A study of posture shifts during sleep and the effects of supine-avoidance therapy in patients with supine-predominant obstructive sleep apnea

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Bachelor of Medical Science, 2015

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Thesis
Submitted to Flinders University
for the degree of

Doctor of Philosophy

College of Medicine and Public Health

01 December 2021

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Conference abstracts

Rahimi M, Heath M, O'Grady A, Mercer J, Antic N, McEvoy RD, Vakulin A, Hnin K, Tickner D, Quinn S, Barnes M, Catcheside P. A preliminary analysis of brief arousal and awakening responses associated with posture shifts in sleep, and the impact of supine-avoidance alarm treatment. Journal of Sleep Research 25(Suppl. 2): 237, 2016.

Rahimi M., Antic N, McEvoy RD, Barnes M, Quinn S, Mercer J, Vakulin A, Heath M, O'Grady A, Tickner D, Catcheside PG. The comparative effectiveness of a simple alarm-based supine-avoidance device versus usual care with continuous positive airway pressure for treating patients with supine-predominant obstructive sleep apnea. World Sleep 2019 Congress, Vancouver Canada.

DECLARATION

I certify that this thesis:

Does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Matthew Rahimi

01/12/2021

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisors Professor Peter Catcheside and Associate Professor Andrew Vakulin. Peter has been a tremendous role model for me both as a scientist and as an outstanding character throughout this journey and I will always be grateful for his advice and his insight. My appreciation also goes to Andrew and his continuous support as a great mentor.

Also, many thanks to Dasha Loutchkina, Alison Pinczel, Denzil Paul, Dr Dimitar Sajkov, Rohit Philip, Dr Jason D'Costa, Dr Jeff Bowden, Dr Anand Rose, Dr Karen Latimer, A/Prof Brian Smith, Dr Mark Jurisevic, Dr Andrew Thornton, Dr Aeneas Yeo, Dr Parmjit Singh, Dr Zafar Usmani, Dr Vinod Aiyappan for study, technical and/or clinical support. I am grateful to all the participants and laboratory staff at the Repatriation General Hospital whom without their help the SUPA trial and the works of this thesis would not have been possible. I would like to specifically thank the excellent researchers and research assistants at the Adelaide Institute for Sleep Health whom over the years I learned a great deal from them. In particular I would like to thank Professor Doug McEvoy, Dr Jeremy Mercer, the late Prof Nick Antic my good friend Dr David Stevens, Mandy O'Grady, Alison Pinczel, Hiro Tojo, Melanie Health and Alison Teare.

To my parents: your sacrifices made it possible for me to work toward my goals. Your words and virtues will always be a part of me and I am eternally grateful for your prayers.

To my Wife, Lisa, your love and support kept me going. I would have never been where I am today without you. I love you.

GLOSSARY OF ABREVIATIONS

3% ODI	3% oxygen desaturation indices
AASM	The American Academy of Sleep Medicine
AHI	Apnea hypopnea index (events·hr-1 sleep)
AQoL-8D	Assessment of Quality of Life
BMI	Body Mass Index
CPAP	Continuous Positive Airway Pressure
ECG	Electrocardiogram
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyography
ESS	Epworth Sleepiness Scale
HR	Heart Rate
ISI	Insomnia Severity Index
N1	Non-REM Stage 1 Sleep
N2	Non-REM Stage 2 Sleep
N3	Non-REM Stage 3 Sleep
NREM	Non-Rapid Eye Movement
OSA	Obstructive Sleep Apnea
$PaCO_2$	Partial Pressure of Carbon Dioxide
PSG	Polysomnography
PSQI	The Pittsburgh Sleep Quality Index
PT	Positional Therapy

REM	Rapid Eye Movement
SaO_2	Oxygen Saturation
SD	Standard Deviation
SDOSA	Supine-Dependent Obstructive Sleep Apnea
SSS	Snoring Severity Score
TST	Total Sleep Time
WASO	Wake After Sleep Onset
EOG	Electrooculography

Thesis Summary

In the first experimental study reported in Chapter 2, results from the SUpine-avoidance for Positional sleep Apnea (SUPA) trial are reported. This study was designed to establish if supine-avoidance is non-inferior to CPAP in reducing sleepiness and to compare treatment compliance between supine-avoidance versus CPAP in patients with obstructive sleep apnoea (OSA) only during supine sleep. 66 patients with supine dependent obstructive sleep apnea (SDOSA) and Epworth sleepiness scale (ESS) ≥8 completed baseline measurements, including questionnaires, inactive supine-avoidance for 1 week for supine-time measurements and in-home full sleep study. Participants were then randomised to receive active supine-avoidance or CPAP treatment, followed by a cross-over to the remaining treatment after 6-8 weeks. Repeat questionnaires, sleep studies and treatment compliance measurements were collected after 6-8 weeks on each treatment. Non-inferiority was assessed from the change in ESS with supine-avoidance compared to CPAP using a conservative pre-specified non-inferiority margin of 1.5. Average nightly use over 6-8 weeks of each treatment was also examined and compared between treatments. At baseline, participants had 47.6±20.4% supine sleep and ESS 10.3±3.9. At the end of 6-8 weeks of treatment, the reduction from baseline in ESS with supine-avoidance (mean [95%CI] -1.9 [-2.9 to -0.9]) was no worse than CPAP (-2.3 [-3.3 to -1.3], difference -0.2 [-1.3 to 0.9]). Average treatment usage was substantially higher with supine-avoidance compared to CPAP (5.6 [5.0 to 6.3] versus 3.9 [95%CI 3.2 to 4.6] h/night, p< 0.001). These findings support that alarm-based supine-avoidance is

non-inferior to CPAP at reducing sleepiness and achieves superior treatment adherence in patients with SDOSA.

In the second study (Chapter 3), physiological responses to posture shifts with and without a supine-avoidance alarm device were examined as a marker of sleep disturbance. From the data collected on polysomnography (PSG) nights of participants in the SUPA trial, posture shifts were systematically investigated to see whether they are preceded by electroencephalogram (EEG) detectable arousal/awakenings and if so, how long it takes for sleep to resume. Key secondary aims were to characterize the temporal relationship between EEG responses to posture shifts during sleep with vs without a supine-avoidance alarm, and to investigate the impact of supine alarms on overall sleep quality.

Posture shift data recorded via PSG and supine-avoidance devices were extracted via custom algorithms to detect posture shifts lasting ≥5-seconds. EEG data 30 secs before and after each posture shift were then examined to assess wake versus sleep and arousals prior to and the time taken to achieve sleep following PSG recorded posture-shifts.

The study population was comprised of 56 participants (61% males) who completed baseline and both treatment PSG nights in the main SUPA trial. These participants exhibited a mean±SD age 53.6±11.2 years, BMI 31.4±8.1 kg/m², AHI 17.2±6.7 /hr (supine AHI=40.3±40.7 /h). From a total of 376 (baseline) vs 249 (supine-avoidance) posture shifts (median [IQR] 6[4-9] vs 6[3-9] per patient), the majority [347/376 vs

222/249; 91[75-100] vs 100[84-100]%) were associated with prior wake or an arousal. The hazard of remaining in the supine posture following posture shifts to supine was around 4-fold lower with active versus inactive supine-avoidance treatment (hazard ratio 4.3 [95% CI 3.7 to 4.9]), with a marked reduction in post-shift supine time (median [IQR] 0.2 [0.1 to 0.3] minutes versus 18.5 [11.0 to 39.6] minutes. Sleep resumed quickly following posture shifts to supine from prior sleep, with no difference with versus without the supine-alarm (0.5 [0.1 to 1.4] versus 0.5 [0.2 to 1.3] minutes). Sleep onset time was considerably longer following shifts to the supine posture from prior wake, but were also not different with versus without the active supine-avoidance alarm (4.9 [1.3 to 8.5] versus 6.1 [2 to 13.9] minutes).

Most posture shifts occur shortly after an arousal or during established wake supporting the presence of higher centre involvement in posture shifts. Thus, supine-alarm device events occurring after supine shifts from sleep typically coincide with a brief posture-shift related return to wake, followed by a rapid return to sleep minimally impacted by the alarm *per se*. This study presents strong evidence to support that supine-avoidance alarms effectively limit supine sleep time with no discernible further sleep disturbance beyond that associated with posture shifts themselves.

In the third study (Chapter 4), snoring was objectively examined in patients with supine-predominant sleep apnea. This study was a sub-study of the SUPA trial that investigated the effect of posture on snoring severity and the effect of a supine-avoidance alarm device on snoring. This is the first study to present objective data on snoring frequency and to compare the effects on snoring of a supine-avoidance alarm

device compared to CPAP. Snoring frequency was analysed objectively in both supine sleep and non-spine sleep during baseline and supine-avoidance treatment PSG nights in the full study population. Analysis was also performed on a subgroup of participants who mainly snored on their back (defined as supine snorer on the basis of snoring frequency at least 2x higher in supine compared to non-supine sleep). The frequency of discrete snoring events ≥50 dBA was significantly reduced by CPAP compared to baseline and supine-avoidance therapy in the full study population ($p<0.001$, baseline= 48.9 [16.7 to 188.7] snores/h, supine-avoidance= 36.8 [6.3 to 233.7] snores/h, CPAP= 4.2 [2.1 to 29.5] snores/h). Both CPAP and supine-avoidance therapy reduced snoring frequency in supine sleep (Baseline= 66.3 [22.9 to 186.7], supine-avoidance= 13.2 [0.7 to 67.1], CPAP= 8.5 [1.6 to 44.3] snores/h). In supine snorers both supine-avoidance therapy and CPAP produced a statistically significant reductions in total frequency of snoring.

This study showed a simple supine-avoidance alarm device in patients with supine dependent sleep apnea does not substantially reduce snoring frequency. In contrast, CPAP was substantially more effective in reducing snoring although even with CPAP some residual snoring remained.

Thesis Aims

The primary objectives of the work presented in this thesis were as follows:

The following aims were addressed in the work presented in Chapter 2;

Aim 1: To investigate whether supine-avoidance therapy via a vibratory alarm device is non-inferior compared to CPAP therapy in reducing sleepiness in patients with supine-predominant OSA.

Aim 2: To examine the efficacy of supine-avoidance therapy via a vibratory alarm device compared to CPAP therapy in reducing the apnea/hypopnea index in patients with supine-predominant OSA.

Aim 3: To examine participant adherence to treatment with supine-avoidance therapy via a vibratory alarm device versus CPAP therapy over 6-8 weeks of each therapy in patients with supine-predominant OSA.

The work presented in Chapter 3 addressed the following further aims;
Aim 4: To investigate the temporal relationship between EEG and posture shifts during sleep.

Aim 5: To examine the effect of a vibratory supine-avoidance alarm device on the time taken to return to sleep following attempts to shift to the supine posture during the sleep period.

The work presented in Chapter 4 was designed to address the final thesis aims;
Aim 6: To examine the effect of a vibratory supine-avoidance alarm device on snoring event frequency during sleep in patients with supine-predominant OSA.

Aim 7: To examine the effect of a vibratory supine-avoidance alarm device on snoring frequency during sleep in the sub-group of patients with both supine-predominant OSA and supine-predominant snoring.

Thesis Outline

Chapter 1 Describes the current literature surrounding supine-avoidance therapy and the main existing gaps in knowledge for which the remaining thesis work was designed to help address.

Chapter 2 presents results of a non-inferiority randomised controlled clinical cross-over trial (SUPA trial) to compare the effectiveness of 6-8 weeks of supine-avoidance therapy via a simple vibratory alarm device compared to 6-8 weeks of CPAP therapy in reducing sleepiness in patients with supine-predominant OSA.

Chapter 3 presents a detailed analysis of posture shifts in patients with supine-predominant obstructive sleep apnea specifically seeking to examine if posture-shifts occur primarily from wakefulness or following a brief arousal from sleep and if a supine-avoidance alarm device negatively impacts the time-taken to resume sleep following overnight supine-posture shifts.

Chapter 4 presents an in-depth analysis of supine-avoidance therapy via a vibratory alarm device compared to CPAP therapy on snoring frequency in supine-predominant

obstructive sleep apnea patients and a sub-group of patients who also demonstrated supine-predominant snoring.

Chapter 5 summarises the overall contribution of this thesis work to advancing the field of sleep medicine and research specific to supine-avoidance therapy for supine-predominant sleep problems, outlines the key limitations of the work and highlights future directions for research in this area.

CHAPTER 1. A review of supine dependent obstructive sleep apnea and an emerging new generation of positional therapy

Key points

Question: This Chapter explores the current evidence from the existing literature on supine-avoidance therapy and CPAP therapy in OSA patients and highlights key gaps in knowledge with a particular focus on patients with supine-dependant OSA.

Key Findings: There is limited available evidence to support the treatment efficacy, compliance and the degree of symptom reduction with supine-avoidance therapy in patients with supine-dependent OSA.

Meaning: Objective data remain needed to determine if supine-avoidance therapy can be used as a viable treatment option for a sub-group of OSA patients who are diagnosed with SDOSA in clinical settings.

1.1 Introduction

Around ~30%-65% of obstructive sleep apnea (OSA) patients can be classified as supine dependent (SDOSA), which is traditionally defined based on an apnoea/hypopnea index (AHI) during supine sleep at least twice that of non-supine AHI (Mador et al., 2005a; Marshall et al., 2007; Senaratna et al., 2017; Adams et al., 2017), indicating a substantially higher proportion of breathing interruptions in supine compared to non-supine sleep. For this group, one of the simplest forms of treatment could potentially be to simply avoid supine sleep.

Traditionally, supine-avoidance has been achieved using tennis ball treatment (TBT) (Oksenberg et al., 2006; Bignold et al., 2009), or a similar approach, which involves strapping an object (e.g. tennis ball or another hard object or airbags or similar approaches) to the back to discourage supine sleep through discomfort or a physical impediment to lying supine. TBT is reasonably effective at reducing supine sleep and overall AHI and is low cost (Skinner et al., 2008). However, the inherent discomfort of this approach is problematic for long-term use and around 90% of SDOSA patients report abandoning TBT due to discomfort after only 3 months (Bignold et al., 2009).

Patient acceptance and compliance with continuous positive airway pressure (CPAP), the main first-line treatment recommended for OSA, is also problematic. Although not specifically designed to target SDOSA patients, CPAP therapy is very effective at reducing AHI and improving sleep quality and is most often recommended when patients report excessive sleepiness during the day and exhibit a moderate to severe

AHI (Kribbs et al., 1993; Weaver et al., 2007). However, similar to TBT, treatment compliance remains a significant issue as around 50% of patients recommended CPAP find the mask and pressure uncomfortable and fail to use it for at least 4 hours per night (the cut-off generally accepted as minimum usage for therapeutic benefit), or do not even commence CPAP due to reasons such as high cost of acquiring CPAP, or psychological factors around claustrophobia (Weaver and Grunstein, 2008).

A recent new generation of “smart” supine-avoidance devices show significant promise for effective treatment for patients with SDOSA. These small devices are typically strapped around the chest (Bignold et al., 2011; Dieltjens et al., 2015) or sometimes the neck (Levendowski et al., 2014) and are designed to vibrate each time the user moves on their back during sleep to alert and discourage the wearer from remaining supine. Randomised control trials have shown that these devices can be effective in reducing supine sleep and supine AHI (Van Maanen and De Vries, 2014; Bignold et al., 2011; Berry et al., 2019). Nevertheless, these trials have only been conducted in small samples with little focus on treatment compliance. Consequently compliance relative to CPAP, the current recommended best-practice treatment for OSA, remains unclear. Given very poor acceptance and usage of traditional discomfort-based supine-avoidance treatment, both adequate effectiveness and treatment acceptance and usage compared to established mainstream treatments remain critically important to demonstrate before new generation supine-avoidance treatments can be recommended as a viable treatment option in patients with SDOSA.

Multiple criteria have been used to define and categorise the SDOSA, and this warrants consideration in the context of supine-avoidance treatments given potential impacts on treatment selection, effectiveness and ultimately patient acceptance and adherence to treatment for improving sleep and health outcomes.

A further relevant area for which available literature is currently lacking is the current understanding of the physiological sequence of events associated with posture shifts during sleep. Knowledge regarding these events is likely to importantly guide how positional therapy may impact the physiological propensity for upper airway obstruction and the severity of obstructive breathing events and arousals in SDOSA patients. A leading hypothesis, that either wake or an arousal may be prerequisites for higher cortical co-ordination of body movements necessary to achieve a posture shift during the sleep period remains to be systematically examined. Thus, objective data and a systematic analysis of the electroencephalographic (EEG) sequence of events around posture shifts remain warranted in the context of supine-avoidance treatments. Other physiological changes likely to be temporally associated with posture shifts, such as heart rate and respiratory rate changes also remain to be investigated. Establishing the temporal relationships between physiological changes and posture shifts remains important for evaluating the impacts of a vibration alarm, a key characteristic of new generation supine-avoidance devices that aim to discourage supine sleep but with minimal sleep disruption.

This chapter outlines the range of criteria used to define SDOSA for guiding supine-avoidance treatments, and the available evidence regarding the effectiveness of

SDOSA treatments. A further focus is on trials comparing traditional supine-avoidance therapy with CPAP and new generation positional therapy devices, and on studies examining the timing and nature of physiological changes around the time of posture shifts during sleep.

1.2 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is the most common form of sleep disordered breathing and is characterised by recurrent narrowing (hypopnea) or complete closure (apnea) of the upper airway during sleep. OSA results in intermittent oxygen desaturations, along with frequent arousals that fragment sleep. OSA severity is conventionally determined by the apnea/hypopnea index (AHI), which reflects the number of apneas and/or hypopneas that occur during each hour of sleep. Using current scoring criteria, OSA severity is often categorised as mild with an AHI of 5-15, moderate with AHI 15-30, and severe with AHI greater than 30 (Berry et al., 2012).

Based on an AHI>5, the prevalence of symptomatic OSA ranges from 9% to 38% and is generally higher in men (Senaratna et al., 2017). With an AHI >15, the estimated prevalence of symptomatic OSA in the general population ranges from 6% to 17%, but reaches as high as 49% in older age groups and in obese men and women (Senaratna et al., 2017). Other community cohort studies (Heinzer et al., 2015; Benjafield et al., 2019) suggest that asymptomatic OSA affects roughly 50% of the adult population and that symptomatic OSA impacts around 1 billion people globally (Benjafield et al., 2019; Benjafield et al., 2018).

In a randomised controlled CPAP withdrawal cross-over study OSA related frequent awakenings and hypoxemia have been found to increase stress hormones such as cortisol and to increase blood glucose and fatty acid levels (Chopra et al., 2017) that may ultimately contribute to long-term autonomic, inflammatory, hemodynamic and metabolic disturbances. In cross-sectional studies, OSA has consistently been found to be associated with cardiometabolic problems such as hypertension, stroke, heart failure, cardiac arrhythmias and type 2 diabetes mellitus; and ultimately increased all-cause mortality (Guilleminault et al., 2005; Stein and Pu, 2012; Parish and Somers, 2004; Marshall et al., 2008; Heinzer et al., 2015; Dredla and Castillo, 2019). OSA is also independently associated with increased incidence of mental health problems, including depression and anxiety (Ejaz et al., 2011).

Furthermore, and likely as a result of chronic sleep fragmentation, OSA often results in excessive daytime sleepiness (EDS) associated with increased risk of motor vehicle and workplace accidents, memory loss and reduced workplace productivity (Maspero et al., 2015; White and Younes, 2012). In the United States, undiagnosed OSA has been estimated to contribute an annual economic burden to the community of $149.6 billion a year (Sulivan, 2015). In Australia, the estimated cost of untreated OSA to the economy through direct and indirect costs such as through accidents and lost work-place productivity is around $21 billion a year (Economics, 2017). Thus, it is clearly important that OSA is not only identified and comprehensively diagnosed, but effectively treated via appropriately targeted approaches that can ultimately be demonstrated to effectively and cost-effectively improve individual and public health.

Whilst there is growing research into different endotypes or phenotypes of OSA and their variable aetiology, the predominant cause of OSA clearly remains failure of upper airway musculature to successfully maintain upper airway patency through a combination of anatomical and non-anatomical compromise (Eckert, 2016; Edwards et al., 2017; Edwards et al., 2014). OSA patients show some morphological abnormalities in their craniofacial and pharyngeal measurements, including increased soft palate length and thickness and reduced cross-sectional area compared to healthy adults (Johal et al., 2007).

