeneessier et al.[20]	Saudi Arabia	Prospective	77	61	43	**77%**	**NA**	**56%**	**18%**
2018	Al Otair et al.[20]	Saudi Arabia	Prospective	113	58	43	**74%**	**NA**	**53%**	**NA**
2018	Al Khadra et al.[19]	Saudi Arabia	Retrospective	104	60	47	**NA**	**NA**	**79%**	**NA**
2018	Bhattacharjee et al. [21]	USA	Prospective	12	51	49	**75%**	**25%**	**33%**	**50%**
2018	Bouloukaki et al.[22]	Greece	Prospective	252	63	43	**61%**	**34%**	**33%**	**36%**
2018	Mandal et al. [26]	England	Prospective	37	60	51	**NA**	**NA**	**49%**	**16%**
2020	Kreivi et al.[23]	Finland	Prospective	206	52	46	**83%**	**46%**	**62%**	**69%**

Age is in years. BMI is in kg/m^2. BMI = body mass index.

Table 2.3. Rates of pulmonary hypertension in OHS study populations.

Pub. Year	Author	Study Location	Study Design	Size	Age	BMI	Technique	Definition of PHT (mmHg)	Prevalence of PHT
1988	Sugerman et al. [27]	USA	Prospective	26	44	NA	RHC	mPAP>20	88%
2001	Kessler et al. [28]	France	Prospective	26	61	40	RHC	mPAP>20	59%
2012	Castro-anon et al. [29]	Spain	Prospective	30	69	42	TTE	RVO	43%
2013	Alzaabi et al. [5]	UAE	Retrospective	18	55	45	Records or TTE	Not clear	33%
2013	Kauppert et al. [6]	Germany	Prospective	21	64	45	RHC	mPAP>20	81%
2013	Marik et al. [30]	USA	Retrospective	61	59	49	TTE	SPAP>35	77%
2014	Held et al. [31]	Germany	Retrospective	18*	62	36	RHC or TTE	mPAP>25 (rest), or >50 (ex), or TTE SPAP>50	N/A Mean 49mmHg

2015	Alawami et al. [8]	New Zealand	Retrospective	47	60	49	TTE	SPAP>30	88%
2017	Almeneessier et al. [17]	Saudi Arabia	Prospective	77	61	43	TTE	SPAP>40	69%
2017	Onofri et al. [32]	Spain	Prospective	7	60	50*	TTE	SPAP>40	42%
2018	Corral et al. [33]	Spain	Prospective	221	60	44	TTE	SPAP>40	55%

Age is in years. BMI is in kg/m^2. PHT definition is in mmHg. BMI = body mass index; PHT = pulmonary hypertension; RHC = right heart catheterisation; TTE = transthoracic echocardiogram.

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Table 3.1. Baseline characteristics

	OHS (N=45)	OHAD (N=32)	P value
Age (years)	51 (14)	61 (11)	0.002
Gender (% female)	33	31	0.85
BMI (kg/m^2)	52 (8.5)	43 (7.2)	<0.001
Neck circumference (cm)	50 (4.7)	48 (4.5)	0.17
Waist circumference (cm)	145 (14)	133 (10)	<0.001
Hip circumference (cm)	149 (18)	134 (15)	0.001
Smoking status (% smoker) ^	51	97	<0.001
Spirometry			
FEV1 (L)	1.9 (0.77)	1.4 (0.58)	N/A
FEV_1 (% predicted)	60 (19)	48 (19)	N/A
FVC (L)	2.4 (0.97)	2.3 (0.84)	0.19
FVC (% predicted)	62 (18)	64 (22)	0.57
FER (%)	81 (5.9)	60 (9.7)	N/A
ABG			
$PaCO_2$ (mmHg)	54 (8.2)	54 (7.4)	0.86
PaO_2 (mmHg)	64 (15)	59 (10)	0.09
Bicarbonate (mmol)	32 (6.4)	32 (4.6)	0.75
Base Excess (mmol)	6 (3.9)	6 (4.0)	0.88
pH	7.39 (0.03)	7.39 (0.03)	0.46
PSG			
AHI (events/hour)	87 (34)	59 (35)	<0.001
Arousal (events/hour)	63 (38)	51 (32)	0.22
%TST <90%	76 (29)	78 (25)	0.77
%TST <80%	39 (30)	26 (22)	0.08
%NREM Sleep	89 (7.7)	89 (8.8)	0.68
%SWS	14 (18)	14 (15)	0.99
%REM Sleep	11 (7.7)	11 (8.8)	0.66

Displayed as mean (standard deviation), except for %TST <90% and %TST <80%, which are displayed as median (interquartile range).

^Smokers included ex-smokers (OHAD=17, OHS=13) and current smokers (OHAD = 14, OHS=10)

N/A – not applicable

Table 3.2 Baseline Measurements and Changes with Treatment Related to Quality of Life, Quality of Sleep and Sleepiness Scores

	OHS [Mean (SD)]	OHAD [Mean (SD)]	Baseline Intergroup Differences~	
	Baseline	Baseline	Mean (CI)	P Value
ESS	14 (5.6)	12 (5.4)	-1.1 (-4.0, 1.1)	0.27
Global PSQI	10 (3.2)	11 (4.8)	0.66 (-1.3, 2.6)	0.50
SF36				
Physical Component	29 (9)	32 (11)	2.6 (-2.3, 7.5)	0.30
Mental Component	33 (18)	27 (17)	-5.7 (-14, 2.9)	0.19

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburg Sleep Quality Index; SF36 = Medical Outcome Survey Short Form 36

~Adjusted for baseline values of the variables analysed and age

Table 3.3 Comparison of Impact of PAP therapy on Quality of Life, Quality of Sleep and Sleepiness Scores in OHS and OHAD

	OHS [Mean (SD)]		OHAD [Mean (SD)]		Intergroup Differences~	
	Baseline	Post-PAP (3m)	Baseline	Post-PAP (3m)	Mean (CI)	P Value
ESS	14 (5.6)	6.3 (5.2)**	12 (5.4)	6.4 (5.4)**	1.5 (-2.1, 5.1)	0.42
Global PSQI	10 (3.2)	6.3 (4.2)**	11 (4.8)	7.2 (3.4)**	0.19 (-2.6, 3.0)	0.90
SF36						
Physical Component	29 (9)	35 (13)*	32 (11)	34 (11)	-4.2 (-12, 3.6)	0.28
Mental Component	33 (18)	41 (19)*	27 (17)	41 (16)**	4.4 (-7.9, 16)	0.48

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburg Sleep Quality Index; SF36 = Medical Outcome Survey Short Form 36

~Adjusted for baseline values of the variables analysed and age

* $p<0.05$ intragroup difference (Post-PAP (3m) – baseline)

** $p<0.01$ intragroup difference (Post-PAP (3m) – baseline)

BPAP adherence in OHS: 6.1 ($\pm$2.1) hours

CPAP adherence in OHS: 5.8 ($\pm$2.4) hours

BPAP adherence in OHAD: 4.1 ($\pm$2.5) hours

CPAP adherence in OHAD: 5.6 ($\pm$2.3) hours

Table 3.4 Baseline Neurocognitive Outcomes in OHS and OHAD

	OHS [Mean (SD)]	OHAD [Mean (SD)]	Baseline Intergroup Differences~	
	Baseline	Baseline	Mean (CI)	P Value
PVT				
Lapses	9.2 (12)	8.9 (11)	-0.3 (-6.0, 5.4)	0.92
Median: RT (ms)	338 (96)	338 (82)	0.2 (-44, 44)	0.99
Mean Slowest 10% 1/RT (s)	1.9 (0.89)	1.9 (0.63)	0.002 (-0.38, 0.39)	0.99
Digit Span Forward	7.3 (2.8)	7.2 (2.0)	-0.03 (-1.3, 1.2)	0.96
Digit Span Backward	5.2 (2.5)	5.2 (2.0)	-0.03 (-1.2, 1.1)	0.96
Trail Making Test	116 (54)	132 (51)	15 (-14, 44)	0.30
Digit Symbol Substitution	43 (13)	36 (11)	-7.7 (-14, -1.4)	0.02

Abbreviations: PVT = psychomotor vigilance test; RT = reaction time

~Adjusted for baseline values of the variables analysed and age

* $p<0.05$ intragroup difference (3m – baseline)

Table 3.5 Impact of PAP therapy on Outcomes of Neurocognitive Tests in OHS and OHAD

	OHS [Mean (SD)]		OHAD [Mean (SD)]		Baseline Intergroup Differences~	
	Baseline	Post-PAP (3m)	Mean (CI)	Post-PAP (3m)	Mean (CI)	P Value
PVT						
Lapses	9.2 (12)	5.5 (12)	8.9 (11)	6.0 (11)	0.8 (-7.5, 9.1)	0.85
Median: RT (ms)	338 (96)	310 (89)	338 (82)	306 (67)	-4.6 (-64, 56)	0.88
Mean Slowest 10% RT (s)	1.9 (0.89)	2.2 (0.74)	1.9 (0.63)	2.2 (0.59)*	-0.02 (-0.54, 0.50)	0.95
Digit Span Forward	7.3 (2.8)	7.6 (2.9)	7.2 (2.0)	8.2 (2.0)	0.65 (-1.25, 2.5)	0.49
Digit Span Backward	5.2 (2.5)	5.7 (2.5)	5.2 (2.0)	5.4 (1.9)	-0.24 (-1.9, 1.4)	0.77
Trail Making Test	116 (54)	96 (36)	132 (51)	116 (43)	4.2 (-32, 40)	0.82
Digit Symbol Substitution	43 (13)	47 (11)	36 (11)	40 (13)	0.6 (-8.3, 9.5)	0.89

Abbreviations: PVT = psychomotor vigilance test; RT = reaction time

~Adjusted for baseline values of the variables analysed and age

* $p<0.05$ intragroup difference (Post-PAP (3m) – baseline)

BPAP adherence in OHS: 6.1 ($\pm$2.1) hours

CPAP adherence in OHS: 5.8 ($\pm$2.4) hours

BPAP adherence in OHAD: 4.1 ($\pm$2.5) hours

CPAP adherence in OHAD: 5.6 ($\pm$2.3) hours

Table 4.1. Baseline characteristics

	Recruited OHS Participants (N=28)
Age – yr	55 ± 12.5
Female sex – no. (%)	13 (46)
Race or ethnic group – no. (%)	
- White	21 (75)
- Polynesian	4 (14)
- Other	3 (11)
BMI – kg/m^2	54 ± 9.9
Weight – kg	152 ± 31.3
Smoking status	
- Non-smokers – no. (%)	13 (46)
- Ex-smokers – no. (%)	10 (36)
- Current smoker	5 (18)
Cardiovascular History	
- Hypertension – no. (%)	13 (46)
- Diabetes mellitus – no. (%)	9 (32)
- Dyslipidaemia – no. (%)	6 (21)
- Ischaemic heart disease – no. (%)	4 (14)
- Arrhythmia – no. (%)	5 (18)
- Echo abnormality – no. (%)	5 (18)
Spirometry	
- FEV1 – L	2.07 ± 0.68
- FEV_1 % predicted	67 ± 16.7
- FVC – L	2.60 ± 0.87
- FVC % predicted	65 ± 14.1
- FER – %	80 ± 5.7
ABG	
- $PaCO_2$ – mmHg	49 ± 2.6
- PaO_2 – mmHg	64 ± 7.9
- Bicarbonate – mmol	31 ± 1.7
PSG	
- AHI – events/hour	88 ± 31
- %TST<90% – %	72 ± 29
- SpO2 average – %	83 ± 6

Displayed as mean ± standard deviation or number of participants (percentage of total).