Upper airway collapse is likely to be further exacerbated by obesity and aging effects. For example, increased fat mass around the neck may also contribute to reduced pharyngeal diameter and mass loading effects on pharyngeal muscles to promote an increased propensity for upper airway collapse (Ahbab et al., 2013; Kim et al., 2014). Abdominal obesity may also promote cranial displacement of the diaphragm and increased collapsibility of the pharyngeal airway through a combination of reduced lung volume and axial tension on the airway (Stadler et al., 2009). When a person transitions from wake to sleep, there is also an abrupt reduction in neural drive to the pharyngeal muscles in the upper airway (Wilkinson et al., 2008), likely directly causing increased upper airway resistance and reduced patency in patients with OSA vulnerable to airway collapse (Stadler et al., 2010). OSA patients also show evidence of poorly coordinated activation of the upper airway muscles and unfavourable biomechanical properties, leaving them susceptible to frequent upper airway collapse (Bilston and Gandevia, 2014).

Recent trends in sleep medicine have been pushing for more targeted therapies for OSA towards a more 'precision medicine' approach (Eckert, 2016; Deacon et al., 2016; Zinchuk et al., 2016). This recognizes that various phenotypes/endotypes exist in OSA, where targeted therapies delivered based on underlying causal mechanisms and/or types of clinical presentation are more likely to achieve maximal treatment efficacy, adherence and thus overall effectiveness. This strategy is likely to achieve improved outcomes for patients compared to the current approach of one-size-fits-all treatment, predominantly via CPAP, which is typically followed by further trial and error treatments which ultimately fail in many patients who do not accept or effectively use CPAP and other alternatives before being lost to follow-up with uncertain outcomes (Eckert, 2016).

The remainder of this narrative review firstly evaluates the existing literature on OSA pathophysiology and current treatment options for SDOSA patients and supine-predominant snorers, and then focusses on sleep position effects in SDOSA patients. Finally, available literature regarding a new generation of non-discomfort-based supine-avoidance devices are examined.

1.3 Literature selections methods

PubMed and Google Scholar were searched for relevant peer reviewed journal articles on OSA, its treatments and physiology. Search strategies aimed firstly to identify relevant publications on obstructive sleep apnea, CPAP effectiveness, patient adherence to treatment and secondly to identify articles regarding the role of physiological responses to position and posture shifts in sleep and how an alarm device may impact OSA severity. These included searches for randomized control trials comparing CPAP to positional therapy, as well as literature surrounding new generation supine-avoidance devices. Given an apparent gap in knowledge regarding the impact of supine-avoidance on OSA and very few relevant articles on the physiology of posture shifts during sleep, searches included articles from 1980 to 2019 selected on the basis that supine dependent OSA was first formally recognised in the mid 1980's (Cartwright et al., 1985). The reference section for each article found was also searched to identify further relevant articles. Keywords used in online searches along with Boolean terms where appropriate included sleep disordered breathing, obstructive sleep apnea, BuzzPod, Nightshift, Night Balance, positional therapy, CPAP therapy, compliance, adherence, supine dependant OSA and supine-avoidance.

1.4 OSA pathophysiology

Traditionally, OSA was considered to reflect anatomical abnormalities, such as a small oropharynx and an abnormally collapsible upper airway that is mostly compensated by increased pharyngeal dilator muscle activity when awake but inadequately compensated during sleep (Figure 1.1) (White and Younes, 2012). However, in line with current concepts of differing endotypes/phenotypes, the aetiology and mechanisms underpinning OSA remain poorly understood and likely differ between individual patients.

The pathophysiology of OSA is clearly more complex than simple anatomical deficits and/or neuromuscular factors alone, with growing evidence to support that more complex and inter-dependent respiratory control, low arousal threshold and ventilatory control instability also play important roles (White and Younes, 2012). During sleep, reduced neural drive to the pharyngeal muscles in the upper airway associated with loss of wakefulness inputs to postural and respiratory muscle tone likely contribute to reduced patency (Wilkinson et al., 2008; Kubin, 2016) , along with a greater reliance on autonomic respiratory control compared to wake.

It is increasingly evident that OSA is a heterogenous disorder with multiple physiological mechanisms influencing its severity (Figure 1.1).

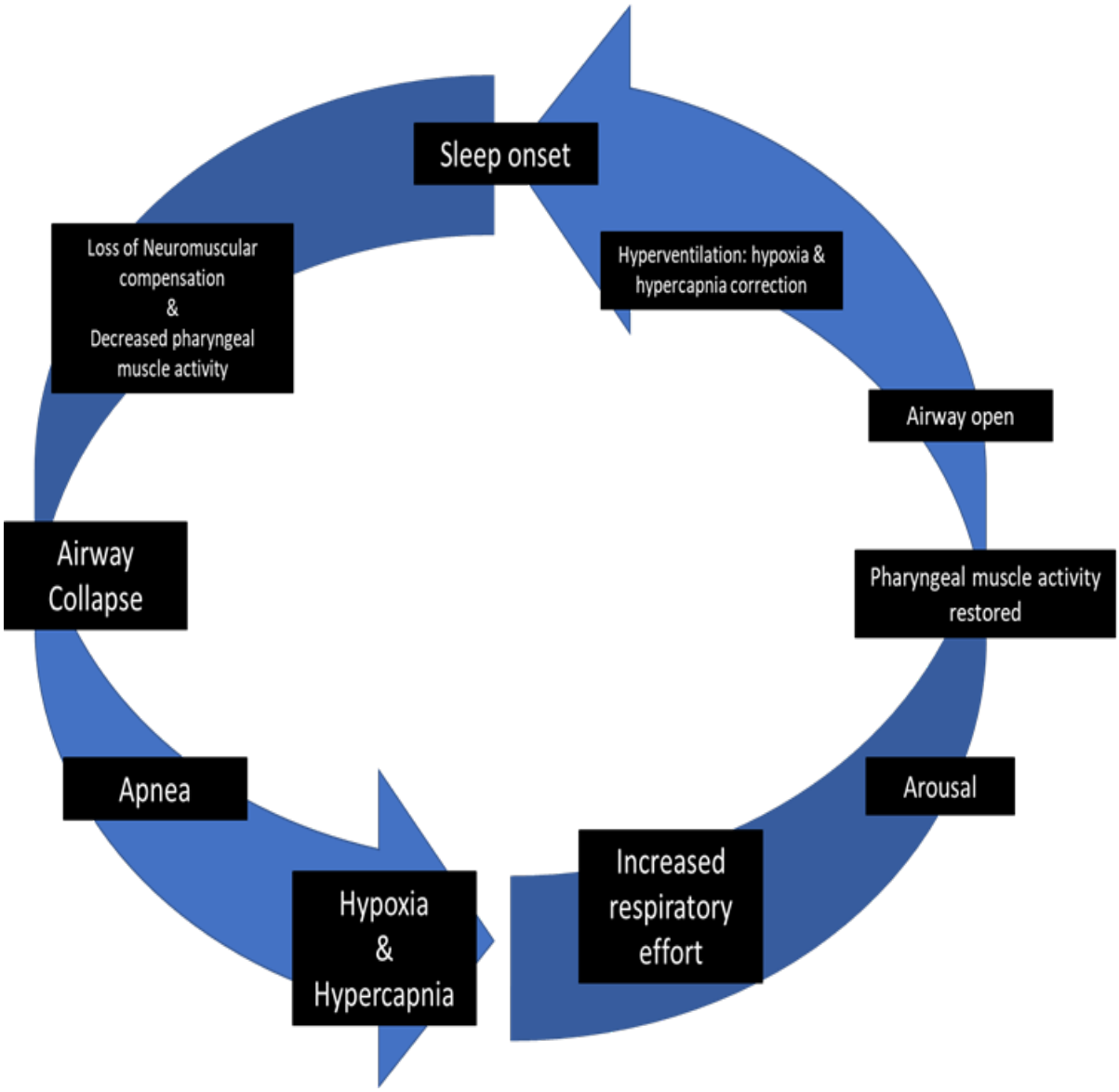


Figure 1.1 Obstructive sleep apnea - cycle of events contributing to frequent apnea/hypopnea during sleep.

1.5 Current treatments

Therapeutic and cost-effective treatments for OSA already exist, but patient acceptance, adherence and access to treatment are all major ongoing problems. A large community survey of 10,000 people aged between 18 to 64 suggested around 6% of the Australian population seek medical help for problem snoring and/or OSA, with 2% reporting subsequent treatment (Marshall et al., 2007); implying that many who seek specialist help do not receive or accept treatment. The Sleep Health Foundation (2017) in Australia reported that 17% of people fall asleep on the job and 29% report making errors at work due to sleepiness (Adams et al., 2017). In combination with estimates that over 80% of adults with OSA remain undiagnosed (Young et al., 1997), this suggests that the burden of treatable OSA and problematic snoring in the community is very large and under-managed. There are several treatment strategies available for patients discussed below.

1.5.1 Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) therapy is the current gold-standard clinical treatment for OSA. CPAP uses an air pump and well-sealed facial mask to create a pneumatic splint to maintain airway patency. This approach is highly effective in normalising breathing in sleep and improving sleep quality and daytime symptoms (Giles et al., 2006). However, CPAP is cumbersome and many patients find it uncomfortable. Side effects are also common with patients reporting claustrophobia, mask leaks and dry eyes and throat (Abdelghani et al., 2009; Bahammam et al., 2015;

Krieger, 1992). Individuals also often remove their CPAP during the night and fail to put it back on (Fan et al., 2019) thus leaving them untreated, potentially especially during the latter part of the night where REM-related OSA and impacts may be most severe (Appleton et al., 2016). Adequate adherence to CPAP therapy, somewhat arbitrarily defined as at least 4 hours use per night for more than 4 nights a week, is highly effective in reducing AHI and improving sleep quality and daytime sleepiness in compliant users (Dempsey et al., 2010; Greneche et al., 2013; Mcevoy et al., 2016). However, CPAP adherence is often poor, and several large randomised controlled trials demonstrate that average CPAP usage is generally below the 4 hour cut-off widely accepted as minimum level of compliance needed for effective long-term treatment (Mcevoy et al., 2016; Fan et al., 2019). CPAP only controls obstructed breathing while an appropriately fitted mask remains in place, and daytime deficits return with a single night of missed treatment (Kribbs et al., 1993). Around 50% of patients recommended CPAP reject it at the outset (Lee et al., 2017), with a further 12-25% of patients who commence treatment abandoning it within 3 years (Engleman and Wild, 2003a). Even patients who continue on CPAP long-term have been shown to demonstrate poor treatment adherence (Weaver and Grunstein, 2008).

On the other hand, CPAP adherence in more recent very large real-world CPAP manufacturer data sets appears to be much higher. Cistulli et al (2019) found in a database of over 2.6 million CPAP users that 75% of patients used CPAP ≥4 h/night on ≥70% of nights in the first 90 days of use and with average daily use per night round 5.5 hours. Similarly, in a larger and longer-term analysis in over 4 million CPAP users, Drager et al (2021) reported that over 80% of patients met conventional criteria of

acceptable CPAP adherence at 3 months, with 75% remaining adherent at 1-year. These apparently discrepant findings with earlier studies may well reflect improved patient engagement tools and changes in testing and insurance criteria for the provision of CPAP, particularly in the USA (Drager et al., 2021). However, higher adherence rates should also be expected in patients who have already committed to using CPAP compared to earlier studies that predominantly investigated CPAP uptake and usage in clinic patients recommended therapy for OSA.

Behavioural interventions may improve CPAP uptake and adherence to some degree, but ultimately the intrusive nature of mask treatments will likely continue to limit widespread acceptance and usage. CPAP is particularly poorly tolerated in milder and asymptomatic cases of OSA (Engleman and Wild, 2003a) and may not be considered a practical primary treatment for mild and relatively asymptomatic OSA or simple snoring. In addition, the burden of wearing a CPAP mask all night for supine dependent OSA may be considered excessive to physicians and patients alike. Although CPAP generally improves bed partner sleep quality (Parish and Lyng, 2003), treatment related disturbance of bed partner sleep can also be a barrier to treatment adherence in some patients (Weaver et al., 2003).

CPAP can also pose a significant financial burden and barrier for some patients, depending on country-specific reimbursements offered through health systems and individual insurance status (Hillman et al., 2006; Weaver, 2006). In Japan, all CPAP therapy costs are paid for by the health system, which has led to high rates of patients who initiate CPAP treatment but low long-term adherence (Tanahashi et al., 2012). In

Israel, CPAP acceptance is significantly greater (~50%) when patients receive financial incentives amongst low socioeconomic echelons (Tarasiuk et al., 2012). A recent study in India found that 60% of patients choose not to buy CPAP citing financial constraints (Goyal et al., 2017). CPAP non-buyers may choose to rent a CPAP machine, but are more likely to have significantly worse compliance when compared to CPAP buyers (Goyal et al., 2017). For the many patients who refuse or choose not to start CPAP therapy, there may be several factors besides financial cost involved in their decision. These could include a family member or acquaintance reporting prior difficulties with CPAP, patients lack of education or perceived need for treatment, living/not living with a partner or simply a fear of or dislike due to the intrusive nature or perceived burden of long-term use of CPAP (Bahammam et al., 2015; Engleman and Wild, 2003b; Goyal et al., 2017; Lee et al., 2017; Weaver, 2006).

As effective as CPAP therapy may be in normalising OSA and symptoms, significant adherence issues and its economic burden has prompted calls for non-CPAP treatment options that are sufficiently efficacious, but more acceptable to patients. Thus, superior treatment outcomes appear likely to be possible through more effectively targeted treatments more specifically targeted to OSA phenotypes or endotypes, and that are more acceptable to patients for more regularly and effective long-term use.

1.6 CPAP alternatives

The main non-CPAP treatments currently in use for OSA include weight-loss (through diet or bariatric surgery), mandibular advancement splint (MAS) devices designed to pull the lower jaw forward to open and stiffen the airway, and upper airway surgery such as modified uvulopalatopharyngoplasty, coblation channelling of the tongue, hyoid suspension and maxilla-mandibular advancement (Kneisley, 1998; Marshall et al., 2007; Basyuni et al., 2018; Carvalho et al., 2012).

1.6.1 Weight loss

There is a strong association between OSA and obesity so weight loss if often strongly recommended as a desirable treatment option to treat and reduce OSA symptoms (Dempsey et al., 2010; Kim et al., 2014; Stadler et al., 2010; Stadler et al., 2009; Supriyatno et al., 2010; Roche et al., 2020). A 10% increase in excess body weight relative to normal body weight is associated with a 32% increase in AHI (Peppard et al., 2000) and a 6-fold increase in the odds of developing moderate to severe OSA (Peppard et al., 2000). Weight loss of around 20 kilograms can successfully reduce AHI by almost 20 events per hour (Smoots and Pisani, 2004). Additionally, leptin, a peptide produced by fatty tissue that regulates homeostatic inflammation, metabolism and sympathetic nerve activity, has been found to influence upper airway patency and resistance along with sleep structure (Imayama and Prasad, 2017). Leptin appears to play a complex role in OSA and its severity as it can be both a bi-product of OSA (via leptin resistance) and a marker of cardiovascular diseases and obesity (Martin et al.,

2008; Wannamethee et al., 2007). Patients diagnosed with OSA show a higher level of leptin that is positively correlated with more severe OSA. Imayama et al. (2017) investigated leptin levels in 32 obese men compared to 32 matched obese men without OSA. Leptin levels were higher in obese men with OSA, suggesting a potential role of OSA in leptin resistance. Leptin resistance in OSA patients could hinder weight loss efforts and may contribute to worsening of OSA.

Although weight loss is strongly recommended for obese or overweight patients with OSA, effective and sustained weight loss is generally very difficult to achieve and maintain for most patients. Patients who choose to undergo weight loss surgery, such as Roux-en-Y gastric bypass (RYGB), often show effective treatment outcomes in the short term, but may return to preoperative BMI in the longer-term (Hawkins et al., 2017).

1.6.2 Mandibular advancement splint (MAS) device and surgical treatments for OSA

The effectiveness of MAS and surgery is more variable and difficult to predict compared to CPAP (Mackay et al., 2013). MAS devices greatly differ in types and design with many variants available on the market. MAS devices generally increase the diameter of the airway through soft tissue displacement by protruding the mandible forward which in turn changes the jaw and tongue position to help open and stiffen the upper airway (Casey, 2015). MAS efficacy is variable, and although AHI reductions can range from around 30% to 70% in different groups of patients (Basyuni et al.,

2018), and some individuals show good treatment outcomes, in others MAS can be totally ineffectual.

Most MAS studies have focussed on AHI as the primary outcome. However, AHI shows only weak relationships with symptoms for which patients seek treatment so may not be the best outcome measurement from which to gauge effective treatment outcomes for patients. Side effects of MAS devices such as hypersalivation, dry mouth, dental pain, gingival irritation, myofascial pain and temporomandibular joint (TMJ) discomfort may also impact both treatment effectiveness and tolerance (Basyuni et al., 2018).

Surgical treatments for OSA aim to increase airway patency by targeting specific sites of obstruction, which often differ between individual patients (Carvalho et al., 2012). There are several surgical methods available and each have different success rates and variable outcomes depending on the selected patients and procedures. For example, tongue surgeries including posterior midline glossectomy or radiofrequency ablation show success rates ranging from around 25% to 80% (Kezirian and Goldberg, 2006; Nelson and Barrera, 2007). Maxillomandibular advancement (MMA) has perhaps the highest rate of success (80%-90%) with approximately equivalent effectiveness compared to nasal CPAP (Caples et al., 2010; Holty and Guilleminault, 2010). In addition to the general risks involved with any surgery, sleep apnea increases surgical anaesthesia risks (Carvalho et al., 2012; Casey and Teodorescu, 2015; Franklin et al., 2009). Patients often require endotracheal intubation given that anaesthesia poses an airway risk in OSA patients, which in turn may lead to a longer

hospital stay. Other surgical risks include excessive bleeding, infection, deep vein thrombosis, additional breathing problems and allergic reaction to anaesthesia (Carvalho et al., 2012).

One other important factor to consider, especially in clinical settings, is adherence to therapy. There are strong interactions between perceived symptoms, adherence to treatment and treatment outcomes in patients with OSA. For example, asymptomatic patients are less likely to perceive treatment benefit and thus to adhere to treatment compared to patients who perceive symptom improvements and are therefore more likely to be treatment adherent (Weaver and Grunstein, 2008). This phenomenon is not restricted to OSA and a World Health Organization report concluded that 50% of patients living with chronic conditions do not adhere to treatment (De Geest and Sabate, 2003), quite similar to adherence rates observed in patients who frequently discontinue CPAP treatment after 6 months (Kribbs et al., 1993). Adherence to therapy is thus an important focus of new and emerging treatments for OSA where treatments typically aim to maximise effectiveness through both high efficacy and adherence. Hypoglossal nerve stimulation (HNS) is a relatively new treatment where upper airway neuromuscular stimulation is used to reduce airway collapsibility. HNS has been shown to substantially reduce AHI (Eastwood et al., 2020; Friedman et al., 2016; Steffen et al., 2018; Strollo et al., 2014) and to be well tolerated by most patients, but is generally less efficacious compared to CPAP (Hofauer et al., 2019; Kent et al., 2016; Kezirian et al., 2014). Given that HNS devices are implanted adherence rates are typically high. However, adverse events such as pain, tongue abrasions or

internal/external device malfunction can also limit treatment adherence in same cases (Kompelli et al., 2019).

Given that OSA is a heterogeneous disorder with multiple anatomical and non-anatomical factors contributing to aetiology and severity, pharmacological agents targeted to a range of relevant physiological factors have the potential to usefully treat OSA. For example, sedative drugs such as Zopiclone, have the potential to help treat patients with a low arousal threshold who arouse to relatively mild obstruction that could potentially be compensated through increased breathing effort and upper airway muscle recruitment with a higher arousal threshold. Zopiclone has been studied in short-term trials typically involving only one night, so long-term adherence data remain lacking (Carberry et al., 2017; Eckert et al., 2011; Roth et al., 2005). In the largest and longest duration randomised double-blind parallel group study to date of Zopiclone for the treatment of OSA, Carter and colleagues (2018) found treatment adherence over one month to be high in both treatment and placebo groups (mean±SD 93.4%±11.0% and 93.7%±9.7%, respectively). However, only one third of patients reported to be willing to continue to take medication if it were available beyond the trial.

There is also evidence to support that ineffective upper airway dilator muscle recruitment can be improved with targeted pharmacotherapy using serotonergic, noradrenergic and antimuscarinic medications such as atomoxetine and oxybutynin. These drugs have also been mostly studied in single night randomised controlled conditions using relatively small sample sizes and no adherence data reported (Taranto-Montemurro et al., 2019).

A hypersensitive ventilatory control system (high loop gain) has also been recognised to likely play an important role in promoting unstable breathing in many individuals with OSA. Consequently, medications such Acetazolamide, or O_2 therapy, targeted to reduce loop gain could potentially be useful in some patients. Acetazolamide has been shown to be effective in reducing AHI in OSA (Schmickl et al., 2020), but as with other recent pharmacotherapies, long-term adherence data are relatively lacking as most studies have only examined the effectiveness of Acetazolamide at high doses given only for one night (Edwards et al., 2012; Javaheri, 2006). In the few longer-term studies of Acetazolamide, many patients reported discontinuation of treatment due to adverse drug effects (Debacker et al., 1995; Ulrich et al., 2015; Sakamoto et al., 1995; Latshang et al., 2012).

Non-CPAP treatments typically show poorer and less predictable efficacy outcomes and thus more variable success rates compared to CPAP and, much like CPAP, this includes a component of variable adherence. More accessible and acceptable treatments than those currently available are clearly still needed to more efficiently and effectively treat patients with OSA long-term. One particularly promising form of treatment, and the primary focus of the work described in this thesis, is supine avoidance in patients with supine-predominant respiratory disturbances during sleep.

1.6.3 Sleep posture monitoring

There are several proposed methods for measuring and monitoring posture in sleep, although there is no general consensus on how posture measurements should be conducted or classified for the assessment of posture-related sleep disorders (Dingli et al., 2003; Liu et al., 2013; Jeng et al., 2021; Clemente et al., 2020; Ren et al., 2016; Ferrer-Lluis et al., 2021) . Traditionally, in clinical settings, posture is assessed using a combination of periodic manual assessment of video monitoring during a polysomnography study, along with position sensor signal acquisition across the night. With the advancement of PSG recording devices, most systems use tilt-sensing devices or an accelerometer to assess the angle of the position sensor device, usually worn on the chest. PSG systems then typically apply custom algorithms to classify posture, often into 5 basic body positions including left and right lateral, supine, front or prone and upright positions (Dingli et al., 2003). Depending on sensor type and position, this approach is not necessarily entirely reliable and warrants validation against video confirmed posture monitoring of the PSG. The accuracy of PSG posture recordings with ambulatory devices, particularly in home set-up sleep studies remains largely unknown. Other methods such as a dense pressure-sensitive bedsheet (Liu et al., 2013), a wrist worn sensor (Jeng et al., 2021), bed frame mounted sensors (Clemente et al., 2020), a depth sensing camera (Ren et al., 2016), and smart phone tri-axial accelerometer (Ferrer-Lluis et al., 2021) have also to some extent been tested and used for posture monitoring. In general, these appear to achieve greater than 80% accuracy, but have only been tested in relatively limited settings with variable posture classification approaches and small sample sizes. For the most part posture

monitoring has almost exclusively been directed at body position, so very little remains known regarding the effects of head and neck position relative to body position.

1.6.4 Sleep posture - supine-dependent OSA (SDOSA)

Multiple definitions have been used to describe supine-dependent OSA (SDOSA) such as supine isolated (Sutherland et al., 2015) or supine-predominant OSA (Kim et al., 2016). However, there are currently no universal clinical criteria for the diagnosis of SDOSA. Cartwright's classic definition of supine-predominant OSA was defined on the basis of a supine AHI at least twice that of the non-supine AHI (Cartwright et al., 1985). This definition was subsequently adapted by Mador et al. (2005) to include a normal non-supine AHI (<5 /h based on AHI scoring criteria at that time) determined from a minimum of 30 minutes of sleep in each posture and a >50% reduction in AHI between supine and non-supine postures. This definition has advantages over Cartwright's definition for use in clinical practice since, by definition, patients who meet these criteria have clinically significant OSA that would be expected to normalise with successful supine-avoidance treatment given the combination of sufficient accumulated supine-sleep time and elevated AHI contribute to the OSA classification itself. However, further definitions have also been advanced to include somewhat different criteria, such as the Amsterdam positional OSA classification (APOC)(Frank et al., 2015) and a 4:1 supine: non-supine AHI ratio to define supine-isolated OSA which appears to be a more stable measure of supine dependence night to night (Joosten et al., 2014a).

Irrespective of classification methodology, it has also been known for some time that the upper airway is more susceptible to collapse when a person is sleeping supine compared to non-supine positions (Benumof, 2016; Cartwright et al., 1991; Cartwright et al., 1985). Although mechanisms and the degree of influence sleep position on the upper airway remain incompletely understood, gravitational effects on the tongue, upper airway and potentially caudal tracheal traction and lung volume dependent effects may all play a role. Numerous studies show that supine AHI is significantly higher compared to non-supine AHI in a substantial proportion of OSA patients (Berry et al., 2019; Bignold et al., 2009; Bignold et al., 2011; Cartwright et al., 1991; Frank et al., 2015; Ha et al., 2014; Joosten et al., 2014a; Kavey et al., 1985).

Depending on how supine-predominant OSA is defined, between 35%-60% of OSA patients suffer from SDOSA (Mador et al., 2005a; Adams et al., 2017). For sufferers of SDOSA, supine sleep avoidance could be a very simple, low cost and potentially more effective treatment than other forms of OSA treatment (Engleman and Wild, 2003a; Ha et al., 2014). Patients in this group have been shown to be thinner, younger, with lower neck circumference and lower AHI compared to non-positional OSA (Mador et al., 2005a; Oksenberg and Gadoth, 2019).

1.7 SDOSA pathophysiology

Several observations have been made involving anatomical and physiological factors that may play a role in explaining strong associations between posture and OSA. Gravity has major effects on upper airway tissues such as the tongue and soft palate

(Walsh et al., 2008) and on diaphragm position and lung volume that may further influence the propensity for upper airway collapse via airway stiffening effects of tension on the upper airway from the trachea and other intra-thoracic structures (Van De Graaff, 1991). OSA is virtually abolished in the microgravity of space and most patients show more severe OSA when supine (Prisk, 1998).

Airway lumen shape, size and tendency to collapse are determined by factors such as bony structures (e.g. maxilla, mandible) and size of soft tissue (e.g. tongue) that may ultimately define airway behaviour during sleep when neuromuscular compensation responses may be diminished. Pharyngeal area has been shown to decrease in OSA patients when changing posture from sitting to supine, followed by an increase in uvular width and narrowing of the retroglossal airway when patients adopt the supine posture (Walsh et al., 2008). Most of these anatomical changes have been investigated in patients who were awake (Miyamoto et al., 1997; Walsh et al., 2008). In sleeping patients, particularly when supine, lung volume decreases are associated with increased upper airway resistance, although this might just be a normal response to supine sleep (Dempsey et al., 2010; Joosten et al., 2015; Marques et al., 2017). Upper airway muscle function may also play an important role in determining the severity of OSA. During non-rapid eye movement sleep, genioglossal muscle responsiveness to negative pressure pulses has been shown to decrease in the supine compared to lateral decubitus position (Malhotra et al., 2004). Genioglossal EMG activity is also significantly reduced by head/neck rotation in both upright and supine postures suggestive of simultaneous changes in airway stiffness, patency and muscle activity (Otsuka et al., 2000).

However, in most OSA patients AHI is generally higher in the supine position than when sleeping laterally, especially in mild OSA cases, even when the formal definition of SDOSA is not necessarily met (Cartwright et al., 1991; Kavey et al., 1985; Mador et al., 2005b). In a small study of 13 male patients with OSA examined during an all-night polysomnography while inclined at an angle of 60 degrees versus lying supine, AHI was decreased (inclined 19.6 ± 6.9/h versus supine 48.9 ±5.4/h, $p<0.0005$) and both mean and minimum arterial oxyhaemoglobin saturation (SaO_2) were increased (nREM; mean inclined 92.1 ± 0.5% versus supine 90.6 ± 0.8%, $p<0.005$; minimum inclined 80.8 ± 2.1% versus supine 64.8 ± 3.2%, $p<0.005$) (Mcevoy et al., 1986). Similar findings were observed in another study where 8 patients with severe OSA who slept in supine, lateral and 30-degree elevated positions, showed less collapsible airway pressures and a 50% reduction in upper airway opening pressures in lateral and elevated compared to supine positions (Neill et al., 1997).

In addition to an increased AHI, respiratory events have been shown to be more severe and more prolonged in the supine compared to lateral postures (Oksenberg and Silverberg, 1998; Poyares et al., 2002; Edwards et al., 2017). AHI also appears to be less dependent on position in more severe OSA. However, recent evidence suggests that almost one third of patients with severe OSA may also have supine-dependent OSA and hence could also benefit at least to some extent from supine-avoidance therapy (Oksenberg and Gadoth, 2019).

1.8 Discomfort based and position modifying treatments

CPAP, which is designed to treat OSA regardless of underlying causes, is inherently somewhat intrusive and uncomfortable, and despite high efficacy only around 50% of patients recommended CPAP ultimately accept and adequately use it long-term (Catcheside, 2010). MAS devices are also somewhat intrusive and uncomfortable. Consequently, even conventional treatments for OSA are associated with a degree of discomfort.

Supine sleep avoidance has been traditionally achieved by strapping a bulky object, such as a tennis ball, to the back to counteract supine posture shifts through discomfort (Skinner et al., 2008). When appropriately applied to patients with supine-predominant OSA, the 'tennis ball treatment' (TBT) is more targeted, simpler and cheaper compared to CPAP therapy and can be effective in lowering AHI by decreased time spent in supine sleep (Skinner et al., 2008; Jokic et al., 1999). However, in a survey follow-up of patients recommended TBT in clinical practice, almost 90% of patients reported abandoning TBT within a median time of 1 month due primarily to discomfort (Bignold et al., 2009). Thus, discomfort with this traditional approach is clearly highly problematic to the extent that TBT cannot be recommended as a viable long-term treatment for positional OSA. Other supine-avoidance approaches, such as position restricting devices (e.g. supine prevention vest), anti-snoring pillows (Zuberi et al., 2004) and auditory alarms (Cartwright et al., 1991) have been reported, but data to support clinical effectiveness and patient comfort, acceptance and compliance with long-term use remain remarkably limited. An ongoing lack of evidence to support

effective treatment outcomes with these forms of treatment remains problematic for guiding evidence-based treatment recommendations, particularly given strong evidence to support that comfort is fundamentally important to achieve effective treatments that patients will also accept and use long-term.

Although some patients claim to learn to avoid the supine posture during sleep (Bignold et al., 2009; Oksenberg and Silverberg, 1998), there are very few studies to support long-term supine-avoidance conditioning effects with positional therapies. Two studies (Chaudhary et al., 1986; Cartwright et al., 1991) have shown that there might a proportion of patients who learn to avoid supine sleep with or without ongoing use of a supine-avoidance device. There is also some anecdotal evidence that patients claim to have learnt to avoid supine sleep after using a supine-avoidance device (Bignold et al., 2009; Van Maanen et al., 2013). However, there is also some evidence from clinical experience that patients revert to sleeping supine (Oksenberg et al., 2006). Evidence to support the hypothesis that patients may become effectively trained or conditioned to avoid supine sleep remains lacking.

Considering the significant role of posture in influencing OSA propensity and severity and the large number of patients with position-dependent OSA, it is surprising that fundamental knowledge gaps remain regarding posture shifts during sleep and potential positional effects on clinical outcomes. For example, agreed standards for defining positional OSA remain unclear. Perhaps more importantly, knowledge regarding the physiological responses before and after posture shifts during sleep remain remarkably lacking. There is also a dearth of literature comparing usual care

to supine-avoidance therapy, especially when it comes to vibration based alarm devices and their effect on OSA patients or snorers. A better understanding of the pathophysiology of position dependent OSA and treatment outcomes is needed to better manage positional OSA and its symptoms.

1.8.1 Positional therapy and the new generation of supine-avoidance alarm devices

Low adherence to traditional supine-avoidance strategies has prompted exploration of new non-discomfort based supine alarm devices designed to discourage supine sleep with minimal discomfort. These new generation of devices include a sleep position trainer (SPT) (Berry et al., 2019; Laub et al., 2017) and other devices worn on the chest (Bignold et al., 2011) or on the neck (Levendowski et al., 2014; Van Maanen and De Vries, 2014) via a strap, and use a position triggered alarm to vibrate shortly after patients shift to the supine position (Figure 1.2). A vibration stimulus is generally used in preference to an auditory alarm more likely to disturb bed-partner sleep. The concept of using smart devices to avoid supine sleep is relatively new, such that clinical trials investigating the efficacy of these devices and whether they can be used as a successful treatment option for positional OSA remain limited.

Six small randomised clinical trials to date have examined several of these new smart devices and in general showed positive results regarding reduced supine sleep time (Bignold et al., 2011; Levendowski et al., 2014; Van Maanen et al., 2013; Dieltjens et al., 2015; Mok et al., 2020; Hidalgo Armas et al., 2019). In a small proof of concept

study, Bignold (2011) showed that a new generation of supine-avoidance alarm device is effective in reducing supine sleep time from (mean ± SEM) 19.3% ± 4.3% to 0.4% ± 0.3% of sleep ($p < 0.001$) and in reducing AHI (25.0 ± 1.7 to 13.7 ± 1.1 events/h, $p = 0.030$). Dieltjens (2015) compared the addition of a vibration alarm SPT device to MAS therapy in 20 SDOSA patients and found that individually both MAS and SPT were effective in reducing AHI from 20.9 (95% CI 17.0 to 34.0) /h at baseline to 11.0 (6.6 to 14.0) /h and to 12.8 (3.9; 17.9) /h with MAS or SPT, respectively. However, a combination of both therapies had an even greater effect on reducing AHI to 5.5 (3.4 to 7.2) /h. Levendowski (2014) assessed the effectiveness of a neck worn vibration alarm device in reducing supine sleep in 30 SDOSA patients and found that 83% of participants showed an overall reduction of at least 50% in supine sleep time when using the SPT device with supine sleep reduced from 44% of total sleep time at baseline to just 2% at the end of 4 weeks of treatment. In a recent randomised controlled trial, Mok (2020) compared the effectiveness of CPAP vs positional therapy using the NightShift device in patients with excessive daytime sleepiness (ESS>10) to test the hypothesis that supine-avoidance is non-inferior to CPAP at reducing ESS. Although ESS and AHI were reduced with both treatments, the difference in ESS between treatments exceeded the author's pre-specified non-inferiority margin of 1.5, so non-inferiority could not be concluded (Mok et al. 2020).

Hidalgo Armas et al. (2019) also found improvements in AHI and oxygen saturation with 4 weeks of supine-avoidance therapy using a vibrating device; from a median (IQR) baseline AHI of 30.7 (23.2–38.2) to 21.5 (12.4–24.3) /h at the end of treatment. Time spent supine was also significantly reduced from (mean ± SD) 51.5 ± 14.8% to

25.2 ± 21.0% (Hidalgo Armas et al., 2019). However, further studies to determine if time spent supine can be reduced further by more effective devices and if time spent supine is reduced during sleep versus wake remain warranted.

In a larger randomized controlled trial, Laub (2017) and colleagues randomised 101 SDOSA patients to an SPT group (n=52) or a control group (i.e. no treatment, n=49) and found AHI after 6 months of SPT reduced from (mean ± SD) 35 ± 18 /h to 10 ± 9 /h ($p < 0.001$) compared to 18 ± 10/h ($p > 0.05$) in the control group. In addition, in the SPT group the average supine sleep time decreased from 47 ± 22% to 17 ± 18% ($p < 0.001$) compared to 39 ± 21% ($p > 0.05$) after 2 months in the control group (Laub et al., 2017).

A Cochrane Review in 2019 ultimately included only three studies that compared positional therapy with CPAP and concluded that ESS was not different between the two forms of treatment. However, CPAP produced a consistently greater AHI reduction, but with lower adherence to treatment compared to positional therapy (Srijithesh et al., 2019).

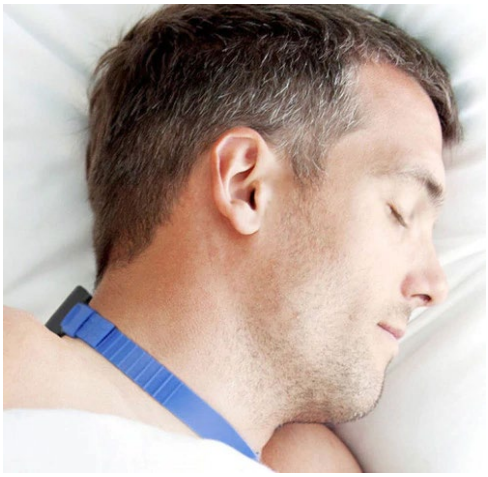


Figure 1.2 Two variants of vibration based supine-avoidance alarm devices. BuzzPOD (Gorman Pty Ltd) worn in the chest (left). Nightshift (Advanced Brain Monitoring, Inc.) worn on the neck (right).

Other vibration-based alarm devices have also been shown to be effective in reducing supine sleep time and overall AHI (Eijsvogel et al., 2015; Van Maanen et al., 2013). Assessment of a neck worn alarm device showed a reduction to <3% supine sleep (compared to ~47% in baseline) and a 50% reduction in overall AHI after several weeks of using the device including 1 night of polysomnography (Levendowski et al., 2014). Two other devices with similar functionality, but strapped around the chest rather than the neck, also showed a significant decrease in supine sleep time (Eijsvogel et al., 2015; Van Maanen and De Vries, 2014; Van Maanen et al., 2013).

Although a range of new generation supine-avoidance devices show promising results for reducing supine sleep time and thus overall AHI in patients with supine-predominant OSA (Laub et al., 2017; Eijsvogel et al., 2015), results to support reduced daytime sleepiness or improved quality of life remain lacking and somewhat

unconvincing. A fundamental issue of existing studies is the use of variable definitions of SDOSA, which likely influences the target populations selected for study and may influence the apparent clinical effects of these devices (Dieltjens et al., 2015; Eijsvogel et al., 2015; Laub et al., 2017; Van Maanen and De Vries, 2014; Van Maanen et al., 2013). In addition, whether standard CPAP therapy is still the better option for SDOSA patients compared to positional therapy remains unknown due to an ongoing lack of objective data regarding how new positional therapies compare to CPAP in terms of efficacy and compliance and thus overall effectiveness to reduce AHI, as well as cost, symptom relief and overall quality of life (Oksenberg et al., 2019).

Ongoing uncertainty with all supine-avoidance treatments, including the new vibration-based alarm devices, arises from a considerable lack of clinical evidence regarding the impact of supine-avoidance therapies on sleep quality. In the context of new generation supine-avoidance devices, it remains unclear if vibration alarms triggered by supine posture shifts might be disruptive to sleep through exaggerated or potentially more prolonged awakenings. Alternatively, posture-shifts themselves may well require either wakefulness or brief arousal to engage higher motor control functions potentially needed for co-ordinated muscle activity necessary to shift body position, in which case an additional alarm may have relatively little impact on the process of returning to sleep following body movements. However, remarkably little is known regarding the sequence of events preceding posture shifts in sleep, with no objective evidence available in the literature to guide if a brief return to consciousness is required to engage muscle activity to change posture, followed by a return to sleep with little or

no conscious perception or lasting memory of the posture change itself (Tassi and Muzet, 2001).

Combination therapies that combine positional and another form of therapy to improve overall treatment efficacy are a further option that has received relatively little attention to date in the literature. At the time of writing, only one study appears to have investigated the effects of combining a supine-vibration alarm with a mandibular advanced device, where combination therapy led to higher therapeutic efficacy when compared to either therapy used alone (Dieltjens et al., 2015). An earlier study to investigate the combination of a tongue retaining device (TRD) and an auditory posture alarm to avoid supine position was reported by Cartwright et al. (1991). This study found that 11/15 (73%) participants achieved an AHI<5 events /h (i.e. a successful treatment response) with combined TRD and posture alarm treatment compared to fewer achieving treatment success with supine avoidance auditory alarm (60%) or TRD (53%) treatment alone. In addition, weight loss may also be usefully combined with positional therapy and obese patients with OSA have been shown to transition into mainly supine-predominant OSA following significant weight loss (Joosten et al., 2017). Thus, supine avoidance therapy combined with weight loss could potentially be curative for some patients.

1.9 Habitual snorers without OSA

Snoring and OSA are part of a continuum of obstructed breathing in sleep. Around 95% of OSA patients snore heavily most or every night (Viner et al., 1991) and there

are strong correlations between snoring frequency and intensity and respiratory and arousal disturbances in sleep (Wilson et al., 1999). Habitual loud snoring is at least as common as OSA, affecting somewhere between 15-54% of all middle-aged adults (Enright et al., 1996; Young et al., 1993).

However, there are no standardised or gold-standard methods for quantifying and classifying snoring, and assessment methods often vary widely between studies. Individual snorer and bed-partner perceptions regarding problem snoring are also highly variable (Hoffstein et al., 1996). The American Academy of Sleep Medicine (AASM) recommends three measures of snoring: an over-head acoustic sensor, a piezoelectric sensor and a nasal cannula pressure transducer (Arnardottir et al., 2016). Comparisons against a microphone attached to the chest show sensitivity and positive predictive values of scoring snore events of 0.78 and 0.98 respectively for an overhead acoustic sensor, 0.55 and 0.67 for a nasal cannula and 0.78 and 0.92 for a piezoelectric sensor (Arnardottir et al., 2016). However, there is also no unified agreement regarding optimal placement of microphones in either laboratory of home PSG settings (Arnardottir et al., 2016; Dafna et al., 2014). This lack of standardisation and agreed measurement guidelines for snoring assessment remains problematic for both research and clinical decision making relevant to snoring.