Table 4.2 Baseline Measurements of Pulse Wave Analysis and Pulse Wave Velocity

	Baseline Measurements Mean ± SD (% outside of recommended target)			**P value**
	All OHS Participants	**No CV Diagnosis**	**Known HTN/CV Diagnosis**	
PWA				
PSBP (mmHg)	137 ± 12	137 ± 12 *(>130 = 22%, >110 = 100%)*	136 ± 13 *(>120 = 100%)*	0.96
PDBP (mmHg)	79 ± 12	84 ± 8 *(>90 = 33%, >80 = 67%)*	76 ± 13 *(>90 = 78%)*	0.17
PPP (mmHg)	58 ± 9	53 ± 8	61 ± 9	0.08
CSBP (mmHg)	124 ± 11	124 ± 11 *(>110 = 100%)*	124 ± 11 *(>110 = 91%)*	0.95
CDBP (mmHg)	81 ± 12	86 ± 8 *(>80 = 55%)*	79 ± 13 *(>80 = 64%)*	0.21
CPP (mmHg)	43 ± 9	39 ± 7	45 ± 8	0.09
PPP:CPP (ratio)	1.35 ± 0.15	1.39 ± 0.10	1.33 ± 0.17	0.44
AP (mmHg)	14.5 ± 8.2	9.5 ± 5.1	17.5 ± 8.3	0.03
Aix (%)	31.5 ± 13.9	23.4 ± 9.8 *(>33% = 27%)*	36.2 ± 13.8 *(>33% = 45%)*	0.04
AIx@75 (%)	33.1 ± 13.6	25.7 ± 9.2	37.3 ± 13.8	0.06
PWV				
cfPWV (m/s)	7.25 ± 0.92	7.25 ± 0.93 *(>10 = 0%)*	7.25 ± 0.92 *(>10 = 0%)*	0.99
cfPTT (ms)	80 ± 14	77 ± 8	81 ± 16	0.53

Abbreviations: PWA = pulse wave analysis, PSBP = peripheral systolic blood pressure, PDBP = peripheral diastolic blood pressure, PPP = peripheral pulse pressure, CSBP = central systolic blood pressure, CDBP = central diastolic blood pressure, PPP = central pulse pressure, PPP:CPP = ratio of peripheral to central pulse pressure, AP = central augmentation pressure, AIx = augmentation index, AIx@75 = augmentation index corrected to a heart rate of 75bpm

Recommended targets:

PSBP: <120mmHg normal; 120-130 mmHg stage 1; 130-140mmHg stage 2; >140mmHg stage 3

PDBP: <80mmHg normal; 80-90mmHg stage 1; >90mmHg stage 2

CSBP: <110mmHg normal; 110-130mmHg stage 1; >130mmHg stage 2

CDBP: <80mmHg normal; 80-90mmHg Stage1; >90mmHg Stage 2

Aix: <33%

Aix@75: <40%

PWV: <10m/s

p-value based on two-tailed non-paired t-test.

Table 4.3 Baseline Serum Cardiovascular Biomarkers

	Baseline Measurements Mean ± SD (% outside of recommended target)		
	All OHS Participants	**No DM Diagnosis**	**Known DM Diagnosis**
Glucose Profile			
Fasting Glucose (mmol/L)	7.00 ± 2.11	8.17 ± 2.69 *(>5.6 = 78%, >7 = 33%)*	6.23 ± 1.1 *(>7 = 33%)*
HbA1c (%)	6.7 ± 1.77	8.1 ± 2.08 *(>5.7 = 56%, >6.5 = 22%)*	5.9 ± 0.87 *(>7 = 20%)*
	All OHS Participants	**No Dyslipidaemia Diagnosis**	**Known Dyslipidaemia Diagnosis**
Lipid Profile (mmol/L)			
Total Cholesterol	4.35 ± 1.48	4.43 ± 1.50 *(>5.2 = 15%)*	3.87 ± 1.28 *(>5.2 = 33%)*
HDL Cholesterol	1.18 ± 0.27 *(<1^{M}, <1.3^{F} = 36%)*	1.17 ± 0.289	1.22 ± 0.12
LDL Cholesterol	2.33 ± 0.90	2.29 ± 0.98 *(>2.6 = 44%)*	2.50 ± 0.40 *(>2.6 = 50%)*
Triglyceride	1.69 ± 0.70 *(>2 = 31%)*	1.62 ± 0.75	2.00 ± 0.24
	All OHS Participants	**No CV Diagnosis**	**Known CV Diagnosis**
Cardiovascular Biomarkers			
Troponin (ng/L)	20 ± 17 *(>14 = 60%)*	12 ± 7	32 ± 21
NT-proBNP (ng/L)	109 ± 95 *(>125 = 43%)*	74 ± 81	171 ± 85
AST/ALT ratio	1.20 ± 0.40 *(>1 = 64%)*	1.17 ± 0.32	1.23 ± 0.48
CRP (mg/L)	19 ± 14 *(>3 = 93%)*	23 ± 17	20 ± 13

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-proBNP = NT pro-B-Natriuretic peptide; AST/ALT ratio = Aspartate Aminotransferase to Alanine Aminotransferase ratio; CRP = C-reactive protein; OHS = obesity hypoventilation syndrome; DM = type 2 diabetes mellitus; CV = cardiovascular

Recommended targets:

Fasting glucose (mmol/L): <5.6 = normal fasting glucose, 5.6-7 = impaired fasting glucose, >7 = diabetic range; target 4-7 in known diabetics [1, 2]

HbA1c (%): <5.7 normal, 5.7-6.5 prediabetes, >6.5 diabetes; target <7% in known diabetics [1, 2]

Total cholesterol: <5.2 mmol/L[3]

HDL: >1.3 mmol/L in females, >1 mmol/L in males[3]

LDL: <2.6 mmol/L[3]

Triglyceride: <2 mmol/L[3]

Troponin (ng/L) : Risk stratification, <6 = low; 6-12 = intermediate; >12 = high [4]

NT-proBNP: >125 ng/L abnormal[5]

AST/ALT ratio: >1 conveys higher cardiovascular risk [6]

CRP: >3mg/L conveys higher cardiovascular risk [7]

Table 4.4 Pulse Wave Analysis and Pulse Wave Velocity Pre- and Post-PAP Therapy

	Baseline Measurements Mean ± SD	**Post-PAP Measurements** Mean ± SD	**p-value**
PWA			
PSBP (mmHg)	137 ± 12	140 ± 19	0.65
PDBP (mmHg)	79 ± 12	80 ± 11	0.88
PPP (mmHg)	58 ± 9	60 ± 15	0.43
CSBP (mmHg)	124 ± 11	126 ± 16	0.89
CDBP (mmHg)	81 ± 12	81 ± 12	0.68
CPP (mmHg)	43 ± 9	45 ± 13	0.25
PPP:CPP (ratio)	1.35 ± 0.15	1.35 ± 0.14	0.79
AP (mmHg)	14.5 ± 8.2	11.9 ± 6.9	0.16
Aix (%)	31.5 ± 13.9	26.0 ± 12.0	0.08
AIx@75 (%)	33.1 ± 13.6	26.4 ± 12.6	0.10
PWV			
cfPWV (m/s)	7.25 ± 0.92	6.94 ± 1.02	0.57
cfPTT (ms)	80 ± 14	90 ± 21	0.13

Abbreviations: PWA = pulse wave analysis, PSBP = peripheral systolic blood pressure, PDBP = peripheral diastolic blood pressure, PPP = peripheral pulse pressure, CSBP = central systolic blood pressure, CDBP = central diastolic blood pressure, PPP = central pulse pressure, PPP:CPP = ratio of peripheral to central pulse pressure, AP = central augmentation pressure, AIx = augmentation index, AIx@75 = augmentation index corrected to a heart rate of 75bpm

p-value based on two-tailed paired t-test.

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Table 5.1 Baseline characteristics

	BPAP (N=16)	CPAP (N=16)	All (N=32)
Age (years)	57 (9.7)	65 (10.7)	61 (10.9)
Gender (% female)	50	13	31
BMI (kg/m^2)	45 (7.8)	40 (5.8)	43 (7.2)
Neck circumference (cm)	46 (4.9)	49 (3.5)	47 (4.4)
Waist circumference (cm)	132 (10.2)	133 (10.7)	133 (10.3)
Hip circumference (cm)	137 (14.1)	131 (14.8)	134 (14.5)
Spirometry			
FEV1 (L)	1.3 (0.6)	1.5 (0.5)	1.4 (0.6)
FEV_1 (% predicted)	45 (19.8)	51 (17.5)	48 (18)
FVC (L)	2.0 (0.9)	2.6 (0.7)	2.3 (0.8)
FVC (% predicted)	58 (23)	68 (20)	64 (22)
FER (%)	62 (8)	59 (11)	60 (10)
ABG			
$PaCO_2$ (mmHg)	57 (8)	52 (5.6)	54 (7.4)
PaO_2 (mmHg)	60 (11)	57 (9)	59 (10)
Bicarbonate (mmol)	33 (5)	31 (3.8)	32 (4.6)
Base Excess (mmol)	6.5 (4.5)	5.5 (3.4)	6 (4.0)
pH	7.39 (0.03)	7.39 (0.03)	7.39 (0.03)
PSG			
AHI (events/hour)	57 (34)	61 (37)	59 (35)
%TST <90%	93 (70-99)	84 (58-96)	85 (68-98)
%TST <80%	28 (17-47)	17 (5-37)	23 (7-43)
%NREM Sleep	90 (9)	87 (9)	89 (9)
%REM Sleep	10 (9)	13 (9)	11 (9)
$TcCO_2$ mean (mmHg)	57 (13)	50 (6)	54 (11)
$TcCO_2$ peak (mmHg)	69 (15)	65 (9)	67 (12)

Displayed as mean (standard deviation), except for %TST <90% and %TST <80%, which are displayed as median (interquartile range). Please note $TcCO_2$ data was only available for 7 of the BPAP arm and 5 of the CPAP arm.

Table 5.2 Baseline Measurements and Changes with Treatment Related to the Primary and Secondary Outcomes of Pulmonary Function and Weight

	BPAP [Mean (SD)]		CPAP [Mean (SD)]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
ABG						
PaCO2 (mmHg)	57 (8)	44 (8)* 0.000	52 (6)	47 (6)^ 0.03	0.06	0.02
Bicarbonate (mmol/L)	33 (5)	27 (3)* 0.000	31 (3)	28 (3)^ 0.02	0.2	0.03
Spirometry						
FEV1 (L)	1.3 (0.6)	1.6 (0.7) 0.17	1.5 (0.5)	1.6 (0.5) 0.85	0.39	0.33
FVC (L)	2.0 (0.9)	2.3 (0.9) 0.22	2.6 (0.7)	2.5 (0.6) 0.85	0.31	0.25
Weight (kg)	125 (28)	124 (28) 0.93	120 (19)	120 (19) 0.98	0.96	0.78

~Adjusted for baseline values of the variables analysed and age, gender, BMI, AHI and FEV1

* p<0.01 intragroup difference (3m – baseline)

^ p<0.05 intragroup difference (3m – baseline)

Table 5.3 Baseline Measurements and Changes with Treatment Related to Secondary Outcomes of Quality of Life , Sleep and Sleepiness

	BPAP [Mean (SD)]		CPAP [Mean (SD)]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
ESS	12 (6)	4 (3)* 0.000	13 (5)	8 (6)* 0.01	NS 0.28	NS 0.2
Global PSQI	12 (4)	6 (3)* 0.002	10 (5)	8 (4) 0.12	NS 0.17	NS 0.2
SF36						
Physical Component	32 (12)	35 (12) 0.45	32 (11)	32 (11) 0.88	NS 0.65	NS 0.67
Mental Component	19 (13)	39 (17)* 0.002	34 (17)	41 (15) 0.22	NS 0.12	NS 0.1

Abbreviations: ESS = Epworth Sleepiness Scale; PSQI = Pittsburg Sleep Quality Index; SF36 = Medical Outcome Survey Short Form 36

~Adjusted for baseline values of the variables analysed and age, gender, BMI, AHI and FEV1

* p<0.01 intragroup difference (3m – baseline)

^ p<0.05 intragroup difference (3m – baseline)

Table 5.4 Baseline Measurements and Changes with Treatment Related to the Secondary Outcomes of Neurocognitive Tests

	BPAP [Mean (SD)]		CPAP [Mean (SD)]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
PVT						
Lapses	13 (13)	8 (13) 0.2	5 (7)	5 (9) 0.95	NS 0.36	NS
Median: RT (ms)	361 (97)	315 (80) 0.12	316 (60)	297 (54) 0.49	NS 0.52	NS
Mean Slowest 10% RT (s)	1.6 (0.7)	2.1 (0.6)^ 0.03	2.1 (0.5)	2.3 (0.6) 0.44	NS 0.3	NS
Digit Span Forward	7 (2)	8 (2) 0.47	7 (2)	8 (2) 0.14	NS 0.64	NS
Digit Span Backward	5 (2)	5 (2) 0.98	5 (1)	6 (2) 0.58	NS 0.72	NS
Digit Span Task	12 (4)	13 (3) 0.65	13 (3)	14 (3) 0.22	NS 0.63	NS
Trail Making Test	129 (39)	116 (42) 0.57	134 (61)	116 (45) 0.34	NS 0.83	NS
Digit Symbol Substitution	36 (12)	39 (16) 0.54	35 (10)	40 (11) 0.3	NS 0.84	NS