Snoring is often trivialised, but negative effects on snorer and bed partner sleep quality can be substantial. Snoring frequently disrupts patient *and* bed partner sleep contributing to insomnia, psychosocial problems and reduced quality of life (Mcardle et al., 2001). Snoring has also been linked to marital problems (Jones and Swift, 2000),

occasional acts of violence including homicide (Pelausa and Tarshis, 1989) and is a leading reason patients seek specialist ear, nose and throat (ENT), and sleep treatments (Mcardle et al., 2001; Marshall et al., 2007). Increased cardiovascular risk from snoring alone is also plausible, via vibration-induced vascular injury and effects of chronic cardiac exposure to large negative intrathoracic pressures thought to cause right ventricular hypertrophy, as has been demonstrated in rats (Salejee et al., 1993). Further animal data show that snoring vibrations are transmitted to the carotid arteries (Amatoury et al., 2006), and that vibration *in vitro* induces arterial endothelial cell inflammation and damage (Curry et al., 2002; Puig et al., 2005). A dose-dependent relationship has also been shown between snoring severity and carotid, but not femoral artery, atherosclerosis (Lee et al., 2008). Available data are therefore consistent with the hypotheses that chronic obstructed breathing in sleep increases adverse cardiovascular outcome risk and that snoring vibrations may contribute to carotid arterial damage, plaque rupture and stroke risk.

Like OSA, snoring propensity and severity can be strongly influenced by posture. Limited epidemiological data are available to guide how many people suffer from only supine-predominant snoring without OSA. However, the American Sleep Association estimates that 90 million Americans suffer from chronic snoring, with around half that number potentially also exhibiting OSA. Snoring, besides being an early sign of possible future OSA, is disturbing to bed partners and may reduce their sleep quality.

Supine-avoidance has been found to be effective in reducing habitual snoring (Cartwright et al., 1985; Jones and Swift, 2000), but there is currently a lack of

evidence to support the effectiveness of new generation supine-avoidance devices for reducing habitual snoring.

1.10 Conclusion

Despite the growing body of knowledge in sleep medicine, further research is needed to better understand the role of supine sleep posture in the pathophysiology of OSA and the efficacy, adherence to treatment and overall effectiveness of non-discomfort supine-avoidance treatment compared to CPAP. There is also limited knowledge regarding the sequence of events associated with posture shifts in sleep and the impact of supine-avoidance alarms on sleep in the post-posture shift period. A better understanding of physiological events accompanying posture shifts, and the importance of supine posture in OSA is needed to more effectively guide improvements of supine-avoidance targeted therapies for OSA.

The work described in this thesis aimed to fill some of the key existing gaps in knowledge regarding the treatment of supine-predominant OSA by means of a simple supine-avoidance alarm device compared head-to-head with CPAP. In the first experimental chapter (Chapter 2) the primary aim was to investigate the efficacy of a vibration-based supine-avoidance alarm device against usual care (CPAP) in reducing sleepiness, the primary symptom complaint of clinical concern in patients with supine-predominant OSA. A secondary aim was to examine the comparative treatment efficacy, adherence and overall effectiveness over 6-8 weeks of treatment with each

therapy. Chapter 3 reports on a detailed analysis of temporal relationships between posture shifts during the sleep period and key relevant physiological responses including wake versus sleep and arousals immediately prior to posture shifts and the time taken for sleep to resume following posture shifts with versus without supine-avoidance alarms. In the final experimental chapter (Chapter 4), the effects of a supine-avoidance alarm device compared to CPAP on snoring in supine-predominant OSA patients was evaluated. The final chapter (Chapter 5) briefly summarises the overall thesis findings and makes recommendations for future research towards further improvements in supine-avoidance therapies for supine-predominant OSA and snoring.

CHAPTER 2. The clinical effectiveness of simple supine-avoidance versus continuous positive airway pressure for the treatment of supine-dependent obstructive sleep apnea : The SUPA randomised controlled trial

Key points

Question: This study sought to test the hypothesis that supine-avoidance via a vibration alarm device is non-inferior to CPAP therapy in reducing daytime sleepiness in patients with supine-predominant OSA and achieves greater treatment adherence over 6-8 weeks of each therapy.

Findings: In 66 patients with supine-predominant OSA supine-avoidance therapy was non-inferior to CPAP in reducing excessive daytime sleepiness and achieved superior treatment adherence.

Meaning: Supine-avoidance is an effective treatment option for patients with supine-predominant OSA

Abstract

Around 50% of OSA patients show supine-predominant OSA, where simply avoiding supine sleep could potentially be a highly effective therapy. However, traditional methods of supine-avoidance, such as strapping a tennis ball to the back, are inherently uncomfortable and most patients self-report abandoning discomfort-based treatments within around one month. Modern non-discomfort supine-alarm devices are now widely available, but evidence remains lacking to support sufficient effectiveness and adherence to treatment to reduce excessive daytime sleepiness compared to standard treatment with continuous positive airway pressure (CPAP).

This study was designed to test the hypothesis that in patients with supine-predominant OSA, alarm-based supine-avoidance is non-inferior to CPAP for reducing daytime sleepiness and achieves superior treatment adherence compared to CPAP over 6-8 weeks follow-up.

66 patients with supine-predominant OSA and Epworth sleepiness scale (ESS) score ≥8 completed baseline measurements including questionnaires, inactive supine-avoidance for 1 week for pre-treatment supine-time measurements, and in-home full polysomnographic evaluation of sleep. Patients were then randomised to active supine-avoidance or CPAP treatment, followed by cross-over to the remaining treatment after 6-8 weeks. Repeat questionnaires, sleep studies and treatment adherence measurements were collected after 6-8 weeks on each treatment. Non-inferiority was assessed from the change in ESS with supine-avoidance compared to CPAP using a pre-specified non-inferiority margin of 1.5. Average nightly use over all

nights, and treatment efficacy in repeat home sleep studies were also compared between treatments.

Patients were predominantly males (62%) aged (mean±SD) 52.8±11.9 years, body mass index 31.9±7.8 kg/m², with a baseline sleep study showing supine-predominant OSA (total, supine and non-supine AHI 18.0±8.9 and 40.2±38.8, 5.0±3.2 /h respectively), a moderate degree of daytime sleepiness (ESS 10.3±3.9) and substantial supine sleep time (47.6±20.4%). After 6-8 weeks of treatment a reduction in ESS with supine-avoidance (mean [95%CI] -1.9 [-2.9 to -0.9]) was no worse than with CPAP (-2.3 [-3.3 to -1.3], difference -0.2 [-1.3 to 0.9]). Average treatment usage was substantially higher with supine-avoidance compared to CPAP (5.6 [5.0 to 6.3] versus 3.9 [95%CI 3.2 to 4.6] h/night, p< 0.001), although efficacy and effectiveness for reducing AHI was lower.

This study supports that alarm-based supine-avoidance is non-inferior to CPAP for reducing sleepiness and achieves superior treatment adherence over 6-8 weeks of treatment in patients with supine-predominant OSA.

2.1 Introduction

Obstructive sleep apnoea (OSA) is the most common form of sleep disordered breathing and affects around 25% of men and 10% of women (Heinzer et al., 2015; Young et al., 2002; Adams et al., 2016). Largely untreated OSA is estimated to cost around $150 billion in direct and indirect financial costs in the USA alone (Economics, 2017; Hillman et al., 2006; Sulivan, 2015). OSA is characterised by frequent upper airway collapse, with periods of absent or severely reduced ventilation and recurrent brief arousals that cause severe sleep disruption and marked repetitive oxidative and cardiovascular system stress. OSA is an established risk factor for excessive daytime sleepiness, cognitive impairment, motor vehicle and other accidents and cardio-metabolic disorders (Tregear et al., 2009; Dredla and Castillo, 2019).

Continuous positive airway pressure (CPAP) is the first-line treatment for OSA and is highly effective in normalising breathing and oxygenation during sleep and improving sleep quality and daytime symptoms. However, CPAP usage is poor and side effects, such as claustrophobia and discomfort, as well as problems associated with mask leaks are common. Between 5% and 50% of patients recommended CPAP reject it up-front (Abdelghani et al., 2009; Bakker et al., 2019; Engleman and Wild, 2003a) and many patients who initiate CPAP treatment and continue to use it long-term show poor treatment adherence with <4 hours usage per night, the most commonly used cut-off for defining acceptable use (Engleman and Wild, 2003b). CPAP is particularly poorly tolerated in milder cases of OSA and thus CPAP is not widely used to treat mild OSA and snoring (Weaver et al., 2003). Alternative treatments include weight loss, oral

devices and surgery to help open and stiffen the airway. However, all have more limited and variable effectiveness compared to CPAP and patient acceptance and adherence are often also poor. For example, weight loss is rarely achieved and maintained long-term, and effectiveness of surgery and oral devices are variable and difficult to predict (Franklin et al., 2009). Consequently, there remains an ongoing need for simple efficacious alternative treatments that patients will accept and use long-term.

2.1.1 Supine-predominant OSA

Around 50% of patients diagnosed with OSA show at least twice as many obstructed breathing events when they sleep supine (Mador et al., 2005a; Omobomi and Quan, 2018), and around 30% exhibit OSA only when supine (Laub et al., 2015; Mador et al., 2005a). This effect is most likely dominated by gravitational effects on the tongue and pharyngeal airway, combined with tracheal traction, lung volume and fluid shift dependent effects. Thus, avoiding the supine sleep posture could potentially be a very simple but clinically useful therapeutic approach in many patients, particularly those with supine-only or supine-predominant OSA. When appropriately titrated and in the absence of significant leaks, CPAP can effectively eliminate OSA regardless of sleep posture. However, poor patient acceptance and adherence remain a significant problem with CPAP, particularly when perceived symptom benefits are low. Thus, alternative strategies with superior patient acceptance and treatment adherence, despite potentially lower efficacy in reducing the AHI compared to CPAP, remain warranted.

Various devices mimicking the traditional “tennis ball treatment” to discourage supine sleep have been shown to decrease OSA severity and to improve quality of life in patients with supine-predominant OSA (Casey, 2015; Skinner et al., 2008; Van Maanen and De Vries, 2014). However, to date there is only one recently reported head-to-head comparative effectiveness trial of CPAP versus supine-avoidance, which showed non-inferior treatment efficacy to reduce AHI and greater treatment adherence with supine-avoidance compared to CPAP, but was not designed to test for non-inferior symptom relief (Berry et al., 2019). Given very low self-reported acceptance of traditional discomfort based supine-avoidance (Bignold et al., 2009), supine-avoidance clearly requires sufficient evidence to support effective long-term treatment and use. Furthermore, given sub-optimal patient acceptance and adherence with CPAP (Abdelghani et al., 2009), and the importance of both treatment efficacy and adherence in determining treatment effectiveness for symptom relief, head-to-head studies of supine-avoidance compared to CPAP are clearly also warranted. Consequently, this study was specifically designed to directly compare sleepiness symptom relief and treatment adherence, efficacy and effectiveness (the product of efficacy and adherence) of a simple supine-avoidance alarm-based device versus usual care with CPAP for treating patients with supine-predominant OSA over 6-8 weeks of each treatment. The primary hypothesis was that supine-avoidance therapy would be non-inferior to CPAP in reducing daytime sleepiness. A key secondary hypothesis was that supine-avoidance therapy would achieve superior treatment adherence when compared to CPAP.

2.2 Method

2.2.1 Study Design

This supine-avoidance for OSA (SUPA) study was National Health and Medical Research Council (NHMRC) funded randomised controlled comparative-effectiveness cross-over study of 6-8 weeks treatment with a supine-avoidance device versus CPAP in patients with supine-predominant OSA. The study was designed as a non-inferiority trial to test the primary hypothesis that the improvement in ESS with supine-avoidance would be non-inferior to that with CPAP. ESS was chosen as the most widely used metric of daytime sleepiness, which is the most concerning clinical issue relevant to OSA. Key secondary outcomes were objective device-measured treatment adherence over 6-8 weeks of treatment, treatment efficacy to reduce the apnea-hypopnea index (AHI, the number of apnea and hypopnea events per hour of sleep) measured via repeat in-home sleep studies on each treatment, and the overall effectiveness to reduce average AHI (the product of efficacy and adherence) over the full course of each treatment.

Randomisation of treatment allocation order was performed by a local pharmacy department at Repatriation General Hospital independent of the investigators, using a minimisation program (MinimPy)(Saghaei and Saghaei, 2011) to avoid imbalance of potentially important confounders between randomised groups; including recruitment site, sex, age (<50 vs ≥50 years), body mass index (BMI <30 vs ≥30 kg/m²), supine apnoea hypopnoea index (AHI <35 vs ≥35 /h), ESS score (<12 vs ≥12). Cut-offs were based on historical clinic median data using the same eligibility criteria. Patients

commenced 6-8 weeks of treatment according to allocation order with no washout period between the two treatments. This reduced participant burden from additional visits and was considered appropriate given extended outcome measures over time up to the end of each treatment and that usual clinical practice does not delay changeover to alternative treatments.

The Adelaide Institute for Sleep Health (AISH) at Flinders University was the lead site for patient recruitment, overall trial management, data collection and analysis. Patients with supine-predominant OSA were screened and recruited from several South Australian hospitals including Repatriation General Hospital, Royal Adelaide Hospital, Ashford Hospital, Memorial Hospital, Queen Elizabeth Hospital and Flinders Medical Centre based on polysomnography (PSG) findings from each patient's initial diagnostic sleep study at the recruitment site. Patients who met the study criteria were then invited to participate in the trial following review and approval from their sleep specialist. All subsequent study procedures were conducted at AISH.

The project was approved by the Southern Adelaide Clinical Human Research Ethics Committee (HREC protocol number 431.13) and was registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR registration number 12613001242718). All participants gave written informed consent.

2.2.2 Patients and procedures

Eligibility criteria were: 1) age ≥18 and <75 years; 2) total AHI ≥ 10 /h (based on American Academy of Sleep Medicine "alternate" scoring criteria (Iber et al., 2007)

used across sites); 3) Epworth sleepiness scale (ESS) score ≥8; 4) Supine-predominant OSA defined as supine AHI ≥ twice non-supine AHI and non-supine AHI <10 /h; and 5) total sleep time ≥ 4 hours with ≥30 min supine and ≥ 30 min non-supine sleep. Criteria 2-4 were based partly on Mador et al (Mador et al., 2005a), to ensure that only patients with supine-predominant OSA associated with at least mild sleepiness were selected where effective supine-avoidance would be expected to successfully treat their OSA. Criteria 5 was selected to ensure adequate time was available to assess supine- vs non-supine OSA severity and sufficient supine-time to warrant supine-avoidance treatment. Patients with any of the following criteria were excluded: 1) prior treatment with CPAP or supine-avoidance therapy; 2) severe sleepiness (history of falling asleep while driving or ESS ≥16) requiring urgent treatment; 3) commercial driver; 4) co-morbidities that might preclude supine-avoidance treatment (e.g. arthritis or mobility problems or a pacemaker where a chest-worn device might interfere); and 5) unwilling to cease current alternative OSA therapies (e.g. mandibular advancement splint).

Posture monitoring and supine-avoidance treatment utilised a chest-worn device (BuzzPOD Model 2, Gorman ProMed Pty. Ltd, Melbourne Australia) to monitor and record body position (at 1 Hz over the full 6-8 week recording period) and discourage supine sleep via a strong vibration stimulus. The vibration stimulus was set to activate after ≥5 consecutive seconds in the supine posture and remained continuous until either a non-supine position was registered, or 2 minutes elapsed. If supine positioning continued beyond 2 minutes a pulsed mode was activated (2-sec periods of alternating vibration off and on) for a further 3-minutes. In the event of failure to discourage

supine-positioning within 5 minutes the device alarm timed-out and de-activated to conserve battery. This device was selected based on previously demonstrated accuracy and reliability for recording body position and established effectiveness for discouraging supine sleep (Bignold et al., 2011).

Following patient consent, participants were provided with an inactivated supine-avoidance alarm device for 7 days to record baseline sleep postures in the home setting. Participants then returned to the laboratory for setup of a baseline home polysomnography study for assessing pre-treatment OSA severity in the home-setting. Patients were then randomized to commence either CPAP or active supine-avoidance therapy for 6-8 weeks before crossing over to the remaining treatment for a further 6-8 weeks with a repeat home PSG within the last week on each treatment.

Patients who were allocated to CPAP were issued an auto-PAP device (AirLiquide Healthcare) to use for 3 nights before transitioning to a fixed pressure device set at the 95th centile pressure, with ongoing telephone and in-person support in the first week and as required for the remainder of CPAP treatment. Patients were instructed in the use of both the supine-avoidance device and CPAP by trained research staff and an experienced CPAP provider. Patients had follow-up appointments after 4 weeks on each treatment to download treatment usage data from each device and to help trouble-shoot any ongoing issues regarding their allocated treatment.

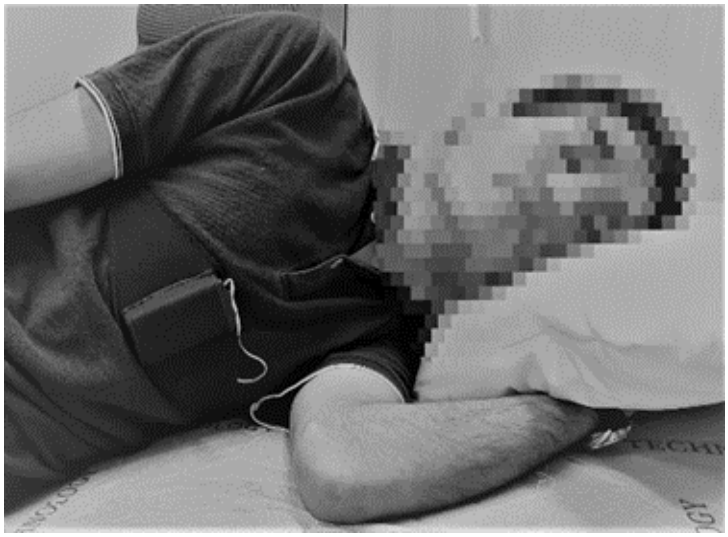


Figure 2.1 Supine-avoidance device (Buzzpod) worn on the chest over the sternum.

2.2.3 Study Measurements

Anthropometric measurements (age, gender, height, weight, waist circumference and BMI), questionnaires and in-home sleep studies were conducted at baseline and at the end of each treatment. Questionnaires included the ESS (Johns, 1992), general health questionnaire (GHQ) (Lundin et al., 2016), assessment of quality of life questionnaire (AQol-8D) (Richardson et al., 2014), Pittsburgh sleep quality index (PSQI) (Mollayeva et al., 2016), functional outcome of sleep questionnaire (FOSQ), insomnia severity index (ISI) (Gagnon et al., 2013), snoring scale score (SSS) (Lim and Curry, 1999), and a simple symptoms, complaints and treatment satisfaction questionnaire.

In-home sleep studies were recorded using an Embletta MPR (REMLogic^{TM}, Pleasanton, California, United States) home-PSG device to record EEG (C3-M2, C4-M1), left and right electro-occulograms (EOG), chin EMG (all sampled at 500 Hz),

nasal cannula pressure and thermistor (sampled at 250 Hz), thoracic and abdominal motion (sampled at 100 Hz), oximetry (sampled at 3 Hz) and body position (sampled at 20 Hz).

All PSGs were scored by a single experienced sleep technician who participated in a regular PSG scoring concordance quality assurance program and remained blind to treatment allocation. Objective CPAP compliance was calculated as the average hours of usage per night, including zero hours when not used, and the percentage of nights used for more than 4 hours. Objective supine-avoidance device usage was calculated on the same basis using device recorded position changes between manual button pushes with confirmatory sleep diary entries recording bed- and rise-times.

Treatment efficacy was assessed from total sleep AHI on each in-home sleep study treatment night. The overall effectiveness of each treatment to reduce average AHI over the full 6-8 weeks of treatment was estimated from the time-weighted product of baseline versus on-treatment supine and non-supine AHI, the estimated fraction of each night spent supine (F_{Supine}) versus non-supine ($F_{Non\text{-}supine}=1-F_{Supine}$; using device measured values for supine-avoidance and baseline week values for CPAP), and the average adherence (h/night) with each treatment relative to average time in bed (h/night; from the baseline week) using the following equation;

$$\text{Estimated Average AHI} = \text{Treatment } (AHI_{Supine} \times F_{Supine} + AHI_{Non\text{-}supine} \times F_{Non\text{-}supine}) \times \text{average treatment hours per night/average time in bed} +$$

$$\text{Baseline night } (AHI_{Supine} \times F_{Supine} + AHI_{Non\text{-}supine} \times F_{Non\text{-}supine}) \times (1\text{-average treatment hours per night/average time in bed})$$

This expression ranges between total AHI at baseline (re-weighted to baseline week supine vs non-supine times) without treatment, through to total AHI on treatment when average treatment hours per night equals total time in bed.