Abbreviations: PVT = psychomotor vigilance test; RT = reaction time

~Adjusted for baseline values of the variables analysed and age, gender, BMI, AHI and FEV1

* p<0.01 intragroup difference (3m – baseline)

^ p<0.05 intragroup difference (3m – baseline)

PAP compliance

BPAP – 4.1 (2.5)

CPAP – 5.6 (2.3)

Significance = 0.096

Table 6.1. Baseline characteristics.

	fCPAP (N=13)	APAP (N=15)	All (N=28)
Age – yr	48 ± 9.0	60 ± 12.4	55 ± 12.5
Female sex – no. (%)	7 (54)	6 (40)	13 (46)
Race or ethnic group – no. (%)			
- White	10 (77)	11 (73)	21 (75)
- Polynesian	3 (23)	1 (7)	4 (14)
- Other	0 (0)	3 (20)	3 (11)
BMI – kg/m²	54 ± 10.3	53 ± 9.9	54 ± 9.9
Weight – kg	149 ± 25.5	154 ± 36.3	152 ± 31.3
Smoking status			
- Non-smokers – no. (%)	5 (39)	8 (53)	13 (46)
- Ex-smokers – no. (%)	4 (31)	6 (40)	10 (36)
- Current smoker	4 (31)	1 (7)	5 (18)
Cardiovascular History			
- Hypertension – no. (%)	4 (31)	9 (60)	13 (46)
- Diabetes mellitus – no. (%)	3 (23)	6 (40)	9 (32)
- Dyslipidaemia – no. (%)	2 (15)	4 (27)	6 (21)
- Ischaemic heart disease – no. (%)	1 (8)	3 (20)	4 (14)
- Arrhythmia – no. (%)	1 (8)	4 (27)	5 (18)
- Echo abnormality – no. (%)	1 (8)	4 (27)	5 (18)
Spirometry			
- FEV1 – L	2.03 ± 0.75	2.11 ± 0.64	2.07 ± 0.68
- FEV_1 % predicted	63 ± 15.8	70 ± 17.5	67 ± 16.7
- FVC – L	2.56 ± 0.99	2.63 ± 0.78	2.60 ± 0.87
- FVC % predicted	63 ± 13.7	67 ± 14.9	65 ± 14.1
- FER – %	79 ± 5.7	80 ± 5.8	80 ± 5.7
ABG			
- $PaCO_2$ – mmHg	48 ± 1.9	50 ± 2.8	49 ± 2.6
- PaO_2 – mmHg	70 ± 6.7	60 ± 6.8	64 ± 7.9
- Bicarbonate – mmol	30 ± 1.4	31 ± 1.8	31 ± 1.7
PSG			
- AHI – events/hour	88 ± 28	89 ± 32	88 ± 31
- %TST<90% – %	72 ± 30	73 ± 30	72 ± 29
- SpO2 average – %	80 ± 8	86 ± 2	83 ± 6

Displayed as mean ± standard deviation or number of participants (percentage of total).

Table 6.2 Baseline Measurements and Changes with Treatment (Respiratory Failure)

	fCPAP [Mean ± SD]			APAP [Mean ± SD]			P Value of Intergroup Differences
	Baseline	3 Months	Intragroup	Baseline	3 Months	Intragroup	
ABG							
$PaCO_2$ – mmHg	48.2 ± 1.9	42.5 ± 1.6	-5.7 ± 1.2***	50.0 ± 2.8	45.9 ± 5.4	-4.1 ± 2.8**	0.30
PaO_2 – mmHg	69.5 ± 6.7	75.6 ± 11.7	5.8 ± 7.7	59.9 ± 6.9	68.4 ± 6.7	8.5 ± 5.4**	0.56
Bicarbonate – mmol/L	30 ± 1.4	28 ± 2.4**	-2.2 ± 1.4**	31 ± 1.8	29 ± 3.4	-2.1 ± 1.9*	0.94

intragroup difference (3m – baseline): * p<0.05 ** p<0.01 *** p<0.001

Table 6.3 Baseline Measurements and Changes with Treatment Related to Quality of Life, Quality of Sleep and Sleepiness Scores

	fCPAP [Mean ± SD]		APAP [Mean ± SD]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
ESS	12.3 ± 6.8	7.5 ± 4.9*	11.1 ± 5.1	7.5 ± 5.6*	0.434	0.428
FOSQ Total	64.5 ± 17.0	88.6 ± 11.0**	69.9 ± 14.5	75.4 ± 17.7	0.025	0.021
SRI Summary	54.2 ± 16.7	72.1 ± 19.6**	56.1 ± 17.6	60.8 ± 22.9	0.072	0.070

Abbreviations: ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcome Sleep Questionnaire; SRI = Severe Respiratory Insufficiency Questionnaire

~Adjusted for age

* $p<0.05$ intragroup difference (3m – baseline)

** $p<0.01$ intragroup difference (3m – baseline)

Table 6.4 Baseline Measurements and Changes with Treatment Related to Cardiovascular Biomarkers

	fCPAP [Mean ± SD)]		APAP [Mean ± SD)]		Intergroup Differences: P value	
	Baseline	3 Months	Baseline	3 Months	Unadjusted	Adjusted~
PWA						
PSBP	138 ± 12	144 ± 16	136 ± 14	136 ± 23	0.53	0.59
PDBP	81 ± 11	82 ± 13	77 ± 14	77 ± 11	0.93	0.94
PPP	57 ± 9	63 ± 16	59 ± 10	58 ± 15	0.48	0.48
CSBP	124 ± 11	129 ± 15	124 ± 11	123 ± 20	0.51	0.53
CDBP	83 ± 11	84 ± 14	80 ± 13	79 ± 11	0.82	0.84
CPP	42 ± 7	46 ± 14	44 ± 10	46 ± 13	0.78	0.74
PPP:CPP	1.37 ± 0.05	1.39 ± 0.12	1.35 ± 0.20	1.31 ± 0.15	0.46	0.26
AP	11.3 ± 6.5	11.6 ± 7.7	16.8 ± 9.1	12.0 ± 7.1	0.12	0.10
AIx, %	26 ± 12	23 ± 10	35 ± 15	29 ± 15	0.32	0.29
AIx@75, %	26 ± 14	25 ± 10	38 ± 12	28 ± 14	0.13	0.10
PWV						
cfPWV – m/s	7.6 ± 1.0	6.8 ± 0.5	7.1 ± 0.9	7.0 ± 1.5	0.49	0.73
cfPTT - ms	75 ± 12	76 ± 5	82 ± 15	100 ± 27	0.25	0.20
Troponin	26 ± 8	5 ± 4	18 ± 6	19 ± 3	0.06	0.05
NT-proBNP	65 ± 49	121 ± 96	126 ± 31	261 ± 79	0.92	0.63

Abbreviations: PWA = pulse wave analysis, PSBP = peripheral systolic blood pressure, PDBP = peripheral diastolic blood pressure, PPP = peripheral pulse pressure, CSBP = central systolic blood pressure, CDBP = central diastolic blood pressure, PPP = central pulse pressure, PPP:CPP = ratio of peripheral to central pulse pressure, AP = central augmentation pressure, AIx = augmentation index, AIx@75 = augmentation index corrected to a heart rate of 75bpm

~Adjusted for gender and age

* $p<0.05$ intragroup difference (3m – baseline)

Table 6.5. Baseline characteristics displayed as mean ± standard deviation, as per protocol

	CPAP (N=9)	APAP (N=12)	All (N=21)
Age – yr	48 ± 8.0	62 ± 11.2	55 ± 12.5
Female sex – no. (%)	4 (44)	4 (33)	8 (38)
BMI – kg/m²	53 ± 9.6	54 ± 10.4	54 ± 10.1
Weight – kg	150 ± 23.0	156 ± 37.6	154 ± 32.3
Spirometry			
- FEV1 – L	2.19 ± 0.74	1.99 ± 0.56	2.08 ± 0.66
- FEV_1 % predicted	64 ± 17.2	67 ± 18.4	66 ± 17.9
- FVC – L	2.75 ± 1.00	2.47 ± 0.72	2.60 ± 0.87
- FVC % predicted	63 ± 14.7	63 ± 14.4	63 ± 14.5
- FER – %	80 ± 5.6	81 ± 5.8	80 ± 5.7
ABG			
- $PaCO_2$ – mmHg	49 ± 2.1	51 ± 2.8	50 ± 2.7
- PaO_2 – mmHg	70 ± 7.2	59 ± 6.9	64 ± 9.0
- Bicarbonate – mmol	30 ± 1.4	31 ± 1.9	31 ± 1.7
PSG			
- AHI – events/hour	99 ± 20	84 ± 33	90 ± 30
- %TST<90% – %	65 ± 34	70 ± 32	68 ± 33
- SpO2 average – %	80 ± 10	86 ± 2	83 ± 7

Table 6.6. Characteristics of OHS participants who had ESS ≥ 10 at end of 3-months PAP therapy

pap_arm	age	sex	bmi	paco2_base	paco2	ess_base	ess
CPAP	56	M	46.91712	53	43	18	13
CPAP	51	M	61.14471	49	42	21	10
CPAP	56	F	52.34375	46	40	16	11
APAP	69	M	43.60465	48	47	21	10
APAP	42	M	57.37029	53	44	17	11
APAP	48	F	69.14063	57	51	4	11
APAP	52	M	54.76657	48	44	18	20

Table 6.7. PAP download data at 3 months follow up; Pres. = Pressure

PAP Arm	Adherence (h)	Set Pres. (cmH_2O)	Med. Pres. (cmH_2O)	90/95th Pres. (cmH_2O)	Max Pres. (cmH_2O)	Leak (L/min)	PAP flowAHI (/h)
fCPAP	6.72±1.70	16.6±2.62	N/A	N/A	N/A	27.72±20.88	1.97 ± 1.05
APAP	4.87±2.38	N/A	10.75±2.99	13.08±3.40	14.13±3.35	30.09±11.45	3.38 ± 3.85

PAP Adherence:

APAP – 4.87h (±2.38h)

CPAP – 6.72h (±1.70h)

P value = 0.061

Table 6.8. Factors influencing PAP adherence

	Pearson's correlation	P value
Median Pressure	0.445	0.054
Leak	-0.438	0.011

Table 6.9. Factors influencing CO_2 improvement

	Pearson's correlation	P value
Adherence	0.173	0.299
Median Pressure	0.270	0.198
Leak	0.205	0.295

Figures and Graphs

Figure 2.1.1a Effects of Obesity on Pulmonary Function[1]

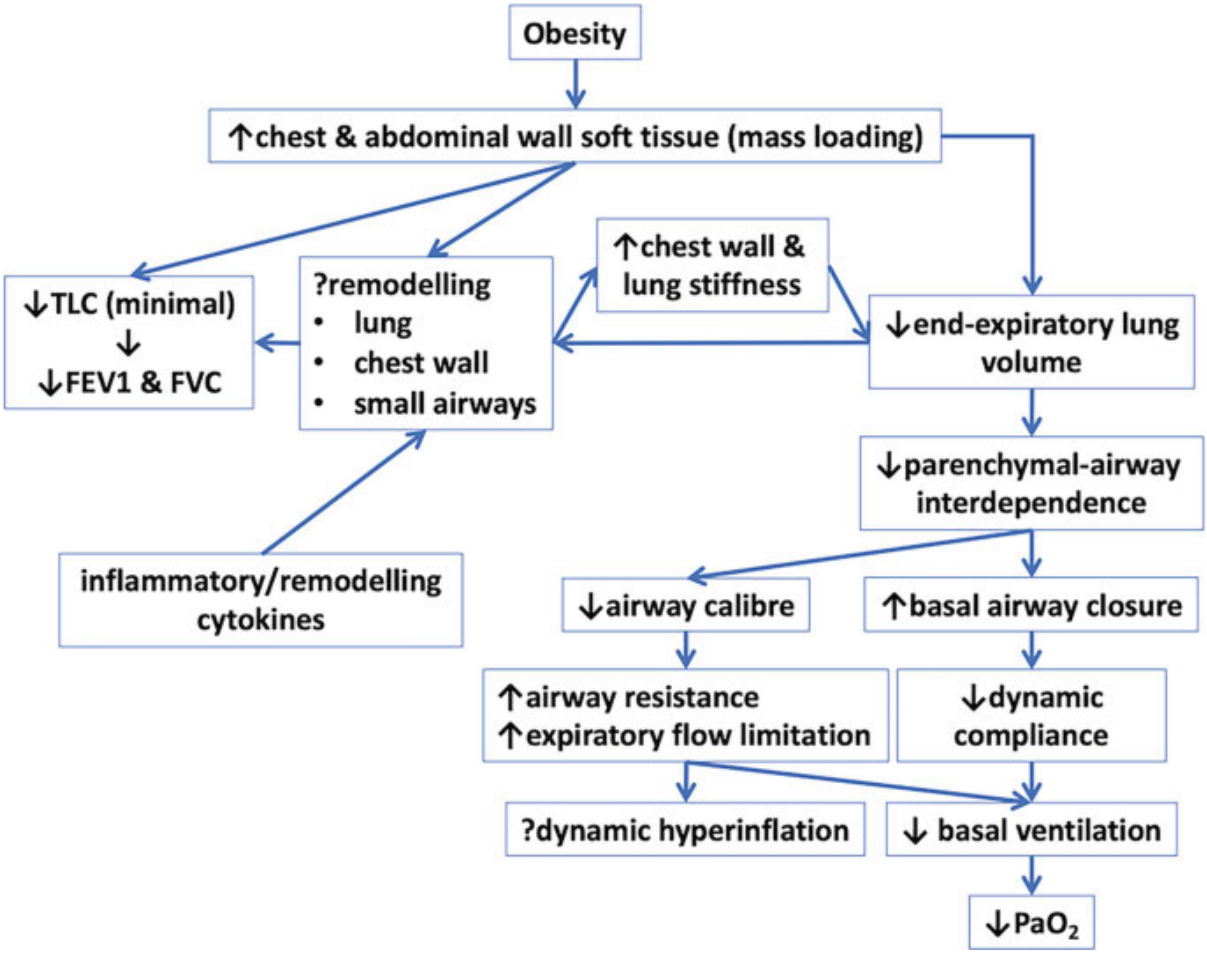


Figure 2.1.1b Effects of Obesity on Pharyngeal Airway Collapsibility [2]