2.2.4 Statistical Analysis

The primary null hypothesis was that the difference in ESS between supine-avoidance and CPAP would be >1.5 ESS units. When designing the study it was considered that expert clinicians in the field would agree that a difference of <1.5 is unlikely to be clinically important. This non-inferiority margin is conservative and was selected before Patel et al (Patel et al., 2018) reported a minimum clinically important reduction in ESS of between 2 and 3. It was estimated that if the true difference between treatments was zero, then 58 patients would be required to reject the null hypothesis to support non-inferiority with a type I error rate of 2.5% (one-sided) in a cross-over trial design.

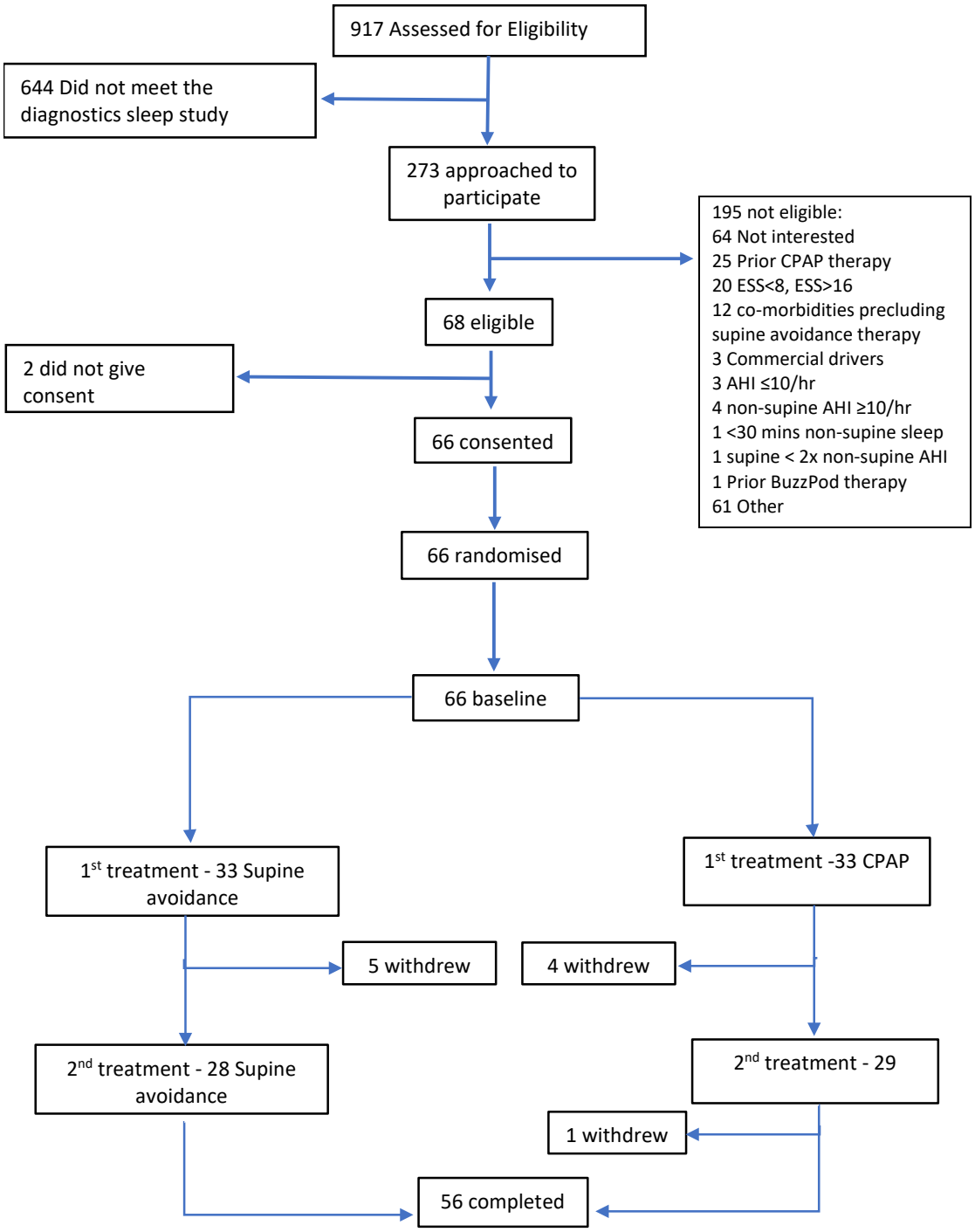
Statistical analysis was performed on an intention-to-treat treatment basis using IBM SPSS Statistics Version 25 and all available data. Normality was assessed using Shapiro-Wilk Tests. The primary outcome was examined by testing if the lower 95% confidence interval bound of the difference in ESS reduction with CPAP minus supine-avoidance did not cross the *a-priori* non-inferiority margin of -1.5. Secondary outcomes were examined using linear mixed effects model analysis with time and treatment as

repeated factors within-subjects using an auto-regressive co-variance structure, treatment order as a fixed effect and subjects as a random effect each with their own intercept. Data are presented as mean±SD or [95% confidence interval] unless otherwise specified.

2.3 Results

The flow of patients and trial procedures employed are shown in Figure 2.2. A total of 917 patients were assessed for eligibility across all sites. 273 met the initial screening criteria and were approached to participate in the study and further screening. Sixty-four patients declined to participate and a further 61 were excluded for other reasons, the majority due to excessive distance from the study site. Overall, 68 patients met the study criteria and 66 consented to participate. Recruitment began in January 2014 with final visits in October 2017. A total of 10 patients discontinued treatment (5 during each arm of the study) before their final visit, such that fifty-six patients completed the full study.

Figure 2.2 SUPA trial flow of patients throughout the study.



Baseline characteristics of study participants are shown in Table 2.1. Participants were predominantly middle-aged, overweight or obese males with mild-to-moderate OSA, but with severe OSA when sleeping supine, which accounted for around 50% of total sleep time, consistent with supine-predominant OSA and the study selection criteria.

Table 2.1 Patient Characteristic.

Parameter	***Whole group***	***Supine-avoidance treatment 1st Group***	***CPAP treatment 1st Group***
N (% Male)	66 (62.1%)	33 (63.6%)	33 (60.6%)
Age (yr)	52.8 ± 11.9	54.1 ± 12.7	51.5 ± 11.0
Height (cm)	171.9 ± 9.1	173.2 ± 8.8	170.7 ± 9.4
Weight (kg)	93.8 ± 21.4	96.3 ± 24.4	91.4 ± 18.0
Body Mass Index (kg/m²)*	31.9 ± 7.8	32.2 ± 8.4	31.6 ± 7.2
Diagnostic sleep study			
Total sleep time (min)	357.0 ± 61.1	351.3 ± 59.7	362.7 ± 62.7
Non-supine sleep time (min)	186.2 ± 79.8	183.0 ± 79.2	189.3 ± 81.5
Supine sleep time (min)	170.2 ± 81.4	169.3 ± 80.6	171.2 ± 83.5
Supine sleep time (%sleep)	47.6 ± 20.4	48.0 ± 20.6	47.1 ± 20.5
Total AHI (/h) †	18.0 ± 8.9	19.1 ± 10.1	17.0 ± 7.4
Non-supine AHI (/h)	5.0 ± 3.2	4.6 ± 2.7	5.4 ± 3.5
Supine AHI (/h)	40.2 ± 38.8	46.1 ± 50.9	34.3 ± 19.7

Data are presented as mean ± SD or number (%) of patients.

* The body-mass index is the weight in kilograms divided by the square of the height in meters.

† The apnea‑hypopnea index is the number of apnea and hypopnea events per hour of sleep

There were no significant treatment order effects on any outcome. Both CPAP and supine-avoidance reduced the ESS compared to baseline (Figure 2.3 and Table 2.2). Furthermore, the reduction in ESS with supine-avoidance was non-inferior to that with CPAP, as the lower limit of the one-sided 95% confidence interval for the mean difference did not cross -1.5, the pre-specified margin of non-inferiority.

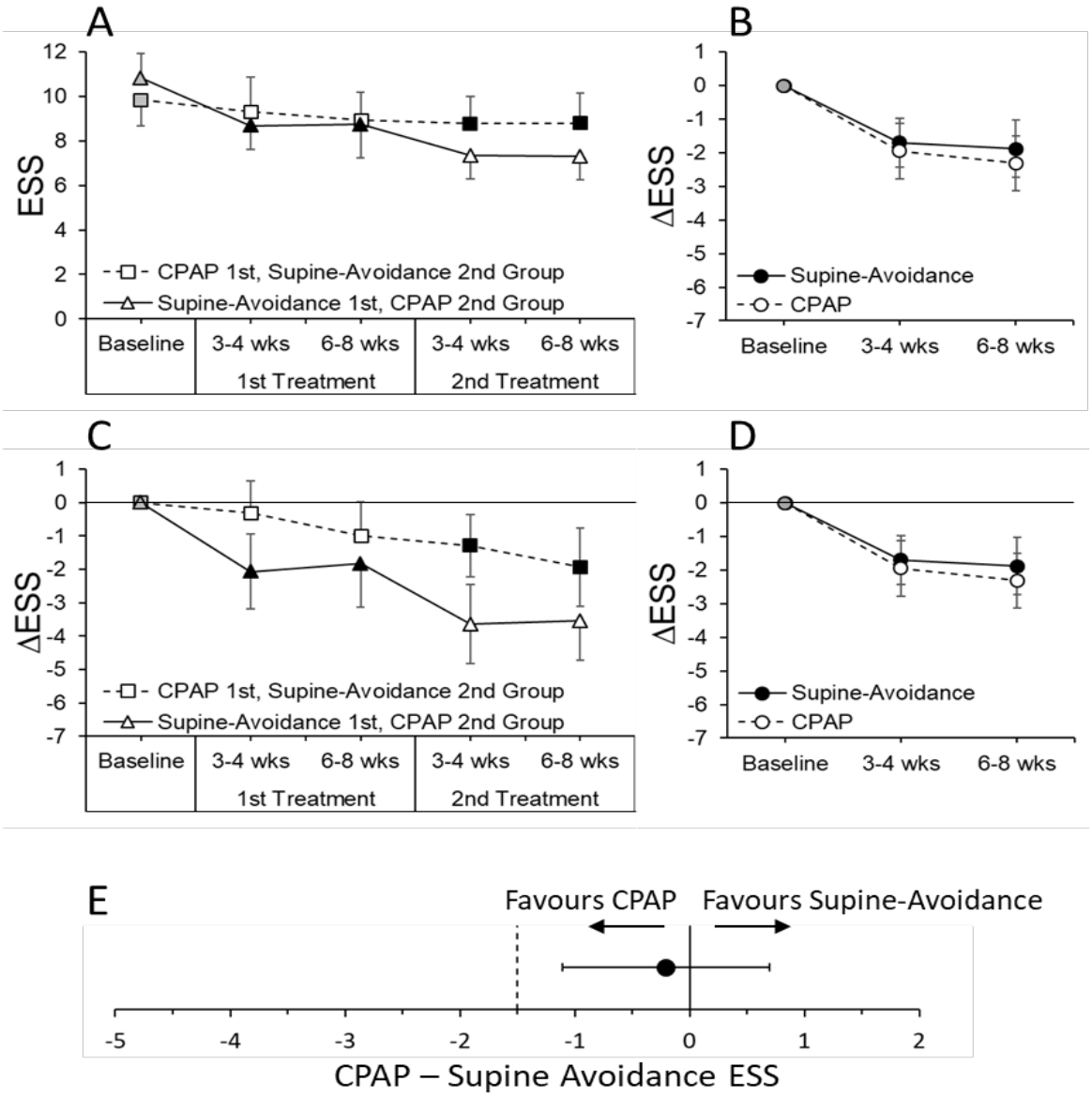
Table 2.2 shows device recorded usage data for supine-avoidance and CPAP. During the baseline period prior to commencing active treatment patients used the posture device (with inactive alarm for baseline monitoring of overnight posture) for around 8 hours almost every night in the home setting. Overnight supine time was consistently lower in the home compared to in-laboratory diagnostic and in-home baseline sleep study nights (around 25% of time in bed compared to around 50% and 30% of sleep time respectively). The device estimated percentage of time in bed spent supine was markedly reduced from around 25% over the baseline week to around 3% on active supine-avoidance treatment, with a reduction in average supine period duration from around 20 minutes to less than 2 minutes from an average of 5 alarm events per night. Most alarms resulted in a rapid shift to a non-supine posture, including 7917 and 8176 of 9552 alarms (82.9% and 85.6%) within 30 and 60 sec respectively. However, 730 of 9382 (7.8%) alarm events during non-PSG treatment nights, and a lower proportion of alarm events during PSG treatment nights (5 of 170 or 2.9%, Fisher's p=0.013), failed to discourage supine positioning before the alarm time-out at 5 minutes. Across all nights of 6-8 weeks of each treatment, patients used supine-avoidance therapy over 2 hours per night more than CPAP, and with a greater percentage of nights used for 4 hours or more hours per night.

Table 2.2 Device data at baseline (inactive supine-alarm) and from 6-8 weeks of active supine-avoidance versus CPAP treatment.

	Baseline	*Supine-avoidance*	*CPAP*	*CPAP-supine-avoidance difference*	*P Value*
N	62	59	62	57	
Nights available for use	9.7 [8.8 to 10.7]	52.6 [48.3 to 57.0] *	45.9 [41.9 to 50.0]	-6.0 [-12.2 to 0.2]	0.172
Average use (h/night)	7.9 [7.7 to 8.2]	5.7 [5.0 to 6.3] *	3.9 [3.2 to 4.6]	-1.7 [-2.5 to -0.9]	<0.001
Average use on nights used (h/night)	8.1 [7.8 to 8.3]	7.4 [7.0 to 7.7] *	5.2 [4.6 to 5.7]	-2.2 [-2.7 to -1.7]	<0.001
% nights used	98.3 [97.0 to 99.6]	75.4 [68.7 to 82.2]*	67.5 [58.8 to 76.2]	-7.1 [-16.6 to 2.3]	0.541
% nights used >4 h/night	97.3 [95.7 to 98.8]	71.8 [64.4 to 79.1]*	51.3 [42.3 to 60.3]	-19.4 [-29.1 to -9.6]	<0.001
Supine time (%time in bed)	23.9 [20.1 to 27.7]	2.9 [1.2 to 4.5] *			
Supine periods (/night)	7.3 [6.6 to 8.0]	5.1 [4.3 to 6.0] *			
Supine period duration (min)	17.7 [14.7 to 20.6]	1.9 [1.1 to 2.7] *			
Alarms (/night)		4.7 [4.0 to 5.5]			

Values are mean [95% confidence interval].*Indicates p<0.05 compared to baseline.

Figure 2.3 Epworth sleepiness scale (ESS) changes from baseline over the course of supine-avoidance versus CPAP treatment.



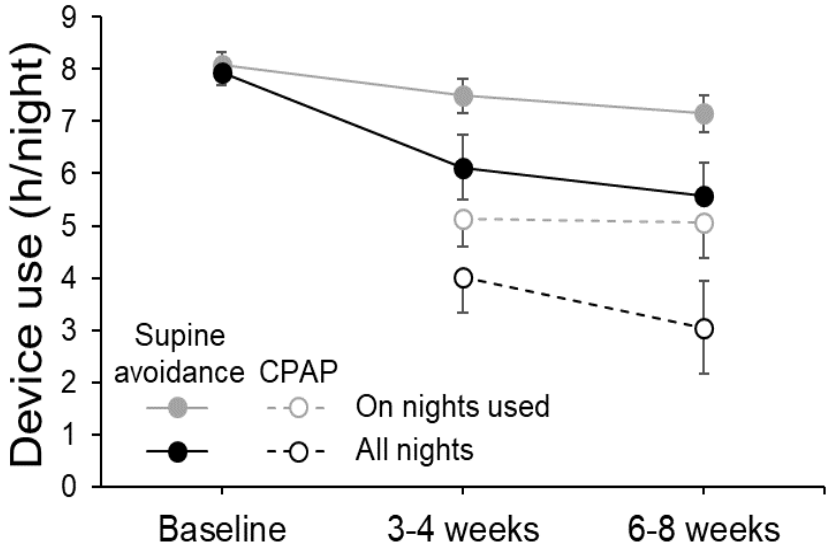
A) ESS (Epworth Sleepiness Scale) at baseline, 3-4 weeks of each treatment in each randomisation group and B) both groups combined. C) Change in ESS from baseline in each randomisation group and D) both groups combined. E CPAP-supines avoidance ESS difference between treatments. N=66 patients (33 in each group) at baseline. Values are mean±95% confidence intervals. A-D symbols in grey indicate values at baseline, open symbols indicate values during CPAP treatment and black filled symbols indicate values during supine-avoidance treatment.

The effects of CPAP versus supine-avoidance therapy on objective home sleep study measures of sleep, sleep posture and questionnaire outcomes are shown in Table 2.3. Both treatments reduced the amount of N1 sleep, total AHI, supine AHI, arousal index and 3% ODI, but with greater reductions in total AHI, arousal index and 3% ODI with CPAP compared to supine-avoidance. More patients achieved an AHI <10 /h during the home sleep study on CPAP compared to supine-avoidance (32% vs 12% Fisher's test p=0.017). CPAP also reduced non-supine AHI, but there was a substantially greater reduction in supine sleep time with supine-avoidance than with CPAP. Other indices of sleep quality, such as sleep efficiency, were not altered by either treatment. Both treatments also reduced the supine vs non-supine and on- versus off-treatment time-weighted estimated average AHI to a similar degree over the full-course of each treatment.

The complaints and treatment satisfaction questionnaire at the end of each treatment arm showed that 68% (34/50) of study participants would continue to use supine avoidance therapy compared to 55% (29/53, p=0.225) who said they would continue to use CPAP. At the end of the full-study, participants were also asked about their treatment preference, although only 22 patients answered the last treatment preference question. A significantly higher proportion of participants [72% (16/22)] reported that they preferred the supine avoidance therapy and were willing to continue with treatment compared to a preference for CPAP treatment [28% (6/22), p=0.006]. Two patients reported that they felt they had learned to avoid supine sleep and therefore did not require ongoing treatment. There were no significant changes with treatment or differences between treatments in PSQI, AQoL-8D or SSS. However,

both treatments reduced the ISI, with a greater reduction following CPAP than with supine-avoidance (Table 2.3).

Figure 2.4. Supine-avoidance versus CPAP device usage over the course of the trial.



Values are group means±95% confidence intervals of average nightly device use with supine-avoidance (filled symbols) and CPAP (open symbols) device treatment at baseline and after 3-4 and 6-8 weeks of treatment. During the baseline period participants wore the supine-alarm device with the alarm inactive, followed by randomisation to active supine-avoidance or CPAP for 6-8 weeks before cross-over to the remaining treatment; with device data downloads at 3-4 and 6-8 weeks of each treatment. Grey indicates device recorded hours of use on nights with device use. Black indicates data from all nights, including zero hours when not used.

Table 2.3 Sleep study parameters at baseline and after 6-8 weeks of each treatment.