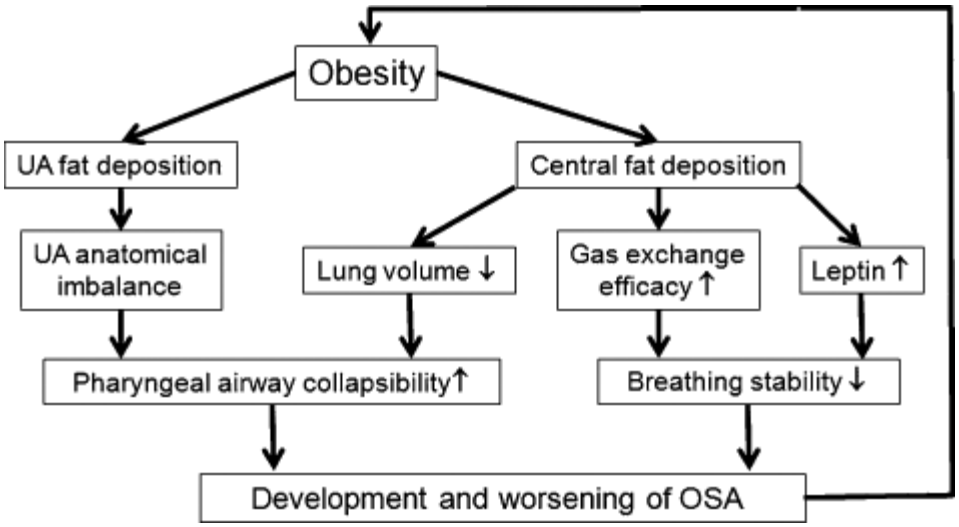


Figure 2.1.2a Obesity and Cardiovascular Disease: Pathophysiological Mechanism [3]

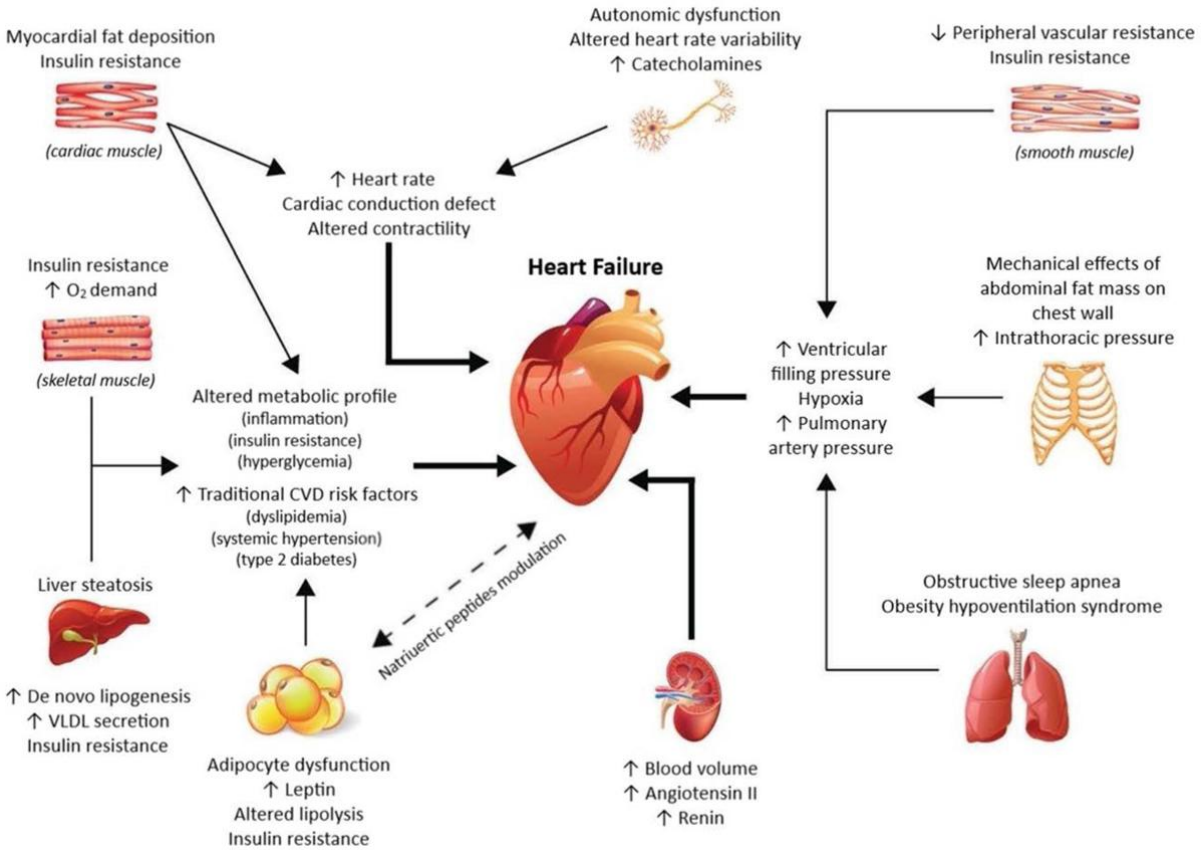


Figure 2.2.5a Pathophysiological mechanisms of OHS[4]

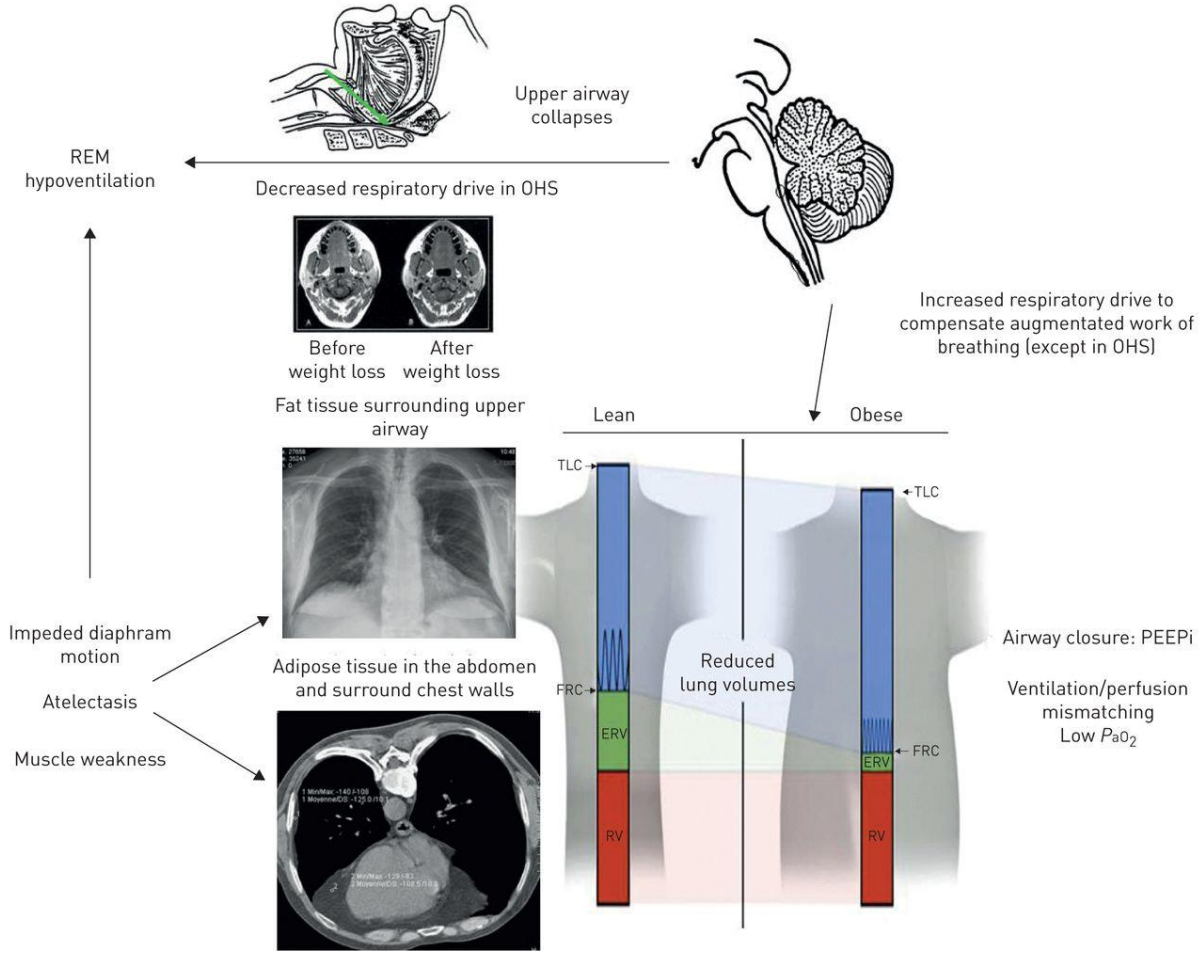


Figure 2.2.5b Influence of OSA events on the development of hypoventilation[5]

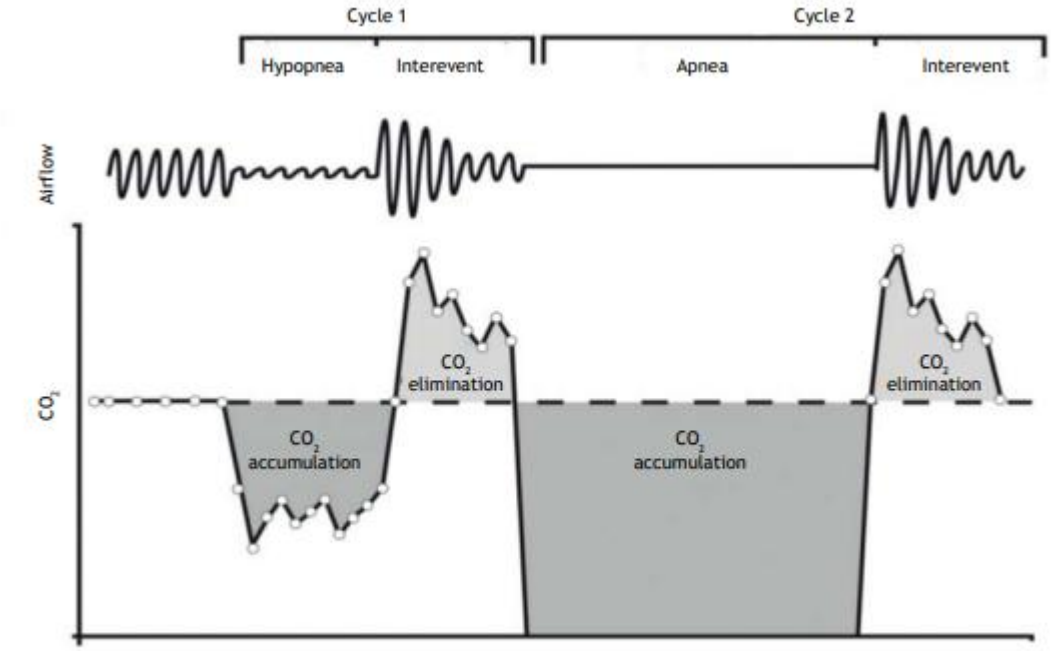


Figure 3. Influence of obstructive sleep events on hypercapnia. Adapted from Berger et al.[31]

Figure 2.3.1

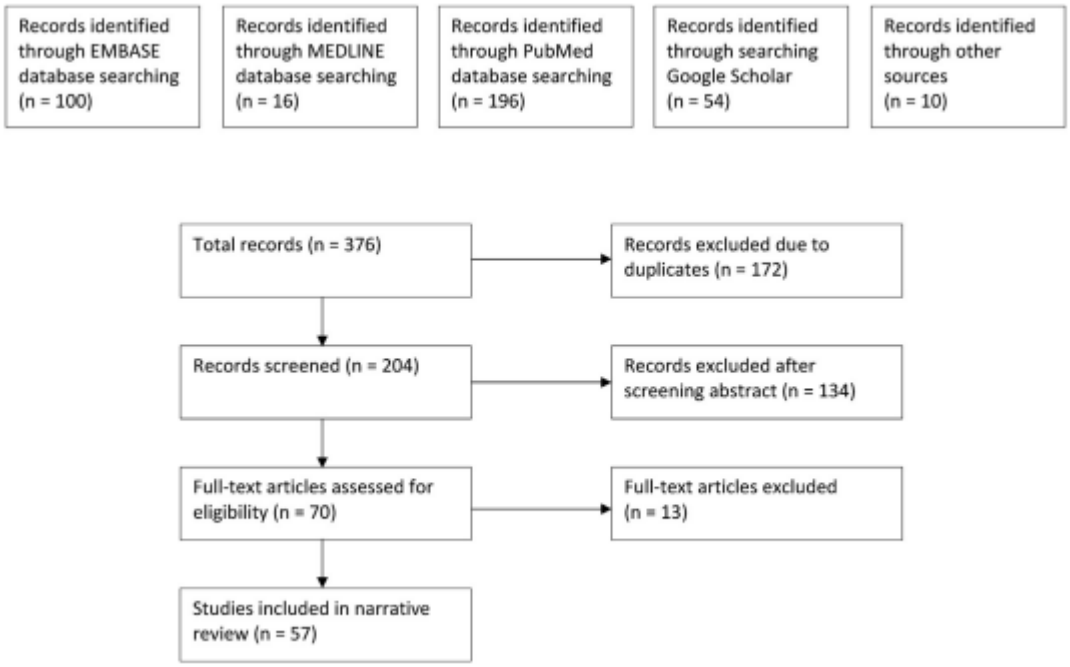
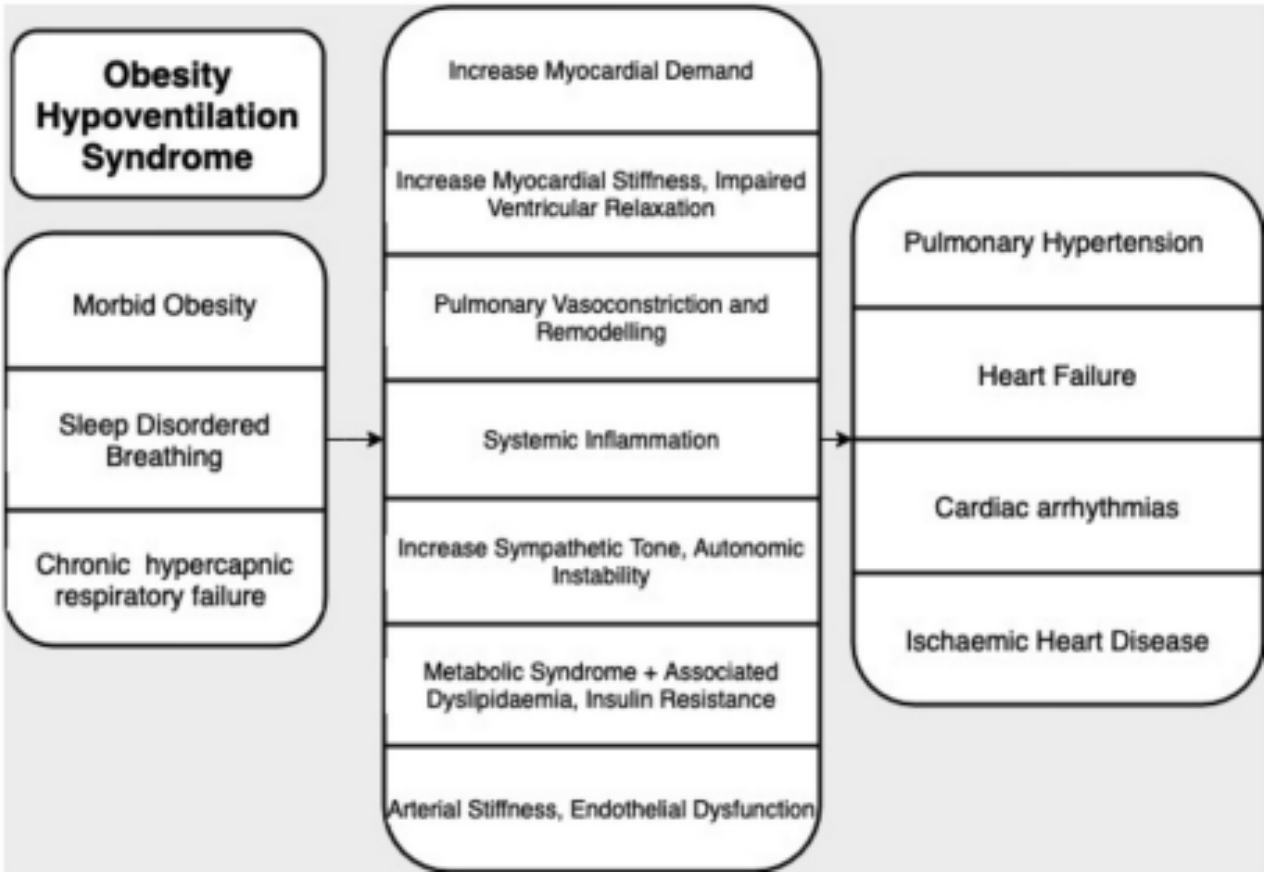
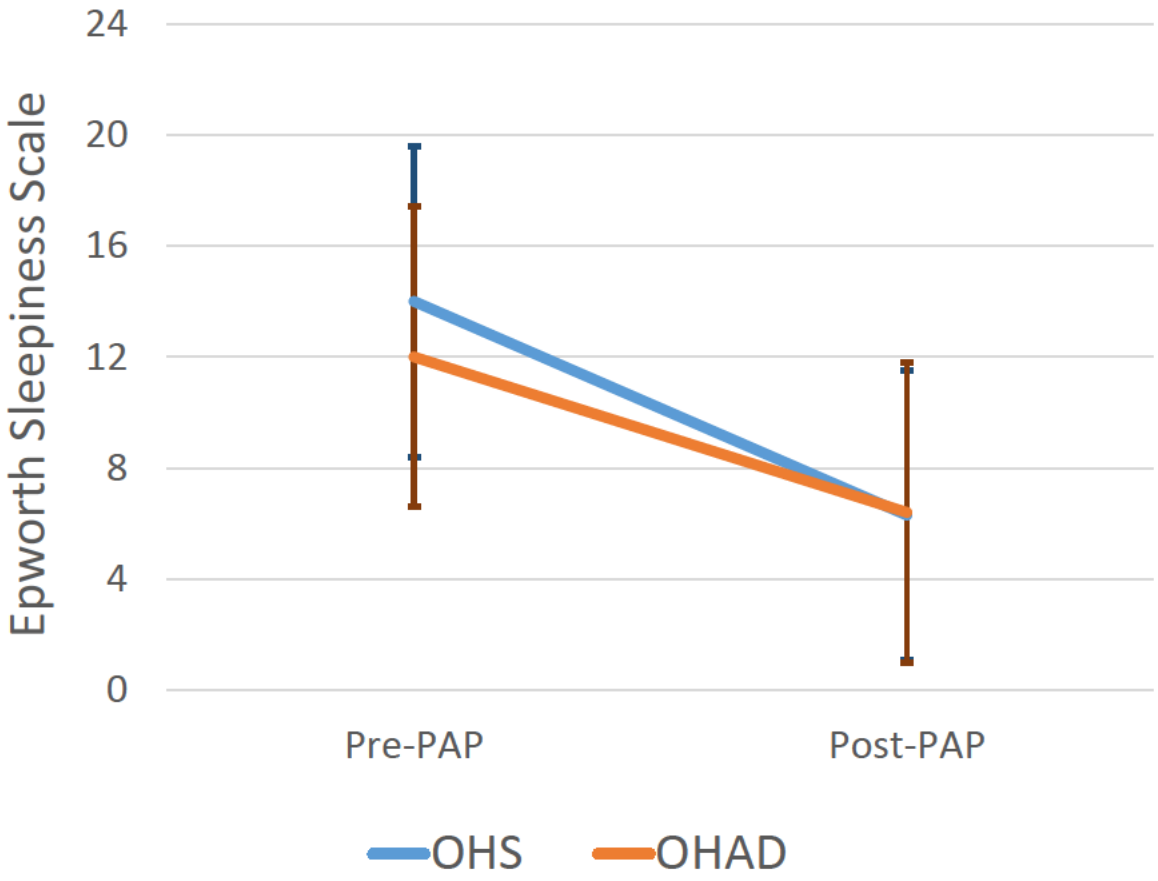

Records identified through EMBASE database searching (n = 100)
Records identified through MEDLINE database searching (n = 16)
Records identified through PubMed database searching (n = 196)
Records identified through searching Google Scholar (n = 54)
Records identified through other sources (n = 10)
Total records (n = 376)
Records excluded due to duplicates (n = 172)
Records screened (n = 204)
Records excluded after screening abstract (n = 134)
Full-text articles assessed for eligibility (n = 70)
Full-text articles excluded (n = 13)
Studies included in narrative review (n = 57)

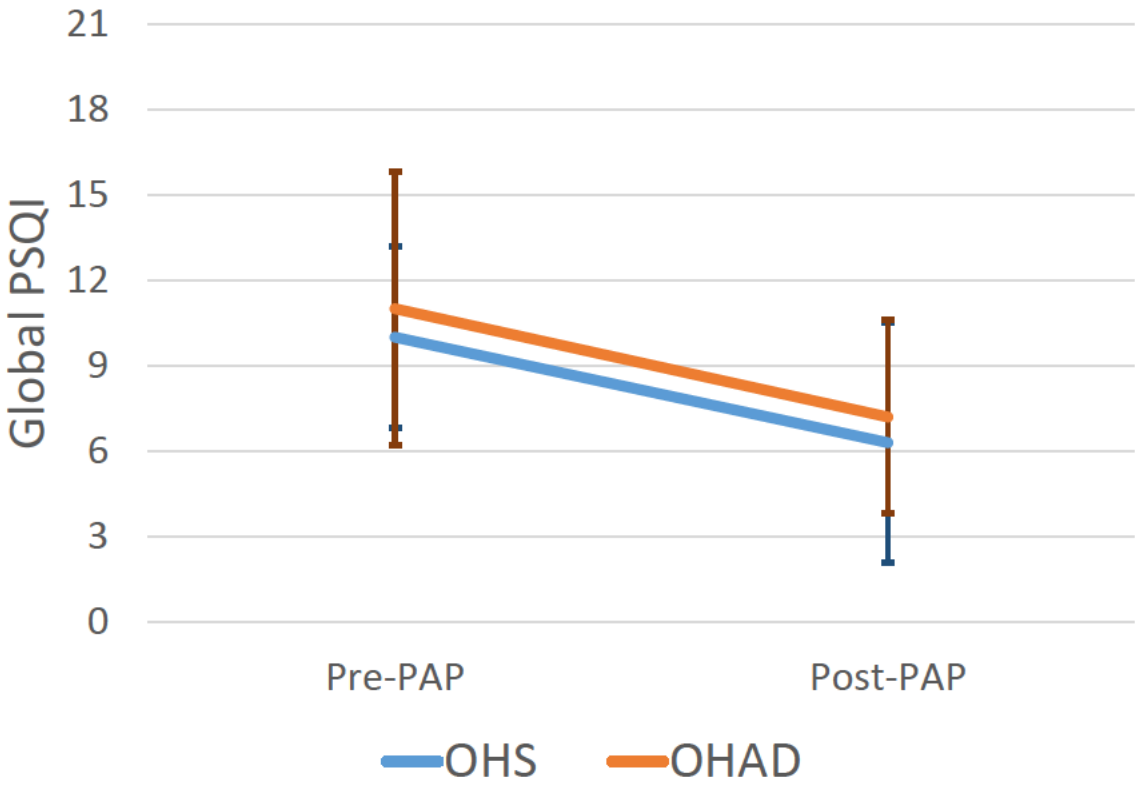
Figure 2.3.2 Contributing Mechanisms to the Development of Cardiovascular Diseases in OHS[6]