		Change from baseline at 6-8 weeks of treatment			
	Baseline	**Supine-avoidance**	**CPAP**	**CPAP-supine-avoidance difference**	**p-value**
N	66	53	52	49	
Sleep study parameters					
Total sleep time (TST) (min)	391.3 [371.8 to 410.7]	-3.3 [-26.7 to 20.0]	-1.5 [-30.6 to 27.6]	-2.6 [-40.5 to 35.2]	0.634
Sleep onset latency (min)	22.9 [17.1 to 28.7]	-0.5 [-11.1 to 10.0]	2.9 [-7.1 to 12.9]	-0.8 [-12.6 to 11.0]	0.933
Wake after sleep onset (min)	51.3 [42.6 to 60.0]	-7.0 [-17.5 to 3.6]	-7.3 [-18.4 to 3.9]	-2.9 [-15.1 to 9.3]	0.996
Sleep efficiency (%)	81.2 [78.4 to 84.0]	2.5 [-1.8 to 6.9]	0.5 [-2.8 to 3.8]	-1.5 [-6.4 to 3.3]	0.998
Supine sleep time (%sleep)	34.6 [28.8 to 40.4]	-20.3 [-27.1 to -13.4]*	12.8 [3.1 to 22.5]*	30.9 [22.2 to 39.5]	<0.001*
N1 (%TST)	16.2 [13.8 to 18.7]	-3.7 [-6.4 to -1.0]*	-3.9 [-6.5 to -1.2]*	-0.7 [-2.6 to 1.1]	0.760
N2 (%TST)	51.0 [48.3 to 53.7]	3.7 [0.3 to 7.2]*	2.9 [-0.8 to 6.6]	-1.6 [-5.2 to 1.9]	0.995
N3 (%TST)	14.4 [12.1 to 16.6]	-0.2 [-2.8 to 2.4]	0.6 [-2.2 to 3.3]	0.4 [-2.2 to 2.9]	0.998
REM (%TST)	18.4 [16.5 to 20.2]	0.2 [-2.2 to 2.5]	0.2 [-2.4 to 2.7]	-0.1 [-2.9 to 2.7]	0.986
Total AHI (/h)	14.0 [10.8 to 17.2]	-4.2 [-7.8 to -0.6]*	-9.1 [-12.9 to -5.4]*	-5.3 [-9.3 to -1.3]	0.005*
Supine AHI (/h)	27.4 [21.7 to 33.2]	-14.6 [-21.3 to -7.9]*	-17.6 [-24.4 to -10.9]*	-3.2 [-9.2 to 2.9]	0.994
Non-Supine AHI (/h)	7.6 [4.9 to 10.3]	0.4 [-2.4 to 3.1]	-4.0 [-7.7 to -0.3]*	-5.2 [-8.5 to -2.0]	<0.001*
Arousal Index (/h)	20.3 [18.1 to 22.4]	-2.9 [-5.5 to -0.2]*	-7.0 [-9.6 to -4.5]*	-3.6 [-5.9 to -1.2]	0.006*
3% ODI (/h)	10.2 [7.6 to 12.9]	-3.0 [-5.6 to -0.4]*	-6.1 [-9.0 to -3.3]*	-3.3 [-5.5 to -1.1]	0.005*
%Sleep Time SaO_2 <90%	5.1 [3.3 to 6.8]	-0.9 [-3.8 to 2.0]*	-1.4 [-4.2 to 1.3]*	-1.7 [-3.7 to 0.4]	0.047*
Treatment effectiveness					
Estimated average AHI (/h)	11.7 [8.5 to 14.9]	-3.1 [-4.9 to -1.2]*	-4.0 [-6.9 to -1.1]*	-1.3 [-3.3 to 0.6]	0.547
Questionnaires					
ESS	10.3 [9.4 to 11.3]	-1.9 [-2.9 to -0.9]*	-2.3 [-3.3 to -1.3]*	-0.2 [-1.3 to 0.9]	0.956
PSQI	8.3 [7.1 to 9.6]	-0.7 [-1.7 to 0.3]	-0.9 [-1.9 to 0.1]*	0.0 [-0.9 to 0.9]	0.894
AQoL-8D	69.6 [66.2 to 73.0]	0.2 [-1.9 to 2.3]	1.9 [-0.6 to 4.4]	0.5 [-1.2 to 2.1]	0.900
ISI	12.3 [10.9 to 13.7]	-1.4 [-2.6 to -0.2]	-3.6 [-4.7 to -2.4]*	-1.9 [-3.1 to -0.8]	0.011*
SSS	6.1 [5.4 to 6.8]	-0.5 [-1.1 to 0.1]	0.2 [-0.8 to 1.3]	0.5 [-0.6 to 1.5]	0.698

Values are mean [95% confidence interval], N=56. AHI = apnea–hypopnea index; ODI = oxygen desaturation index; ODI 3% = ODI, 3% desaturation; TST = total sleep time; VAS = visual analogue scale. AHI is calculated in supine position. N1 refers to sleep stage 1;

2.4 Discussion

This is amongst the first and largest well-powered randomised controlled trial to evaluate if alarm-based supine-avoidance treatment is non-inferior to CPAP for reducing daytime sleepiness, the primary symptom complaint of clinical concern in OSA, and the second study to directly compare treatment adherence and efficacy for reducing AHI versus CPAP in patients with supine-predominant OSA. The main findings support that simple supine-avoidance alarm device treatment to discourage supine sleep is non-inferior to CPAP in reducing sleepiness in patients with at least mild sleepiness (ESS>8). Furthermore, patient usage over 6-8 weeks of treatment was around 1.5-2 hours per night greater compared to CPAP, through both more prolonged overnight use when used and fewer skipped nights of use. These are important findings given that CPAP acceptance and use are often problematic, particularly in patients with milder OSA typical in supine-predominant OSA (Popescu et al., 2001). These findings are similar to a recent study showing non-inferior treatment efficacy in reducing overnight AHI and greater treatment adherence with a vibration based supine-avoidance alarm device compared to APAP in positional OSA patients (Berry et al., 2019), but where patients were not selected on the basis of sleepiness as in the current study. The findings from this study differ from those of Mok et al. (2020), where non-inferiority of supine-avoidance versus CPAP to reduce sleepiness could not be concluded from a smaller group of more symptomatic patients (ESS>10) (Mok et al. 2020). These somewhat divergent findings could indicate severity-dependent effects, where CPAP may be superior to supine-avoidance for reducing more severe OSA and

sleepiness, or an inadequate sample size in the study of Mok et al. (2020) from which non-inferiority could not be confidently concluded or ruled out.

The efficacy of CPAP for reducing daytime sleepiness and AHI, and problems with treatment adherence are well established (Chen et al., 2015; Mcevoy et al., 2016; Weaver et al., 2007) and formed the basis for selecting CPAP as the optimal treatment comparator for this study. Although comparable and non-inferior to CPAP, the reduction in ESS with supine-avoidance was small, and below the reported minimally important clinical difference for treatment reductions in ESS of 2-3 (Patel et al., 2018). These small changes are likely reflective of relatively mild OSA and symptoms in patients with supine-predominant OSA who typically may not be recommended CPAP. Nevertheless, by study design, all patients had been referred for investigation and treatment, and selected on the basis of at least mildly symptomatic supine-predominant OSA, for which CPAP would be expected to be the most efficacious treatment. Whilst below the usual cut-off of 14 suggestive of insomnia (Gagnon et al., 2013), ISI improvements with both treatments, with larger improvements with CPAP, also support treatment benefits and a degree of OSA and insomnia symptom overlap (Cho Yong et al., 2018). No changes in self-reported sleep quality, quality of life or snoring scale score with treatment even with CPAP are perhaps surprising. This most likely reflects a combination of relatively mild OSA with greater efficacy, but poorer adherence with CPAP, compared to supine-avoidance, such that overall treatment effectiveness for reducing the estimated average overnight AHI and symptoms were more comparable. Given that patients with supine-predominant OSA constitute 30-50% of patients attending sleep clinics, these are important data to support the use of

simple low-cost minimally intrusive supine-avoidance approaches for achieving comparable treatment outcomes with superior adherence compared to CPAP.

Whilst it might appear self-evident that patients with supine-predominant OSA should benefit from supine-avoidance treatment, favourable comparative-effectiveness evidence to support supine-avoidance therapy has previously been lacking. Long-term treatment effectiveness is the product of treatment efficacy, patient acceptance and ongoing adherence to treatment, where all must be sufficiently favourable to support effective outcomes long-term. Given that around 90% of patients commencing traditional discomfort based supine-avoidance with tennis-ball-treatment (TBT) self-report abandoning treatment, most within one month from discomfort (Bignold et al., 2009), TBT clearly cannot be recommended long-term. Similarly, whilst CPAP is highly efficacious, sub-optimal treatment acceptance and adherence also limit long-term treatment effectiveness with CPAP (Weaver, 2006; Weaver and Grunstein, 2008). Thus, more effective treatment outcomes for patients with OSA requires more selective and sufficiently comfortable and efficacious treatment recommendations that patients will accept and use, and with favourable evidence to support their use. In this study supine-avoidance therapy was well accepted and used by participants, with higher use for most of the sleep period and on more nights compared to CPAP. Although efficacy for reducing AHI was reduced, greater treatment usage may help to explain a non-inferior reduction in sleepiness. Furthermore, a higher proportion of participants reported a preference for supine avoidance therapy over CPAP. In combination, these findings support that supine-avoidance alarm-treatment should be considered in appropriately selected patients with supine-predominant OSA, unlike

traditional discomfort based supine-avoidance approaches which clearly cannot be recommended given poor self-reported acceptance and use (Bignold et al., 2009).

Supine sleep avoidance is potentially the simplest and most effective way to treat OSA patients who exhibit sleep apnea mostly or exclusively during supine sleep. Similar to several previous smaller or shorter-term studies, our data strongly support the efficacy of supine-avoidance alarm-based devices for reducing supine sleep time and, when combined with high treatment adherence, to reduce AHI (Bignold et al., 2009; Bignold et al., 2011; Dieltjens et al., 2015; Ha et al., 2014; Levendowski et al., 2014; Van Maanen and De Vries, 2014). However, it should be noted that supine sleep was not completely abolished during supine-avoidance treatment, as indicated by residual supine periods with device measurements over the full treatment period, and independent posture measurements during the overnight sleep study on treatment. This likely reflects a combination of some degree of variability in posture classification with different posture measurement devices (Danker-Hopfe et al., 2009), more restricted movement with additional leads and sensors during sleep study nights, and failure of some alarm events to successfully discourage ongoing supine sleep. We have previously shown good posture classification agreement with supine-alarm device posture classification against in-laboratory video confirmed body position (Bignold et al., 2011), therefore posture classification disagreement is unlikely to have played a major role.

Similar to previous studies (Bignold et al., 2011; Levendowski et al., 2014), we found substantially greater supine time in the in-laboratory diagnostic (around 50% of total

sleep time) and baseline in-home sleep study (around 35% of total sleep time) compared to device estimated supine time (around 25% of time in bed) during the baseline week of home recording with an inactive supine-alarm. These findings support a substantial bias towards more supine-sleep and a higher AHI in most patients with a degree of supine-predominant events with conventional sleep monitoring, especially in a laboratory environment. This warrants careful consideration and potentially assessment of supine sleep habits in the home environment before selecting supine-avoidance over other treatments.

Also of note was that despite a strong vibratory stimulus, achieving comparable or perhaps greater supine-time reduction (to around 3 vs 8% of total sleep time) to a recent study using a different device (Berry et al., 2019), around 8% of all alarm events over the 6-8 week treatment period and 3% on sleep study nights failed to discourage supine positioning before the alarm time-out at 5 minutes. A lower failure rate on sleep study nights might indicate more rapid sleep resumption without more intrusive sleep measurements. Nevertheless, residual supine time from alarm events failing to shift away from the supine posture suggests that alarm improvements remain warranted. Given similar reductions in N1 sleep time with both treatments, with no differences in total sleep time, sleep efficiency or wake after sleep, another somewhat related concern that supine-alarms could potentially interfere with sleep was not supported. Nevertheless, further studies to examine the impact of supine-alarms on temporal relationships between arousal events, posture shifts and the resumption of sleep are likely to be useful.

Limitations

Several potential limitations warrant consideration. The study selection process for identifying patients with supine-predominant OSA reflects somewhat arbitrary criteria conservatively selected as most likely to achieve efficacious supine-avoidance and AHI reduction benefits. However, multiple criteria exist for defining supine-predominance (Joosten et al., 2014b; Frank et al., 2015; Mador et al., 2005a), OSA severity (Hudgel, 2016; Berry et al., 2012) and treatment success, with no clear consensus or robust clinical evidence to support which criteria may be best. Thus, results likely differ with application of alternative patient selection and clinical criteria.

As this was an open label study, self-reported outcomes such as ESS are inevitably prone to potential bias. Patient blinding to different forms of treatment is not possible and all self-reported outcomes with any treatment in usual clinical practice are subject to similar potential bias. Although AHI is clearly more objective, relationships between symptom complaints and AHI are week and patients do not specifically seek treatment for an elevated AHI. Hence, direct comparisons of sleepiness against best available care with CPAP in a cross-over design where each participant serves as their own control was considered the optimal and most pragmatic study design choice for testing the primary non-inferiority outcome. Moreover, substantial reductions in objective measures of supine time, with reduced N1 and arousal index, and similar time-weighted AHI over the full-course of treatment are consistent with comparable treatment effectiveness and symptom relief with both treatments.

Instructions to participants could also be an important element of posture modification therapy success. For example, Neill et al (1997) found different upper airway closing pressure and upper airway opening pressure in a study where patients with OSA were instructed to sleep in either supine, lateral, or 30° elevation postures. Thus, to some extent participant self-selection of posture at sleep onset and the return to sleep following awakenings overnight may importantly influence sleep outcomes. However, although individuals may be able to successfully avoid falling asleep when supine, avoiding shifts to the supine following brief arousals without full awakenings during the sleep period may be resistant to conscious supine-avoidance and learning effects. In this study the intent of supine-avoidance therapy was clear to study participants, so participants may to some extent altered their sleep posture behaviours to help avoid supine-sleep. A more detailed examination of potential changes in posture behaviours and the number of alarm events over the course of treatment would clearly be useful to help evaluate potential behavioural and learning effects.

The estimated average AHI was calculated based on time-weighted averages to adjust for differences in both AHI and times spent in supine versus non-supine postures during sleep. This approach inevitably requires some simplifying assumptions and is partly dependent on PSG scorer assessments of time in bed based on sleep diary entries and signal characteristics suggestive of gross body movements associated with getting into and out of bed. Thus, the validity of these assessments is uncertain. It has also previously been shown that part of a night on CPAP can significantly change AHI for the second half of the night off CPAP (Stöberl et al., 2017), so potential carry-over effects also cannot be discounted. However,

temporal changes may also be confounded by sleep stage distribution and other temporal influences across the night not necessarily related to treatment.

2.5 Conclusion

In summary, this study supports that supine-avoidance therapy via an alarm-based device worn on the chest is non-inferior to CPAP at reducing daytime sleepiness, and achieves substantially greater treatment adherence, with similar overall effectiveness and improvements in AHI and other objective sleep outcomes compared to CPAP. These findings contrast with previous data showing remarkably poor patient acceptance and adherence to traditional discomfort-based supine-avoidance treatment and support the use of non-discomfort alarm based supine-avoidance for treating appropriately selected patients with supine-predominant OSA.

2.6 Acknowledgment

The contributions from the following people are gratefully acknowledged; Dasha Loutchkina for study randomisation assistance; Mandy O'Grady. Alison Pinczel, Denzil Paul and Rohit Philip for technical assistance during the conduct of the trial; Dr Dimitar Sajkov, Dr Jason D'Costa, Dr Jeff Bowden, Dr Anand Rose, Dr Karen Latimer, A/Prof Brian Smith, Dr Mark Jurisevic, Dr Andrew Thornton, Dr Aeneas Yeo, Parmjit Singh, Dr Zafar Usmani and Dr Vinod Aiyappan for their assistance with patient recruitment. This study was funded by a National Health and Medical Research Council (NHMRC) Project Grant (1020892).

2.7 Authors contributions

MR undertook the primary data collation, analysis, interpretation and write-up of this work. PC, RDM, NA, MB, SQ, JM were involved in the conception, design and funding application. MO assisted with data acquisition.

CHAPTER 3. A study of physiological activation responses to posture shifts in sleep and the impact of a supine-avoidance alarm

Key points

Question: This study sought to examine temporal relationships between EEG-defined wake and arousal responses to overnight posture shifts and to examine the effects of a supine-avoidance alarm device and CPAP therapy on overnight posture shift responses.

Findings: The majority of posture shifts during the sleep period were either preceded by wake or an arousal from sleep. Supine-avoidance therapy was effective in reducing supine sleep and was not associated with more prolonged awakenings following supine-alarm events.

Meaning: Supine-avoidance therapy via a vibro-tactile device stimulus worn on the chest is effective for reducing supine sleep without additional sleep disturbance in patients with supine-predominant OSA.

Abstract

Supine-avoidance alarm devices may be useful for treating patients with supine dependent obstructive sleep apnoea (SDOSA). However, little is known regarding temporal relationships between brief arousals/awakening responses and posture shifts during sleep, or the subsequent impact of supine-avoidance alarms on the time taken to return to sleep. This study aimed to assess the frequency and duration of arousal and awakening responses associated with posture shifts during sleep, and to examine how quickly sleep resumes following posture shifts with and without active supine-avoidance alarm treatment. This study was part of a larger randomised controlled trial comparing supine-avoidance versus CPAP therapy in patients with SDOSA. Following a baseline full in-home sleep study (Embletta MPR) with an inactive supine-avoidance alarm device (BuzzPOD, Gorman Promed Pty Ltd), patients were randomised to active supine-avoidance treatment vs CPAP for 6-8 weeks before cross-over to the remaining treatment for a further 6-8 weeks, with a repeat in-home sleep study at the end of each treatment. A technician blinded to supine-treatment data scored arousal and awakening responses (3 to <15-sec and ≥15-sec EEG changes respectively). All posture shifts ≥5-sec in duration commencing from established sleep during baseline and supine-avoidance nights were assessed for arousal/ awakening responses (within -30 to +3 sec). Posture shifts from wake, and sleep onset latency following each posture shift were also examined and compared between baseline and treatment sleep study nights.

Supine sleep was markedly diminished with supine-avoidance device treatment compared to baseline. Around 90% of posture shifts were preceded by either wake or

an arousal with no differences between treatment versus baseline nights. There were statistically significant effects of night ($p<0.001$) and state (wake vs sleep, $p<0.001$) preceding the posture shift but no significant night x state interaction effect on the time spent supine after posture shifts to supine. Almost all posture shifts to supine on PSG nights with active alarm treatment were followed by an alarm, but there were no differences in the propensity or time-course of achieving sleep between baseline and treatment nights.

The findings of this study support that most posture shifts during sleep are preceded by either wake or EEG arousal / awakening such that most supine alarm events are likely to occur during a period of brief cortical activation potentially needed for co-ordinated body movements with minimal effect on the time taken for sleep to resume. Thus, supine alarms themselves do not appear to interfere with the process of returning to sleep following overnight posture-shifts.

3.1 Introduction

Obstructive sleep apnea (OSA) is characterised by frequent partial or complete collapse of the upper airway during sleep. OSA has been associated with poor health outcomes such excessive daytime sleepiness (EDS), high blood pressure, depression and has been linked to a 2-7 fold increased risk of motor vehicle accidents that may lead to heightened risk of fatality (Dempsey et al., 2010; Tregear et al., 2009; Dopp et al., 2007). OSA is a heterogeneous disease with complex anatomical and physiological factors contributing to the initiation and severity of obstructive breathing events. Consequently, patients with OSA likely exhibit a range of phenotypes or endotypes for which improved identification of different phenotypes and causal mechanisms may facilitate better personalised and targeted treatments more likely to effectively and cost-effectively treat individual patients earlier and better than with current usual care. Following diagnosis, most patients with OSA undergo a protracted trial-and-error treatment approach until they either find and accept an effective treatment option, or are lost to ongoing medical care with uncertain but most likely unsatisfactory treatment outcomes.

In current clinical practice continuous positive airway pressure (CPAP) therapy is the standard first-line treatment for OSA patients regardless of phenotypic differences for which current diagnostic testing largely ignores. CPAP provides pressurised air through a mask during the night and is an effective treatment for reducing the apnea/hypopnea Index (AHI) (Sullivan et al., 1981) and normalising symptoms such as excessive daytime sleepiness. However, patient acceptance and regular ongoing

nightly use of CPAP is often limited such that the number of hours of CPAP usage per night are directly associated with CPAP effectiveness for reducing OSA symptoms (Weaver et al., 2007).

Several studies have shown that for CPAP to be optimally effective, patients are required to use the device at least 4 hours/night (Weaver et al., 2007; Wolkove et al., 2008; Bakker et al., 2019). Despite its effectiveness, CPAP is inherently an intrusive treatment and patients' adherence is generally low. Almost 50% of patients who are recommended to use CPAP stop using it after a median of 3 months resulting in their sleep apnea remaining untreated. Alternative treatments to CPAP do exist and include weight loss, upper airway surgery and mandibular advancement splint (MAS) devices. However, all are problematic. Weight loss is hard to achieve and difficult to maintain, MAS and surgery have unpredictable outcomes and surgery carries both surgical and anaesthetic risks, especially in patients with OSA more vulnerable to airway collapse during anaesthesia.

One major factor with significant potential to provide for an efficacious and affordable clinical treatment option for OSA is supine posture effects on OSA severity, which could potentially be markedly reduced via supine-avoidance therapy. OSA is often, although not always, more severe in the supine position so patients can be usefully divided into two groups of "supine dependent OSA" where sleep-related breathing abnormalities predominantly occur while sleeping supine, and "non-positional OSA" where respiratory events occur in both lateral and supine postures during sleep. There is no agreed standard definition of supine-dependent OSA, and depending how it is

defined an estimated 50%-60% of patients with OSA may have supine-dependent OSA with even higher prevalence of around 65% in mild to moderate OSA (i.e. AHI ranging from 5 to 30) (Oksenberg and Silverberg, 2009) and particularly in mild OSA (AHI 5-15 /h), reaching as high as around 87% (Mo et al., 2011). A recent study of 1719 community participants in Switzerland found OSA (AHI≥ 5 /h) to be highly prevalent and present in 71% of the study sample, within which 53% had position dependent OSA (Heinzer et al., 2018). This is an important phenotypic distinction as supine predominant OSA patients may substantially benefit from simply avoiding supine sleep. Thus, positional therapy could potentially be amongst the simplest and most effective treatment options for appropriately selected patients with positional OSA, particularly when treatment adherence with CPAP is often poor and treatment efficacy and patient acceptance and adherence to alternative treatments is more variable.