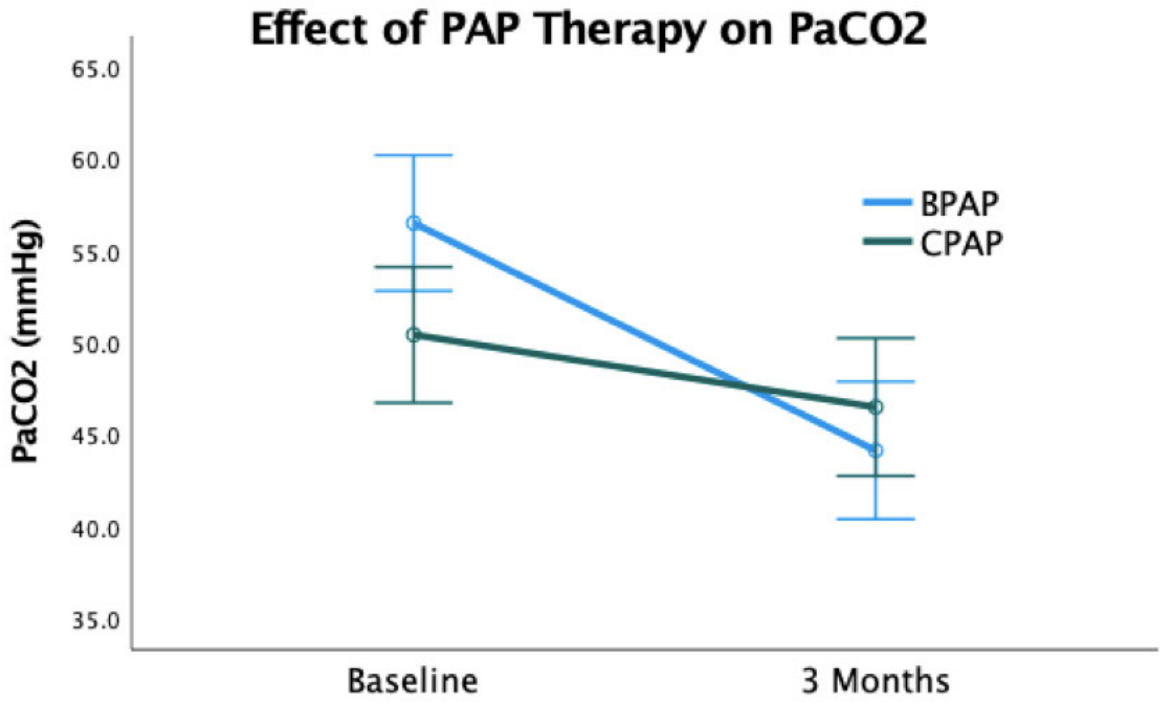
Graph 3.1 ESS Pre- & Post-PAP: OHS vs. OHAD



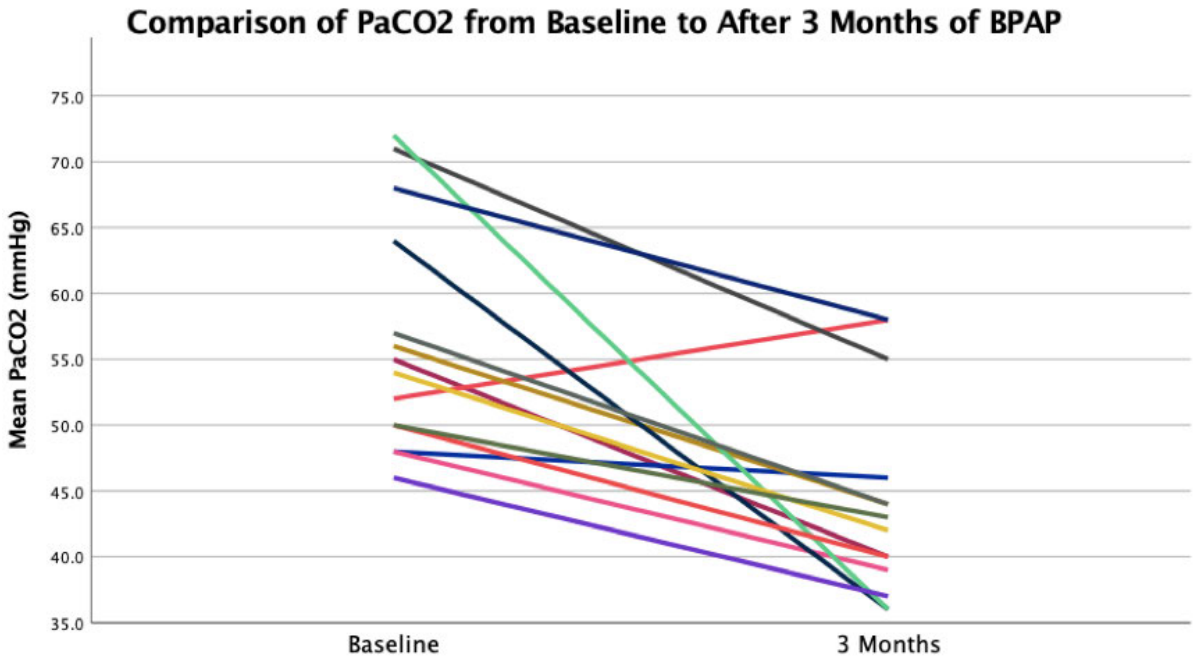
Graph 3.2 Global PSQI Pre- & Post- PAP: OHS vs. OHAD



Graph 5.1 Line graph comparing the treatment effect of BPAP and CPAP on $PaCO_2$



Graph 5.2: Individual value plot comparing $PaCO_2$ change over 3 months of treatment



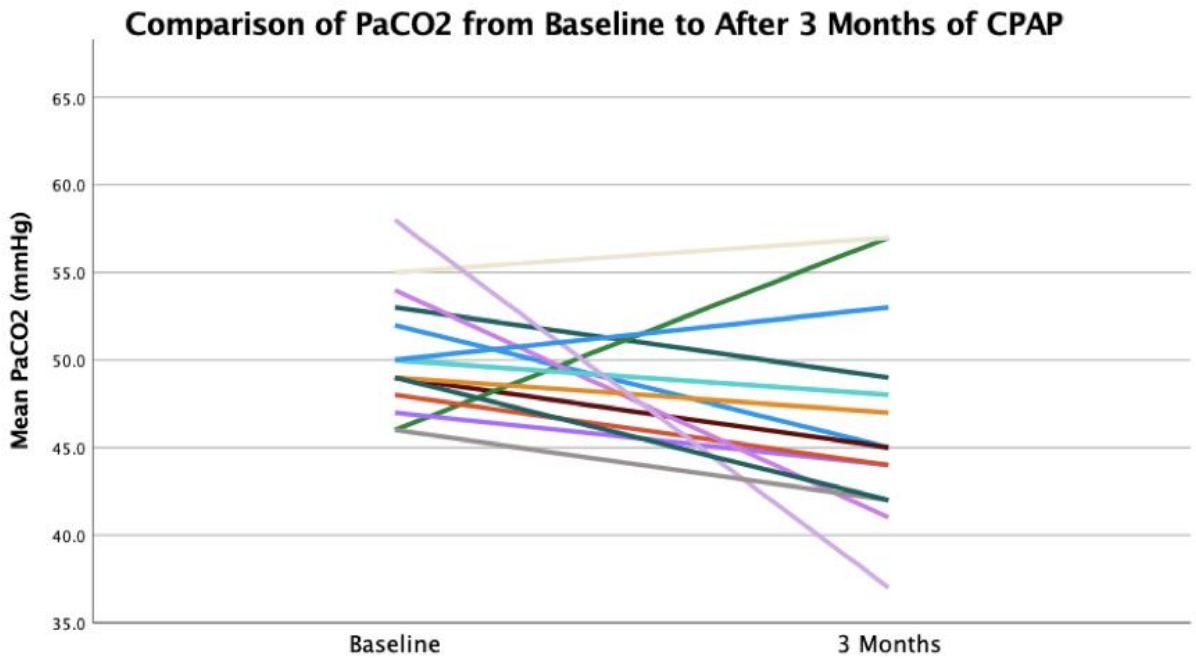
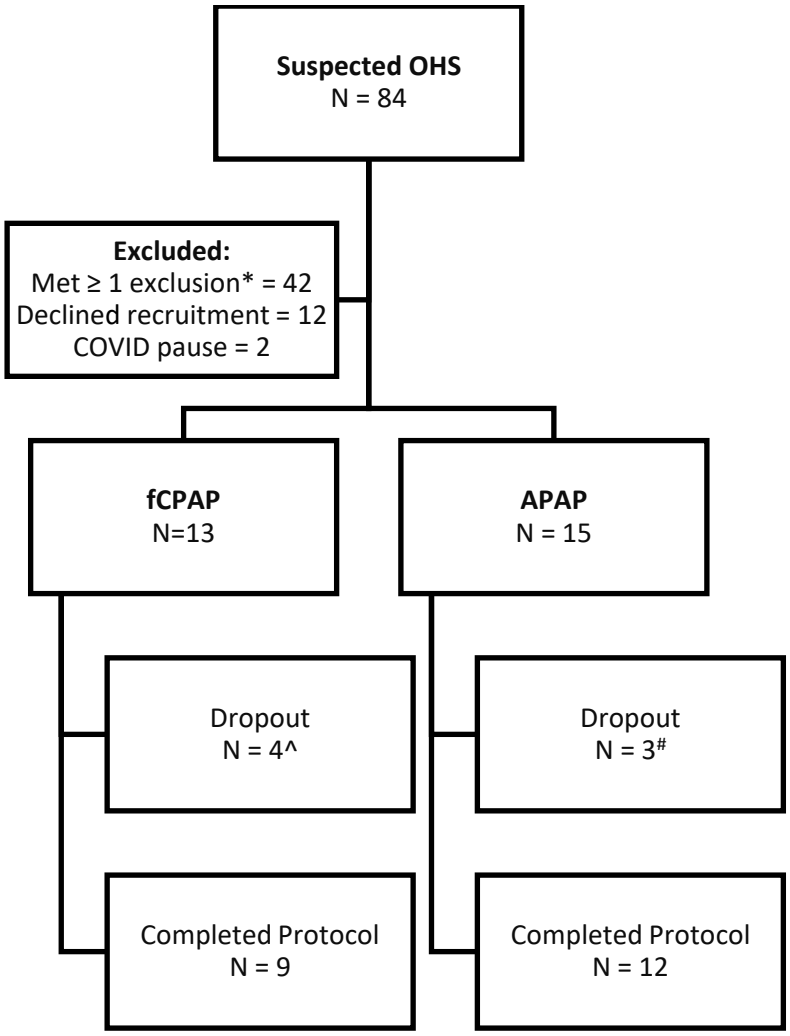
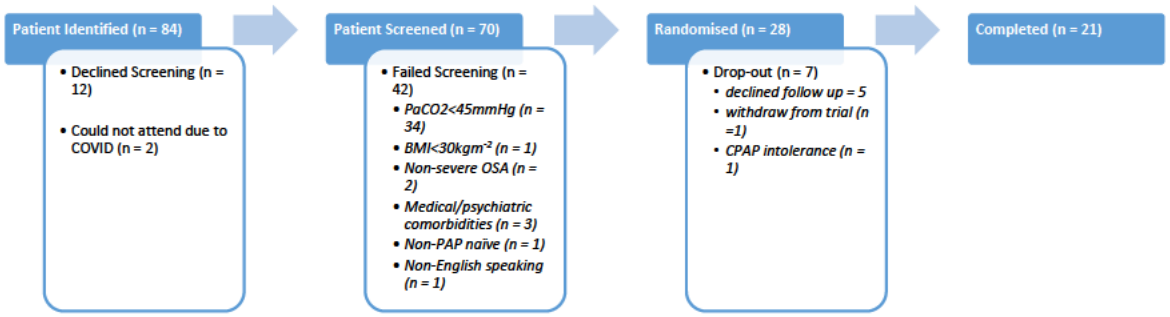


Figure 6.1. Flowchart of the study protocol.