Given a high prevalence of positional OSA and that patients could potentially be treated simply by avoiding the supine position during sleep, supine-avoidance is an appealing treatment option. The work presented in Chapter 2 supports that 6-8 weeks of supine-avoidance alarm treatment is not inferior to CPAP in reducing daytime sleepiness, the primary OSA symptom complaint of greatest clinical concern in OSA. Furthermore patients also showed superior adherence to supine-avoidance therapy supporting the clinical utility of this simple minimally intrusive therapy. However, suitable caution remains warranted given evidence of poorer supine-avoidance alarm device efficacy at reducing AHI, and the combined importance of both efficacy and adherence in determining long-term treatment acceptance and adherence of any

treatment. In the context of supine-avoidance treatment it is important to evaluate the impact of treatment on sleep itself, including posture-shift behaviours and the influence of supine-avoidance alarms on body movements and sleep.

Low adherence to traditional supine-avoidance strategies such as the tennis ball treatment has prompted exploration of new non-discomfort supine alarm devices to discourage supine sleep with minimal discomfort. These new generation devices are worn on the chest (Bignold et al., 2011) or on the neck (Levendowski et al., 2014; Van Maanen and De Vries, 2014) via a strap and use a position triggered alarm to vibrate whenever patients attempt to shift to the supine position, rather than an auditory alarm more likely to disturb bed-partner sleep. In addition to supine alarm treatment, these devices simultaneously record posture during sleep allowing for long-term monitoring of effectiveness to reduce supine time and treatment adherence, which has not previously been possible with traditional supine-avoidance approaches.

Despite effectiveness of vibratory alarm devices there is still ongoing uncertainty with all supine-avoidance treatments, including the new vibration-based alarm devices, regarding the impact of supine-avoidance alarms on sleep quality. In the context of new generation supine-avoidance devices, it remains unclear if vibration alarms triggered by attempts to shift to the supine posture in themselves might cause sleep disturbance. Supine alarms could promote extended wakefulness after a posture shift due to alerting effects of the strong vibration stimulus. Alternatively, posture-shifts themselves may require either wakefulness or brief arousal to engage co-ordinated muscle activity likely necessary to shift body position, in which case an additional

vibration alarm may have relatively little impact on the process of returning to sleep following body movements. Remarkably little is known regarding the sequence of events preceding posture shifts in sleep, with no objective evidence available in the literature to guide if a brief return to consciousness is required to engage muscle activity to change posture, followed by a return to sleep with little or no conscious perception or lasting memory of the posture change itself (Tassi and Muzet, 2001). There have been no studies that have systematically analysed alarms generated by a supine-avoidance device in relation to physiological responses coincident with posture shifts with or without an alarm. In particular, the sequence of electroencephalogram (EEG) events occurring around the time of posture shifts have not been systematically investigated. This study aimed to characterise temporal relationships between EEG and arousal responses to posture shifts during sleep with or without a supine-avoidance alarm to investigate potential alarm-related sleep disturbance. We hypothesised that the majority of overnight posture shifts would occur during wake or following a brief arousal and that sleep would quickly resume following posture shifts irrespective of an active supine-avoidance alarm.

3.2 Methods

This study was a sub-study of a larger comparative effectiveness trial (SUPA trial – Chapter 2) of 6-8 weeks of supine-avoidance treatment versus 6-8 weeks of CPAP for reducing sleepiness in patients with supine-predominant OSA. However, this study specifically reports only on data collected on polysomnography nights at baseline and at the end of each treatment period, with a primary focus on active versus inactive supine-avoidance alarm treatment.

3.2.1 Inclusion and exclusion criteria

Patients with supine-predominant OSA were recruited through sleep clinics at Repatriation General Hospital, Royal Adelaide Hospital, Ashford Hospital, Memorial Hospital, Queen Elizabeth Hospital and Flinders Medical Centre based on polysomnography (PSG) findings from each patient's initial diagnostic sleep study. Patients who met the study criteria were then invited to participate in the trial following review and approval from their sleep specialist.

The inclusion criteria used to select patients and to define supine-predominant OSA were; age 18 and over and less than 75 years, total AHI ≥ 10 /hr, supine AHI ≥ twice non-supine AHI, non-supine AHI <10/h, total sleep time ≥ 4 hours with ≥30 min supine and ≥ 30 min non-supine sleep and Epworth Sleepiness Scale (ESS) ≥8. Patients with any of the following criteria were excluded; prior treatment with CPAP or supine-avoidance therapy, potentially dangerous sleepiness requiring urgent treatment (e.g.

history of falling asleep while driving or ESS ≥16), commercial driver, co-morbidities that may preclude supine-avoidance treatment (e.g. arthritis, pacemaker, mobility problems preventing non-supine sleep), unwilling to cease current alternative OSA therapies (e.g. mandibular advancement splint).

3.2.2 Supine-avoidance treatment

Supine-avoidance was achieved via a posture recording and alarm based vibration device (BuzzPOD, Gorman ProMed Pty Ltd, Melbourne, Australia, Figure 3.1) used in a previous study that demonstrated supine-avoidance efficacy and posture recording accuracy but without direct sleep measurements (Bignold et al. 2011). The device is worn on the chest during sleep using a Velcro strap and pouch, records body position via internal tilt switches sampled at 1 Hz, and records supine alarm events. A strong vibration alarm stimulus, externalised from the device to avoid interference with the internal tilt-switches, can be pre-configured to remain inactive or to activate when ≥5 consecutive samples (seconds) are detected in the supine position. Once activated the device alarm remains continuously active for 2 minutes before switching to a pulsed 5-sec on/5-sec off mode for a further 3 min before the alarm times-out to conserve power when the ongoing alarm has failed to illicit a posture shift. The device has sufficient internal memory and typical battery life to support 4 weeks of continuous use prior to download via a personal computer and universal serial bus (USB) and device software interface.

Figure 3.1 Supine-avoidance device (left) showing externalised vibration motor, and a subject wearing the device (right).

3.2.3 Protocol

After screening and consent study participants were instructed in the use of the device and provided with an inactivated supine-avoidance alarm device for 1 week before returning to the laboratory on the last night to be setup for a baseline home PSG. Subsequently, participants were randomized to receive CPAP therapy or supine-avoidance therapy for 6-8 weeks before crossing over to the remaining treatment for a further 6-8 weeks in order to complete the main trial, which included a repeat home PSG on allocated treatment at the end of each treatment arm.

3.2.4 Measures

Anthropometric measurements including age, gender, height, weight, waist circumference and body mass index (BMI) were determined at baseline and weight and BMI were also determined at the end of each treatment.

PSG signals were recorded using an Embletta MPR (REMLogic™, Pleasanton, California, United States) home-PSG device and included EEG (C3-M2, C4-M1), left and right electro-occulograms (EOG), chin EMG (all sampled at 500 Hz), nasal cannula pressure and thermistor (sampled at 250 Hz), thoracic and abdominal motion (sampled at 100 Hz), oximetry (sampled at 3 Hz) and body position (sampled at 20 Hz). The supine-avoidance device independently recorded sleep posture at a sample rate of 1 Hz.

3.2.5 Polysomnography analysis

An experienced sleep technologist blinded to treatment allocation scored sleep stages and respiratory and arousal events according to American Academy of Sleep Medicine (AASM) alternate criteria (Iber et al., 2007) as described in more detail in Chapter 2. OSA was defined on the basis of an AHI ≥ 10 /h (Ruehland et al., 2011). Total sleep time, sleep onset latency and wake after sleep onset were measured along with arousal index, number of awakenings and arousal durations.

3.2.6 Posture analysis

In order to assess temporal relationships between posture shifts and arousal events with the highest available temporal accuracy, posture data collected on the PSG device (sampled at 20 Hz) and supine-avoidance device (sampled at 1 Hz) were extracted via custom algorithms to detect all posture shifts lasting ≥5-seconds for further analyses. For supine-avoidance device recorded data the duration of each posture shift lasting ≥5-sec was determined and classified on the basis of posture shifts from and to non-supine versus supine postures. The presence and duration of any alarm event associated with shifts to the supine posture were also determined. The same posture duration and shift from and to analysis was applied to PSG recorded posture data using the default device angle cut-offs for classifying postures. The frequency of occurrence, duration and total cumulative time spent in supine versus non-supine postures following each type of posture shift (non-supine to supine, supine to non-supine and non-supine to a different non-supine posture) from both recording devices were also examined. EEG data 30 secs before and after each PSG recorded posture shift were also examined to assess wake versus sleep and arousals prior to and the time taken to achieve sleep following each posture shift. Prior sleep versus wake was determined from the epoch of the posture shift when posture shifts occurred in the last 15-sec of the epoch, or the prior epoch when the posture shift occurred in the first 15-sec of an epoch. Whilst imperfect, this classification strategy maximises the available temporal resolution of traditional 30-sec epoch sleep scoring. Following identification of all ≥5 sec posture shifts, sleep vs wake stage before each posture shift and the onset time of the nearest arousal within 30 sec before to +3 sec after each

posture shift were used to classify the presence of arousal associated with the posture shift. -30 and +3 seconds were chosen on the basis of epoch length used to define sleep vs wake state preceding posture shifts, and to allow for variability in scorer marking of arousal onsets. Sleep onset times following each posture shift were determined on the basis of the number of epochs taken for sleep to resume (i.e. with 30 sec temporal resolution, as typically applies for sleep onset latency calculations). Given no internal clock or synchronisation channel options available to help more accurately temporally align supine-avoidance device posture and alarm recordings to PSG recorded events, it was not possible to more accurately synchronise PSG versus supine-avoidance device posture recording devices. Thus, it was only possible to undertake a meaningful analysis of temporal relationships between posture shifts and EEG defined sleep stage, arousals and sleep onset times using PSG-recorded posture shift, sleep and arousal data independent of the supine-avoidance device recordings.

3.2.7 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23. Normality was assessed using Kolmogorov-Smirnov tests. Normally distributed data are reported as mean ± SD (or 95% confidence intervals as indicated) and were compared between baseline and treatment nights using mixed effects model analysis. The total number of posture shifts under each condition were compared between nights using Fisher's exact tests. Non-normal data are reported as median [interquartile range] and were compared between baseline and treatment nights using Wilcoxon sign-rank

tests. Kaplan-Meier and Cox regression analyses were used to examine the effects of treatment (vs baseline) and sleep vs wake state prior to supine and non-supine posture shifts on the time taken to shift to another posture, and the time taken for sleep to resume following supine and non-supine posture shifts (reported as mean [95% confidence interval]). P values < 0.05 were considered statistically significant.

3.3 Results

56 patients out of 66 enrolled in the main trial successfully completed baseline and both treatment nights for this analysis. Table 3.1 shows the baseline characteristics of the patients included in analysis. Patients were mostly middle-aged men (34 males and 22 female) and obese (BMI>30 kg/m^2), and by study inclusion criteria, all had supine-predominant OSA.

Table 3.1 Basic characteristics of the study population.

Parameter	**Value**
N (% Male)	56 (60.7%)
Age (yr)	53.6 ± 11.2
Body mass index (kg/m²)	31.4 ± 8.1
Diagnostic sleep study	
Supine sleep (%total)	44.6 [33.3 to 64.8]
Total AHI (/h)	14.5 [12.2 to 20.7]
Non-supine AHI (/h)	5.1 [2.3 to 7.5]
Supine AHI (/h)	31.5 [21.4 to 45.0]
Epworth Sleepiness Score (ESS)	10.0 [8.0 to 13.0]

N, Age and Body Mass Index are mean ± SD. Supine sleep, Total AHI, Non-supine AHI Supine AHI, Epworth Sleepiness Score are median [IQR].

There were several technical problems with the acquisition of posture data from PSG files that reduced the number of participants with data available for detailed PSG recorded posture analysis to 54, 38 and 45 baseline, supine-avoidance and CPAP PSG nights respectively. The number posture shifts ≥5 seconds during the sleep period recorded by the PSG device (i.e. Embletta 100x) on each PSG night are shown in Table 3.2. There was no significant reduction in the total number of posture shifts on treatment nights compared to the baseline night. Around 60% of all posture shifts were preceded by wake and most posture shifts from sleep on all three PSG nights were preceded by an arousal such that the majority of all posture shifts were preceded by either wake or arousal from sleep ($P<0.001$, Table 3.2).

Table 3.3 summarises the total number of ≥5-sec posture shifts and alarm events recorded by the supine-avoidance device during the baseline week, PSG nights and subsequent 6-8 weeks of active supine-avoidance treatment use. Figure 3.2 shows the average number of posture shifts per night, their mean duration and total cumulative hours spent following posture shifts from non-supine to supine, supine to non-supine and non-supine to non-supine postures as recorded by the supine-avoidance and PSG devices.

Table 3.2 The number of PSG device (Embletta) recored posture shifts ≥5-sec.

	To Supine	To Non-Supine	Total
Baseline PSG (N=54)			
N shifts	6.0 [4.0 to 9.3]	9.0 [5.0 to 12.0]	16.0 [10.0 to 21.5]
N shifts during sleep	3.0 [2.0 to 5.0]	3.0 [2.0 to 6.0]	6.0 [3.0 to 10.0]
N shifts during sleep preceded by arousal	3.0 [1.0 to 4.5]	2.0 [1.0 to 5.0]	5.0 [2.0 to 9.0]
% Sleep shifts preceded by arousal	100 [75 to 100]	100 [78 to 100]	94 [78 to 100]
% Total shifts preceded by wake or an arousal	100 [90 to 100]	100 [89 to 100]	100 [91 to 100]
Arousal duration (sec)	15.7 [12.5 to 17.4]	15.8 [13.4 to 19.1]	15.9 [13.0 to 17.4]
SOL following shift from sleep (min)	0.5 [0.2 to 1.1]	0.6 [0.3 to 1.5]	0.8 [0.4 to 1.5]
Supine avoidance PSG (N=38)			
N shifts	6.0 [3.0 to 9.0]	9.0 [6.0 to 12.0]	15.0 [8.3 to 20.8]
N during sleep	2.5 [1.0 to 5.0]	3.0 [2.0 to 5.0]	6.0 [3.0 to 10.0]
N shifts during sleep preceded by arousal	2.0 [1.0 to 4.8]	3.0 [2.0 to 5.0]	6.0 [3.0 to 8.3]
% Sleep shifts preceded by arousal	100 [60 to 100]	100 [100 to 100]	100 [84 to 100]
% Total shifts preceded by wake or an arousal	100 [86 to 100]	100 [100 to 100]	100 [93 to 100]
Arousal duration (sec)	15.1 [13.5 to 17.1]	15.3 [13.0 to 17.1]	14.9 [13.3 to 16.7]
SOL following shift from sleep (min)	0.6 [0.1 to 1.4]	0.5 [0.3 to 1.0]	0.5 [0.3 to 1.2]
CPAP PSG (N=45)			
N shifts	5.0 [3.0 to 9.0]	7.0 [5.0 to 12.0]	13.0 [8.0 to 20.0]
N during sleep	2.0 [1.0 to 4.0]	3.0 [2.0 to 5.0]	5.0 [3.0 to 8.3]
N shifts during sleep preceded by arousal	2.0 [1.0 to 3.0]	3.0 [1.0 to 4.0]	4.5 [2.8 to 7.0]
% Sleep shifts preceded by arousal	100 [83 to 100]	100 [83 to 100]	97 [79 to 100]
% Total shifts preceded by wake or an arousal	100 [100 to 100]	100 [94 to 100]	100 [90 to 100]
Arousal duration (sec)	15.7 [13.4 to 17.9]	16.9 [14.2 to 19.5]	16.3 [14.5 to 18.6]
SOL following shift from sleep (min)	0.5 [0.2 to 1.2]	0.5 [0.3 to 1.1]	0.8 [0.4 to 1.4]

All values are presented as median [interquartile range].Sleep onset latency (SOL).

Table 3.3 The total number of ≥5-sec posture shifts and alarm events recorded by the supine-avoidance alarm device.

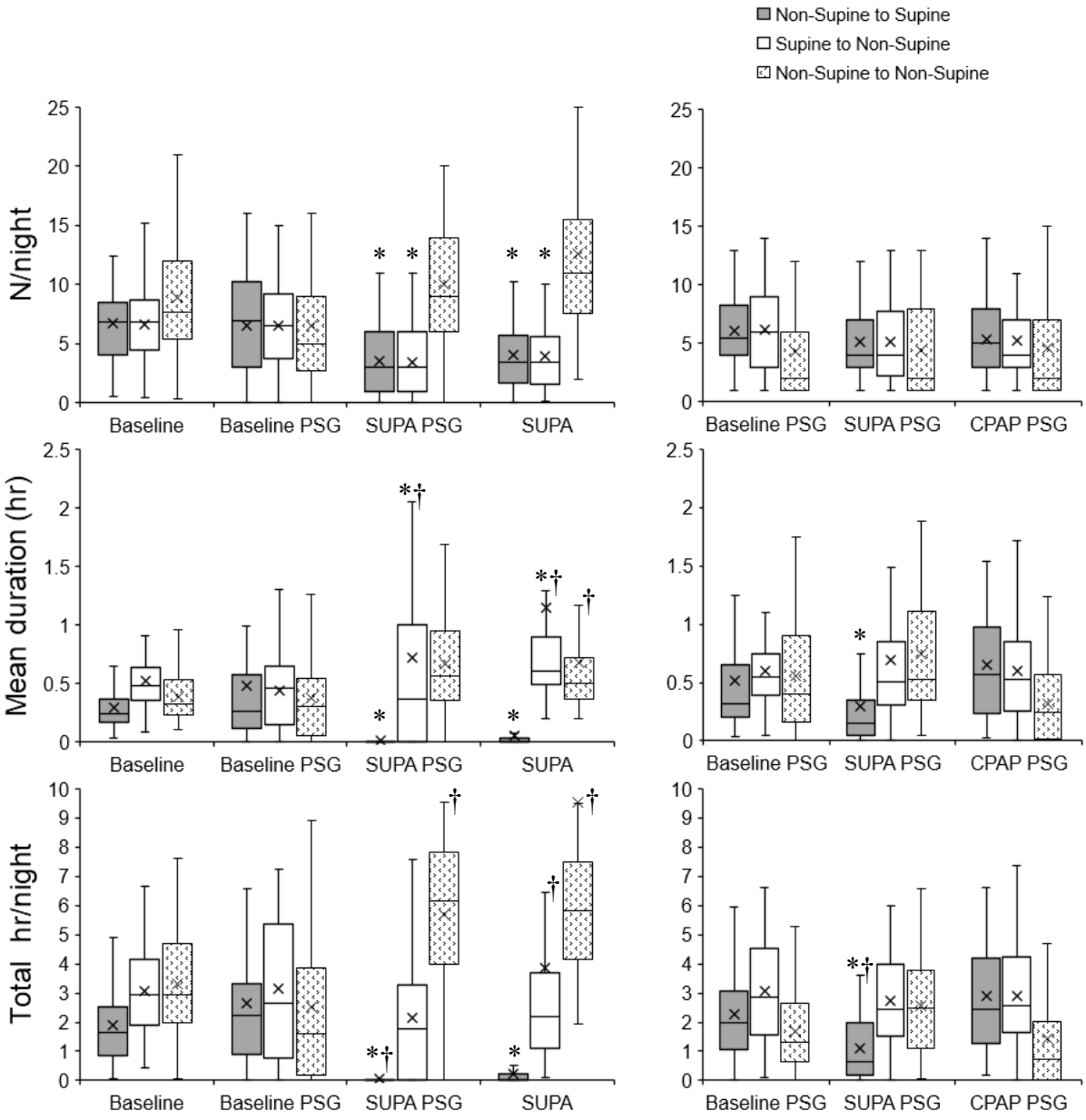
	To Supine	To Non-Supine	Total
	Baseline (N=56)		
N total	3262	7662	10924
N /night	6.9 [4.8 to 8.7]	15.0 [10.5 to 18.2]	21.6 [15.8 to 26.9]
	Baseline PSG (N=50)		
N total	338	657	995
N /night	8.0 [4.8 to 11.0]	13.0 [8.3 to 16.0]	19.0 [13.5 to 26.0]
	Supine-avoidance PSG (N=45)		
N total	161*	611	772*
N /night	4.0 [2.0 to 6.3]*	12.0 [9.0 to 16.0]	16.0 [10.0 to 20.0]
N alarms total	158		
N alarms/night	4.0 [2.0 to 6.3]		
Mean alarm duration (sec)	7.0 [3.4 to 11.7]^		
	Supine-avoidance treatment period (N=56)		
N total	9030	37642	46672
N /night	3.4 [1.7 to 5.8]*	14.9 [11.9 to 20.3]	18.6 [14.3 to 24.8]
N alarms total	8830		
N alarms/night	3.4 [1.6 to 5.4]		
Mean alarm duration (sec)	12.3 [6.6 to 23.7]		

Values are total numbers or median [interquartile range]. *indicates $p<0.05$ vs baseline PSG. ^ vs supine-avoidance treatment period.