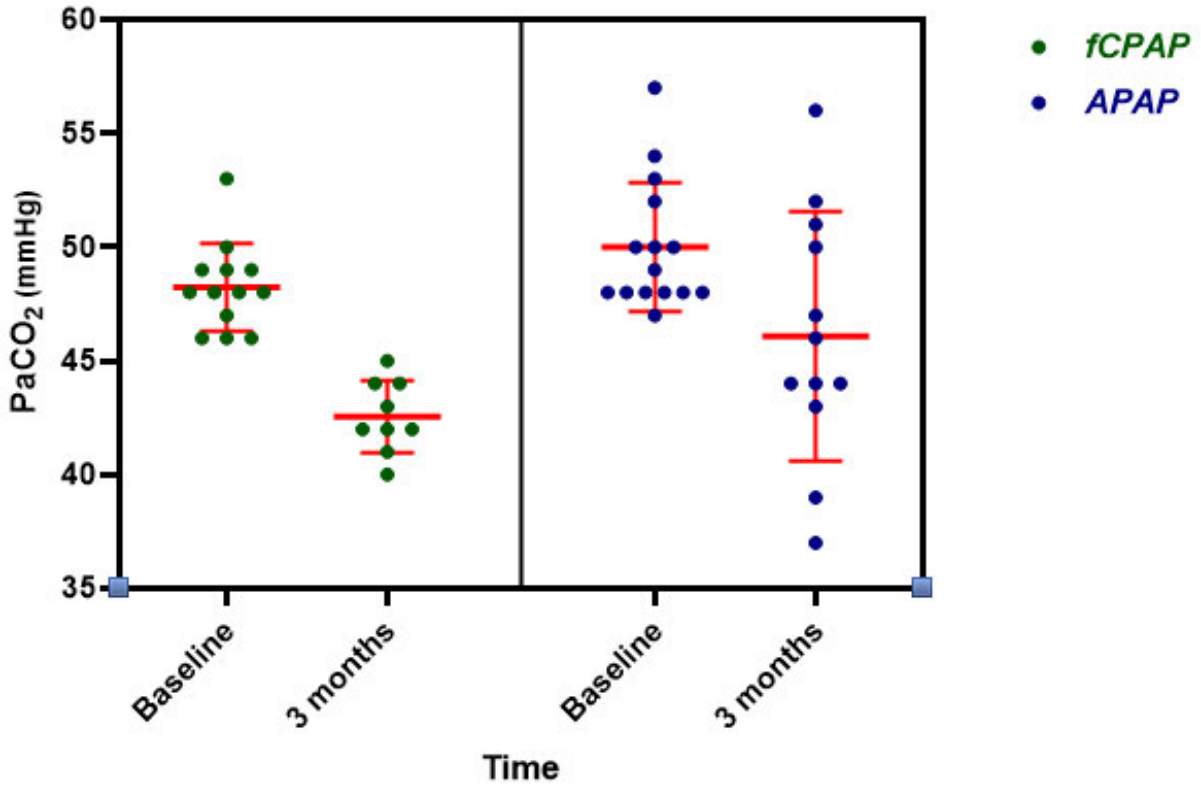


- **Met exclusion criteria: Non-hypercapnic = 34, BMI<30kg/m^2 = 1, Non-severe OSA = 2, Medical/psychiatric comorbidities = 3, Non-PAP naïve = 1, Non-English speaking = 1 ; ^fCPAP dropouts: non-attendance at scheduled follow-up = 2, withdraw from trial =1, CPAP intolerance and decline follow up = 1; #APAP dropouts: non-attendance at scheduled follow-up = 2, hospitalisation and decline follow up = 1. Patients who completed the protocol were analysed for the primary outcome (none excluded from analysis).*

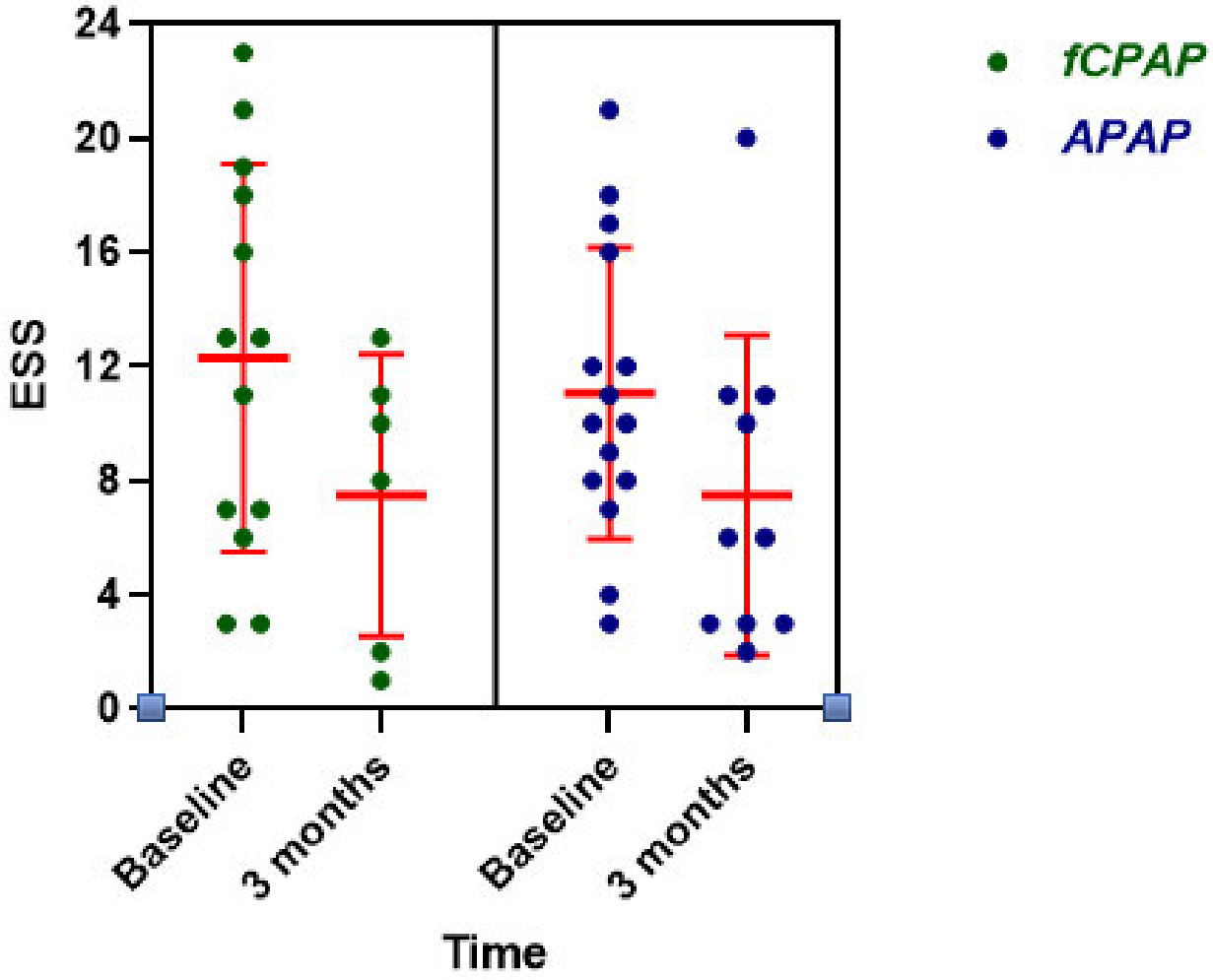
Figure 6.2. Recruitment Funnel.



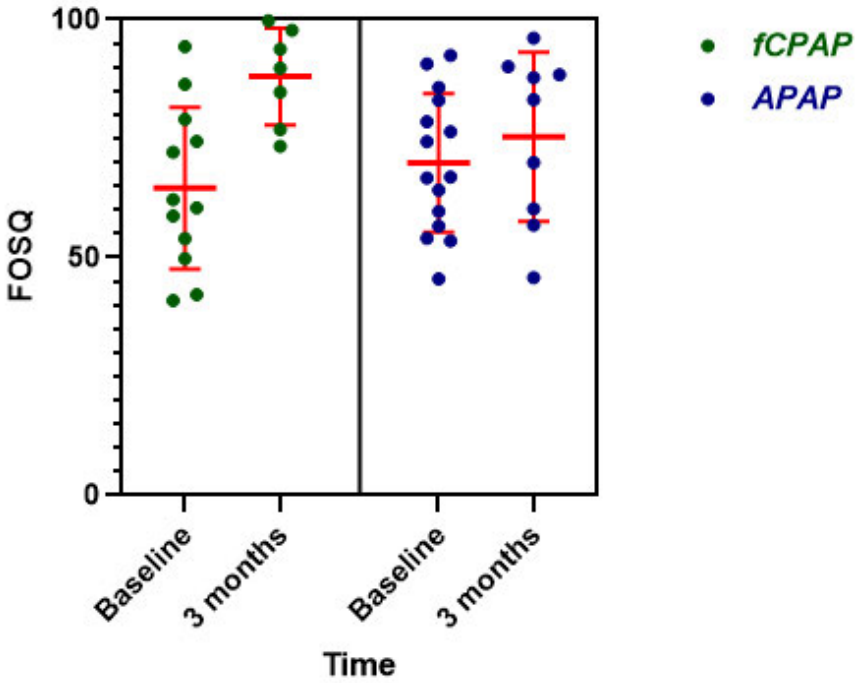
Graph 6.1. Comparison of PaCO2 change between baseline and 3 months with fixed CPAP (fCPAP) and auto-titrating CPAP (APAP)



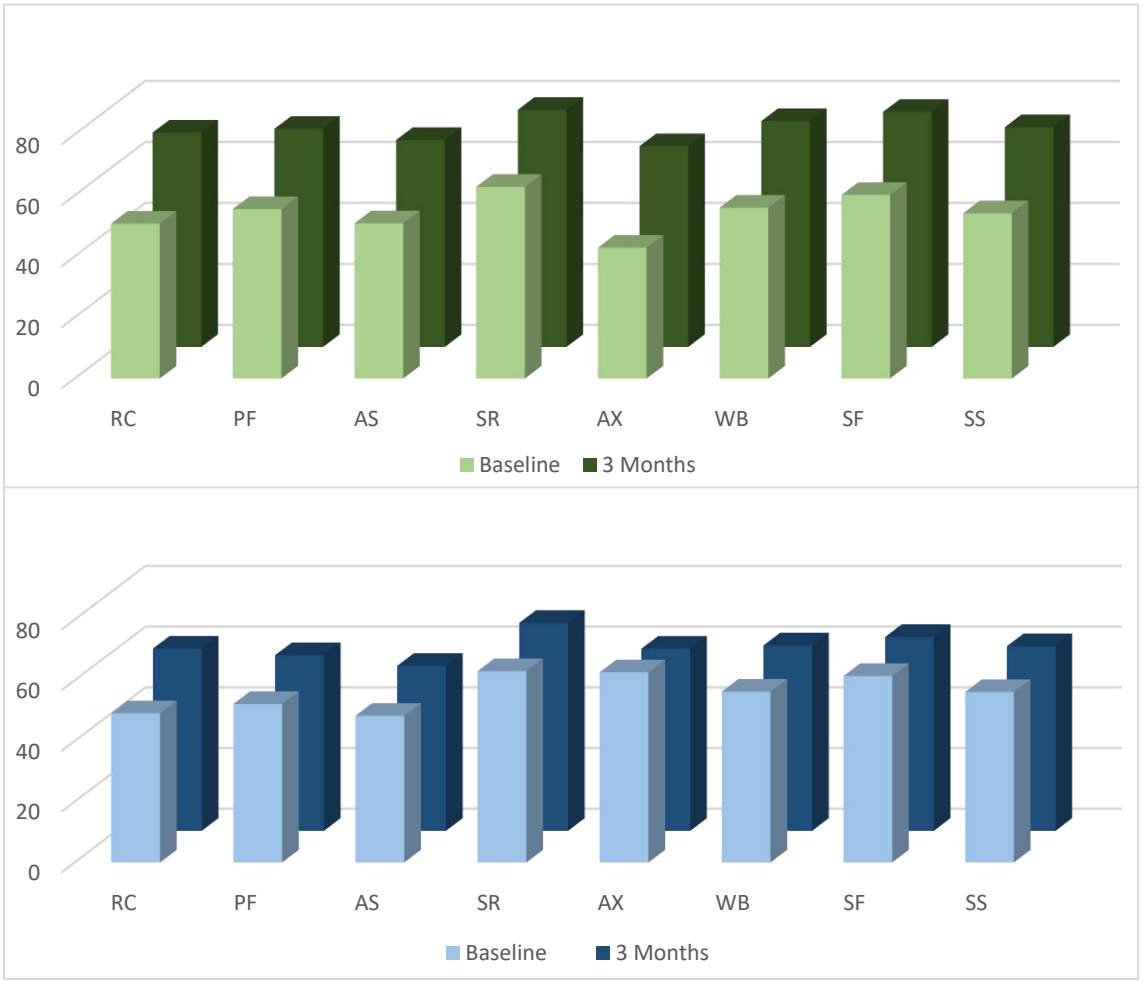
Graph 6.2. Comparison of ESS change between baseline and 3 months with fixed CPAP (fCPAP) and auto-titrating CPAP (APAP)



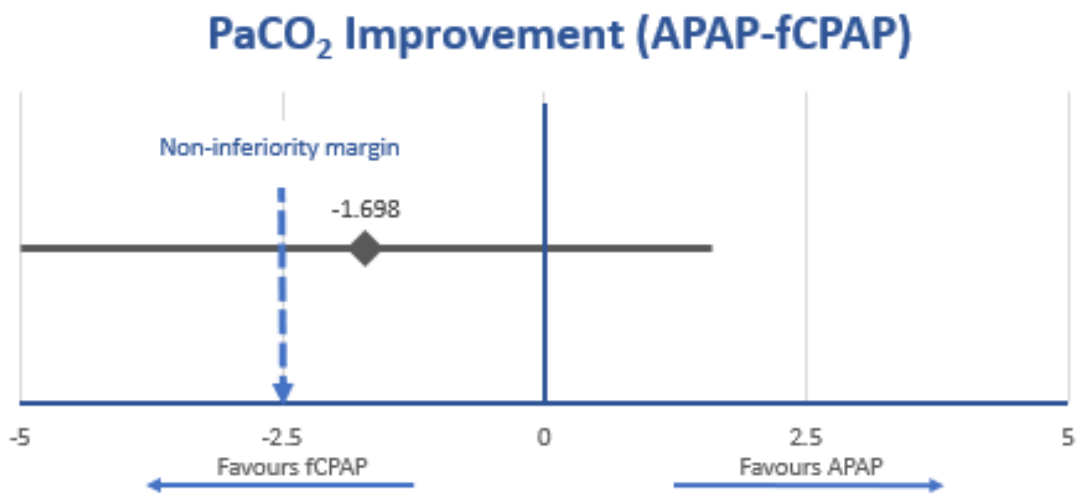
Graph 6.3. Comparison of FOSQ change between baseline and 3 months with fixed CPAP (fCPAP) and auto-titrating CPAP (APAP)



Graph 6.4. Change in components of SRI between baseline and 3 months with fixed CPAP (fCPAP in brown) and auto-titrating CPAP (APAP in blue)

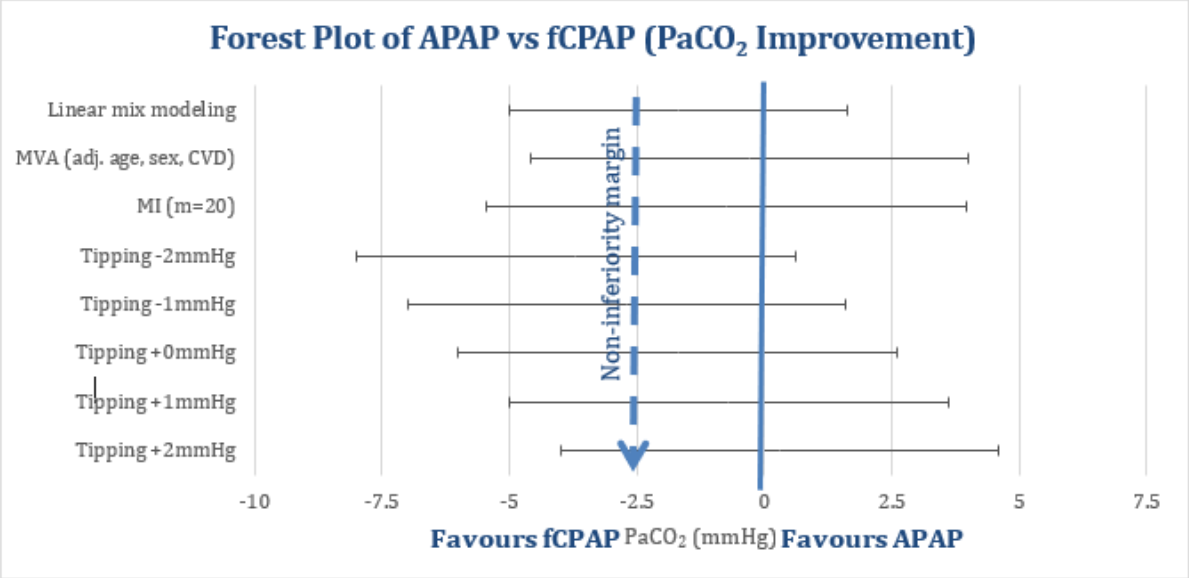


Graph 6.5. Difference between APAP and fCPAP in $PaCO_2$ improvement post-therapy



Displays the confidence interval in relation to non-inferiority margin. X-axis is displaying $PaCO_2$ in mmHg. Non-inferiority was not met as the lower confidence interval is lower than the non-inferiority margin of -2.5mmHg.

Graph 6. Forest plot comparing APAP and fCPAP in $PaCO_2$ improvement post-therapy



Showing various post-hoc analysis (MVA = multivariate analysis with adjustment for imbalanced baseline age, sex, cardiovascular risk factors/disease; MI = multiple imputation (missing at random, 20 imputations); tipping analysis).

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Supplementary Material

Chapter 3 Supplementary Materials:

Method:

Anthropometric Measurements:

Waist and hip circumference was measured using standard techniques[1].

Neck circumference was measured at the level of the cricothyroid cartilage.

BMI was calculated using measured height and weight.

Spirometry/Lung function:

Spirometry was measured using a MicroLab portable spirometry (Micro Medical, Rochester, UK) while static lung volumes were performed using helium dilution (Morgan TLC, UK) in accordance with recommended guidelines[2].

Arterial Blood Gas:

Arterial blood gases were taken with the patient in the seated position and breathing room air during the afternoon of their sleep study and afternoon of their 3 months follow up visit.

Polysomnography:

All patients had laboratory based (type 1) diagnostic and PAP titration studies using commercially available digital sleep systems (Profusion, Compumedics, Melbourne, Australia; or Alice 5, Respironics, Murrysville, PA, USA) following recognised guidelines[3] and scored according to standard criteria[4] by experienced sleep scientists unaware of the patient's involvement in the trial. Additional

monitoring of transcutaneous carbon dioxide (TcCO2) was performed using TCM3 (Radiometer, Copenhagen, Denmark).

PAP Devices:

Patients were discharged on home-style PAP devices – REMstar CPAP or Duet LX Bi-level devices (Respironics, Murrysville, PA); S6 CPAP or VPAP II Bi-level devices (ResMed, North Ryde, Australia) for a 3 months period. A range of commercial masks were trialled with each patient with the final choice dependent on comfort, fit and leak minimisation.

Questionnaires

Questionnaires performed included the Pittsburgh Sleep Quality Inventory (PSQI) [5], the Epworth Sleepiness Scale (ESS) [6] and the Medical Outcomes Study Short Form (SF-36) [7]. Calculation of global PSQI was performed and used to make intra-group and inter-group comparisons.

Neurocognitive Tests:

Patients performed a 10-minute psychomotor vigilance test (PVT) [8] to measure reaction times and vigilance, with the variables of Lapses (reaction time >500ms), Median reaction time and the Mean of the Slowest 10% reaction times reported. This latter metric was reciprocally transformed so that smaller numbers represented slower reaction times and larger numbers faster reaction times. Trails Making Test Part B [9] and Digit Symbol Substitution (DSS) tests [10], used to assess cognitive performance in the domain of executive functioning and attention. Trails Making Test Part B involved assessing the time it takes for a subject to connect circles in ascending order, alternating back and forth from numbers 1 to 12 and letters A through L. Digit Symbol Substitution Test requires a subject to match symbols to numbers according to a key located on the top of the page with the score based on the number of correct symbols within 120 seconds. Verbal memory was assessed with the Digit Span Backward (DSB) and Forward (DSF) tests [10]. Digit Span Forward test requires the subject to remember and reproduce a sequence of numbers in the correct order, while Digit Span Backwards requires the subject to reproduce the sequence of numbers in the reverse order. Testing was performed at similar times at baseline and follow up.

Chapter 6 Supplemental Method:

Inclusion Criteria

- Stable daytime hypercapnia with $paCO_2$ of > 45mmHg
- Severe obstructive sleep apnoea (AHI $\geq$ 30 per hour)
- Long-term positive airway pressure naïve
- Obesity with BMI $\geq$ 30kg/m^2
- Age $\geq$ 18 years old

Exclusion Criteria

- COPD or FER < 0.7
- Other significant pulmonary, neuromuscular, chest wall disease or use of respiratory depressant medication that is expected to contribute towards hypoventilation
- Uncontrolled medical or psychiatric conditions or pregnancy
- Non-English speaking or unable to provide informed consent
- Severe daytime hypercapnia with $paCO_2$ of > 60mmHg
- Already on long-term positive airway pressure therapy

Arterialised blood gas collection

Arterialised blood gases were taken while the participant was seated and breathing room air via direct radial artery puncture or earlobe. Earlobe samples were taken by technicians experienced in the technique as per previously described (spiro 76 Chest). A topical vasodilatory substance was applied to the earlobe 15-30 minutes before sampling. An incision is made in the inferolateral aspect of the earlobe using an Accu-Chek Safe-T-Pro lancing device. A drop of blood is drawn into a thin glass capillary tube. The same analyser was used in both sampling methods. The same arterialised blood collection method was used on an individual participant at baseline and 3 months follow-up visit (both performed in the afternoon).

Spirometry:

Spirometry was measured using portable spirometry (EasyOne Diagnostic, Australia) in accordance with recommended guidelines[11].

Polysomnography:

All patients had laboratory-based (type 1) diagnostic and PAP titration studies using commercially available digital sleep systems (Profusion, Compumedics, Melbourne, Australia; or Alice 5, Respironics, Murrysville, PA, USA) following recognised guidelines[12] and scored according to standard criteria[4] by experienced sleep scientists unaware of the patient's involvement in the trial. Additional monitoring of transcutaneous carbon dioxide (TcCO2) was performed using SenTec Monitioring system (SenTec, Therwil, Switzerland).

PAP Devices:

Patients were discharged on home-style PAP devices – Philips Dreamstation (Respironics, Murrysville, PA) or Resmed Airsense 10 (ResMed, North Ryde, Australia) for a 3 months period. A range of commercial masks were trialled with each patient with the final choice dependent on comfort, fit and leak minimisation.

Questionnaires

Questionnaires performed included the Epworth Sleepiness Scale (ESS)[6], the Functional Outcomes of Sleep (FOSQ)[13], and Severe Respiratory Insufficiency Questionnaire (SRI)[14]. Calculation of FOSQ subscales (general productivity, social outcome, activity level, vigilance, intimate relationships and sexual activity) and FOSQ total score was performed as per scoring instructions[13]. A summary scale for SRI was calculated from individual subscales as per the recommended formula[14].

Pulse Wave Analysis (PWA) and Pulse Wave Velocity (PWV):

Both PWA and PWV measurements were performed using the SphygomCor XCEL (Atcor Medical; Sydney, NSW, Australia), conducted in a temperature-controlled room in the afternoon (between 2-5 pm)[15].

PWA: Peripheral blood pressure was measured using an appropriately sized cuff around the upper arm, centred around the brachial artery. The central aortic pressure waveform is derived from cuff pulsations recorded at the brachial artery using the PWA software. The PWA software determined the augmentation index (AIx and AIx@75). The augmentation index is the ratio of the augmentation pressure to pulse pressure, expressed as a percentage. At least three valid measurements were performed in the sitting position.

PWV: An appropriately-sized femoral cuff was placed around the participant's right thigh, as high as possible. The carotid pulse on the same side was manually palpated. The PWV distance was determined using the direct method with a tape measure between the carotid artery and the top of the femoral cuff. The pulse transit time and calculated PWV were determined using the PWV software. Three valid measurements were performed in the supine position.

References

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