During PSG nights with an active supine-avoidance alarm the number of shifts to supine were significantly reduced in both supine-avoidance and PSG device recorded posture data compared to the baseline PSG night with an inactive alarm. In addition, almost all supine-avoidance device recorded shifts to supine produced an alarm event (Table 3.3).

Active supine-avoidance treatment produced a total of 158 alarm events from 161 ≥5-sec shifts to supine on the PSG night (Table 3.3) and markedly reduced the average duration and total cumulative time spent supine after posture shifts to supine (Figure 3.2). However, on the PSG night there were 5 (3.2%) alarm events associated with ongoing supine sleep time of more than 5 minutes (ranging from 5.6 to 99.3 minutes in duration) most likely indicating sleep-through alarm events. However, it was not possible to accurately align device alarm events with PSG recorded sleep and wake data to clarify if these were sleep-through events. Furthermore, whilst supine-avoidance device recorded posture shifts showed marked reductions in supine time during both PSG nights and the 6-8 week supine-avoidance treatment period (P=0.006, P=0.001 respectively) with corresponding increases in non-supine time (P=0.001, P=0.007 respectively) (Table 3.3 and Figure 3.2), PSG device recordings showed no statistically significant reductions in supine time with supine-avoidance treatment (Table 3.2, Figure 3.2 left versus right panels).

Figure 3.2 Box and whisker plots of the number, duration and total cumulative time spent following each type of posture shift over the course of the study.

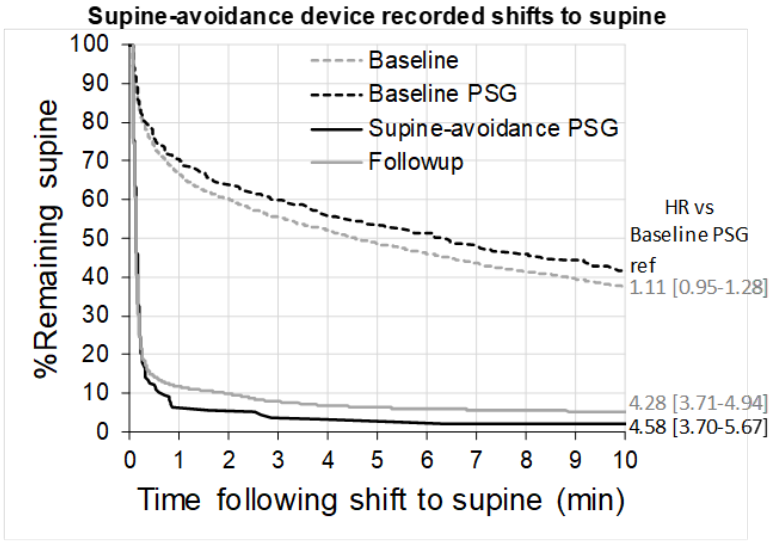


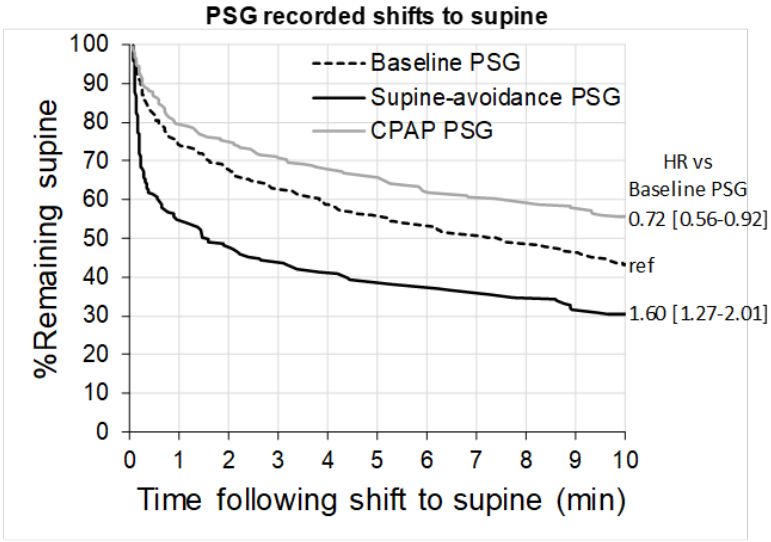
Boxes indicate median, interquartile range and mean (x) number (top), duration (middle) and total cumulative time (bottom) of non-supine to supine (grey boxes), supine to non-supine (open boxes) and non-supine to non-supine (patterned boxes) posture shifts per night. The left panels show supine-avoidance device recorded posture shifts lasting ≥5-sec during the baseline period (7 days), baseline PSG night, supine-avoidance (SUPA) PSG night and subsequent 6-8 week active treatment period. The right panel shows PSG device recorded posture shifts lasting ≥5-sec on the baseline, supine-avoidance (SUPA) and CPAP PSG nights. * indicates $p<0.05$ vs non-supine to non-supine shifts and † $p<0.05$ vs non-supine to supine shifts within the same treatment condition.

Kaplan-Meier curves showing the time spent supine following ≥5-sec supine-avoidance device recorded and PSG recorded ≥5-sec shifts to the supine-posture under each condition are shown in Figure 3.3. There were statistically significant differences in the hazard of remaining supine in the 10-min following shifts to the supine posture with an inactive compared to an active supine-alarm ($p<0.001$). However, there were no differences between the baseline period and baseline PSG nights ($p=0.180$) or between the supine-avoidance PSG versus the remaining all 6-8 weeks of supine-avoidance treatment nights ($p= 0.638$, Figure 3.3). Compared to baseline, the hazard or remaining supine was significantly reduced with active supine-avoidance alarms in both supine-avoidance ($p<0.001$) and PSG ($p<0.001$) device recorded data but was significantly higher with CPAP therapy (Figure 3.2).

Kaplan-Meier curves showing the proportion of PSG recorded posture shift events to supine from sleep or wake associated with ongoing wake are shown in Figure 3.4. The hazard of remaining awake following supine posture shifts from sleep was markedly reduced compared to posture shifts from prior wake ($p<0.001$, Figure 3.4). However, there were no significant differences between nights in the hazard of remaining awake following posture shifts to supine from either sleep ($p=0.941$) or wake ($p=0.306$). Thus, sleep resumed rapidly following supine-posture shifts, particularly from sleep, despite the presence of supine-avoidance device alarms.

Figure 3.3 Kaplan-Meier plots showing the proportion of patients remaining in the supine posture as a function of time in the 10 min following ≥5 sec device recorded shifts to the supine posture (left) and ≥5 sec PSG recorded shifts to the supine posture (right).





N 'at risk' device recorded posture shifts ≥5 sec

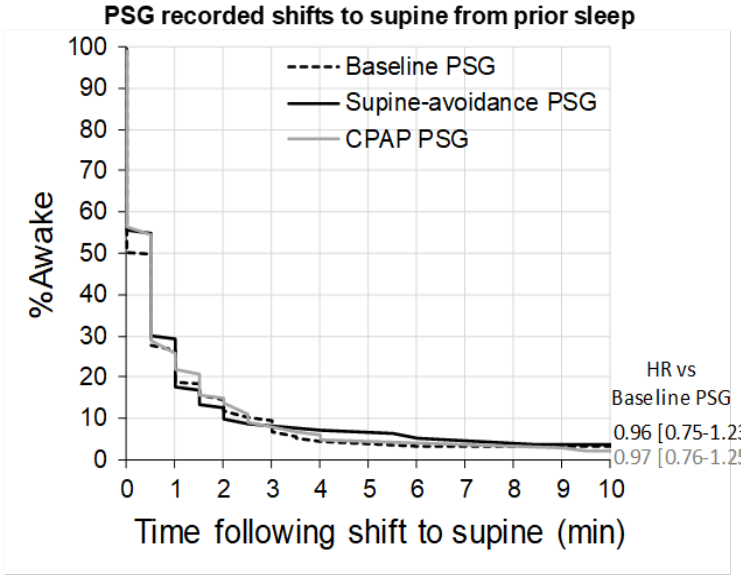
Time (min)	0	1	2	3	4	5	6	7	8	9	10
Baseline	3184	2136	1915	1767	1658	1554	1470	1391	1316	1261	1196
Baseline PSG	328	232	210	197	184	176	169	159	151	146	136
Supine-avoidance PSG	157	10	9	6	5	5	4	3	3	3	3
Followup	8890	1040	882	694	604	561	532	509	495	474	452
N 'at risk' participants											
Baseline	56	56	56	56	56	56	56	56	56	56	56
Baseline PSG	44	44	44	43	43	43	43	42	42	41	40
Supine-avoidance PSG	36	5	5	5	5	5	4	3	3	3	3
Followup	56	46	45	40	38	37	37	35	35	34	34

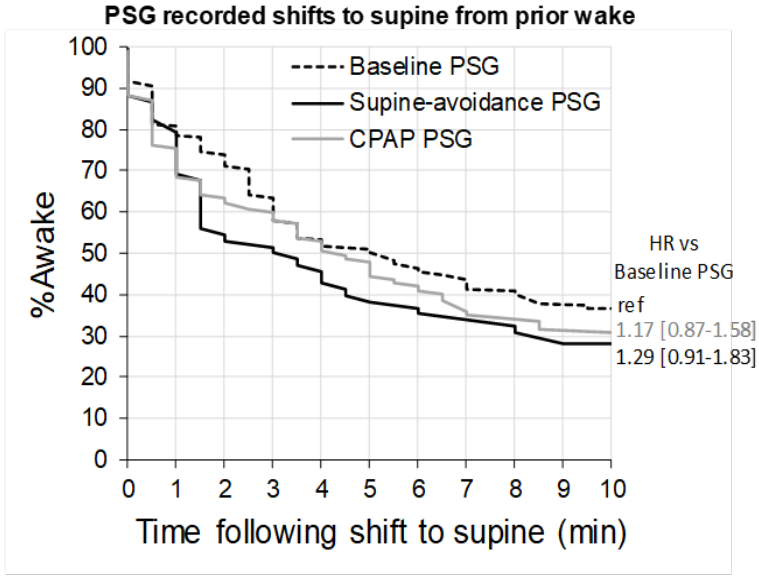
N 'at risk' PSG recorded posture shifts ≥5 sec

Time (min)	0	1	2	3	4	5	6	7	8	9	10
Baseline PSG	293	223	204	189	177	167	160	153	146	140	129
Supine-avoidance PSG	177	97	85	78	73	69	66	63	61	55	53
CPAP PSG	218	173	164	155	148	144	136	132	129	126	121
N 'at risk' participants											
Baseline PSG	49	49	48	48	48	48	48	48	48	47	47
Supine-avoidance PSG	35	30	28	28	26	26	26	26	26	25	25
CPAP PSG	41	41	41	41	41	41	39	39	39	39	39

Baseline (~5-7 nights, grey dashed line) and baseline PSG (black dashed line) nights were recorded with the device supine alarm inactive. Supine-avoidance treatment nights (6-8 weeks, grey solid line) and a supine-avoidance PSG recording night (black solid line) were recorded with the supine alarm activated. HR indicates hazard ratios [95% confidence intervals] versus the baseline PSG night (ref). Tabulated numbers indicate the total number of posture shifts and individual participants 'at risk' of remaining supine over the 10 minutes after the onset of each posture shift.

Figure 3.4 Kaplan-Meier plots showing the proportion of PSG device recorded posture shifts ≥5 sec followed by wake in the 10 minutes after a shift from non-supine to the supine posture from prior sleep (left) versus wake (right) during the baseline, supine-avoidance and CPAP PSG nights.





N 'at risk' PSG recorded posture shifts ≥5 sec from sleep

Time (min)	0	1	2	3	4	5	6	7	8	9	10
Baseline PSG	159	128	120	113	106	102	98	93	87	84	77
Supine-avoidance PSG	113	59	54	48	44	44	42	41	39	34	34
CPAP PSG	101	83	82	79	76	76	69	68	67	65	62
N 'at risk' participants											
Baseline PSG	41	40	38	37	36	36	36	36	35	35	35
Supine-avoidance PSG	34	28	27	26	23	23	23	23	23	21	21
CPAP PSG	38	36	36	36	36	36	34	34	34	34	33

N 'at risk' PSG recorded posture shifts ≥5 sec from wake

Time (min)	0	1	2	3	4	5	6	7	8	9	10
Baseline PSG	139	98	86	78	72	66	63	61	60	57	53
Supine-avoidance PSG	63	38	32	31	30	27	26	24	24	23	21
CPAP PSG	116	90	82	76	72	68	67	64	62	61	59
N 'at risk' participants											
Baseline PSG	45	42	40	37	37	36	35	35	35	33	33
Supine-avoidance PSG	24	17	16	16	15	15	15	14	14	13	13
CPAP PSG	36	36	35	33	32	30	30	30	30	30	30

Prior sleep versus wake was determined from the epoch of the posture shift when posture shifts occurred in the last 15-sec of the epoch, or the prior epoch when the posture shift occurred in the first 15-sec of an epoch. Tabulated numbers indicate the total number of posture shifts and individual participants remaining 'at risk' of remaining supine over the 10 minutes after the onset of each posture shift.

Further analysis of posture distributions in different sleep stages during PSG nights showed that the majority (~60%) of shifts occurred during wake, but with around 17% of posture shifts in N2 sleep and very few posture shifts in deep sleep. However, there were no differences between baseline or treatment nights in posture shift distributions across sleep.

Table 3.4 Distribution of posture shifts as a function of sleep stage immediately prior to the posture shift.

	Wake	N1	N2	N3	REM
Baseline	60.0 [45.6 to 80.0]%	3.1 [0.0 to 11.1]%	16.7 [4.7 to 20.7]%	0.0 [0.0 to 3.3]%	5.0 [0.0 to 25.0]%
Supine-avoidance	59.4 [48.0 to 76.7]%	4.8 [0.0 to 11.3]%	17.4 [9.6 to 27.5]%	0.0 [0.0 to 10.0]%	2.1 [0.0 to 14.0]%
CPAP	66.7 [50.0 to 80.0]%	0.0 [0.0 to 10.0]%	16.7 [7.7 to 25.7]%	0.0 [0.0 to 6.8]%	6.1 [0.0 to 12.5]%

Values are median [interquartile range] of all posture shifts ≥5-sec of any type (non-supine to supine, supine to non-supine or non-supine to supine. N1, N2, N3 indicate the different stages of non-REM sleep. REM: Rapid eye movement sleep.

3.4 Discussion

This is the first study to objectively examine the sequence of EEG events occurring before and after overnight posture shifts and also the first to investigate the effects of a supine-avoidance alarm device and CPAP therapy on posture shifts in patients with supine-predominant OSA. The main findings support that most overnight posture shifts during the sleep period are preceded either by wake or by an EEG discernible arousal or awakening event. Furthermore, a supine-avoidance alarm commencing 5-sec after a shift to the supine posture had no significant impact on the time taken for sleep to resume, and most of the time very effectively discouraged the user from remaining supine.

This study extends the previous findings of Bignold et al (2011), who found that time spent supine is markedly reduced with the same chest-worn posture recording and supine-avoidance alarm device. These new findings clarify that this reflects a combination of reduced supine sleep and wake time, and that posture shift behaviours and supine-avoidance effectiveness remain largely unchanged over 6-8 weeks of ongoing treatment with no major difference compared to baseline in the total number of shifts to supine by the end of 6-8 weeks of supine-avoidance treatment. This supports that patients do not simply learn to avoid the supine posture and appear to require ongoing alarms around 3-4 times per night in order to successfully avoid prolonged supine periods during sleep. Two other alternative vibration based alarm devices used by two separate groups in Belgium and the USA also show significantly reduced time spent supine during sleep (Van Maanen et al., 2013; Levendowski et al.,

2014). However, this is the first systematic study of the time taken to achieve sleep after supine posture shift events.

Unfortunately, it was not possible to accurately align supine-avoidance device versus PSG recorded device data to more comprehensively examine alarm or other physiological activation outcomes with supine-avoidance compared to baseline or PSG treatment nights. Nonetheless, and despite the strong device vibration stimulus and significant reduction in supine sleep, there were clearly occasional prolonged periods of residual supine time. These events are consistent with a rapid return to sleep followed by ongoing failure of the vibration alarm to effectively discourage supine positioning, thus negatively impacting on supine-avoidance efficacy. These are important observations and suggest that further technological improvements to increase supine-avoidance efficacy may be warranted. Nonetheless, overall supine-time remained markedly reduced. There was also no evidence of extended wake following device alarms and no significant difference between the cumulative time that patients spent supine during nights when they were equipped with an activated alarm device compared to baseline nights when the alarm was inactive.

The primary aim of this study was to examine temporal relationships between sustained posture shifts and EEG detected arousals. Analysis of baseline and treatment night sleep studies showed that most (~80%) sustained posture shifts from sleep were preceded by an arousal. These data are consistent with the hypothesis that most but perhaps not all body position shifts arising during sleep are preceded by an arousal. This could suggest that brief cortical activation is not a pre-requisite for all

body position changes in sleep. Alternatively, this could reflect an artefact of manual PSG scoring, which is well known to show considerable within- and between-scorer variability, particularly for arousal events (Ruehland et al., 2011). Consequently, some arousal events may well have been missed. Furthermore, independent manual identification of arousal onsets versus posture shifts may not be sufficiently accurate to reliably identify the onset times of arousal versus posture shift events and may systematically under-estimated the number of posture-shifts associated with cortical arousal. More comprehensive analysis of EEG activation responses, such as with quantitative EEG methods, along with examination of other physiological activation responses such as heart rate/pulse responses around the time of positions shifts may well be useful in future studies, but will need more accurate device synchronisation with sleep study recordings than was possible in this study.

Although how much "*consciousness*" is needed for a posture shift in sleep remains a matter of debate (Tassi and Muzet, 2001), frequent cortical activation preceding sustained posture shifts remains consistent with the concept that posture shifts require EEG activation to engage muscles needed for body movement, and that alarm events occurring shortly after posture shifts likely already coincide with a partial return to wake. Body movements during sleep could primarily be the result of accumulating discomfort associated with staying in one position for an extended period of time (De Koninck et al., 1983) in which case posture shifts might be expected to be distributed across most stages of sleep. In healthy young adults, De Koninck observed most body movements to occur during REM (De Koninck et al., 1983), although others have suggested a trend towards reduced movement with aging and no clear relation to

sleep stage/state (Gori et al., 2004). The current study found that the majority of posture shifts occurred during wake, with fewer initiated from N2, REM and N1 sleep respectively and very few from deep sleep. These findings appear to be largely consistent with the uneven distribution of sleep stages in combination with diminished sensory acuity during sleep, which is particularly prominent in deep sleep and to a lesser extent in REM, N2 and N1 (Tassi and Muzet, 2001; Pare and Llinas, 1995). Thus, a bias towards posture shifts occurring during wake and lighter stages of sleep remains consistent with a combination of accumulating posture discomfort and sleep depth dependence of sensory acuity. It is not clear whether patterns of movement across different sleep stages, or the control of the motor cortex and subcortical circuits are affected by sleep apnea. Further research is needed to better understand the main triggers for posture shifts in sleep and potential relationships between different stages of sleep and movement during sleep in relation to brain activity.

In addition to effectively reducing supine sleep, the supine-avoidance device used in this study did not prolong arousal/awakening responses associated with supine alarms. Most posture shifts from prior sleep were associated with a brief prior arousal followed by a rapid return to sleep within a few seconds to minutes of the position shifts, with no significant lengthening of arousals or sleep onset latency with an active supine alarm. Thus, there was no evidence to support sleep disturbance associated with the alarm *per se*. However, there was also no evidence to support improved sleep with the supine-avoidance alarm or CPAP, other than a previously reported reduction in AHI (Chapter 2). In contrast, when patients were already awake immediately before shifting posture it took considerably longer for sleep to resume, irrespective of the

alarm activation status or use of CPAP. Furthermore, there were clearly some differences in posture shift assessments between PSG and the supine-avoidance devices, with a substantially greater proportion of PSG versus supine-avoidance device recorded posture shifts to supine remaining supine after 10 min. The most likely explanation for these findings is that the normal central placement of the PSG recording device was displaced somewhat laterally due to the presence of the chest-worn supine-avoidance and recording device. Thus, posture assessment from the PSG device may be less reliable compared to the chest-worn device, which has previously been shown to reliably classify posture compared to video-confirmed posture assessments (Bignold et al., 2011). Despite clear posture classification differences, PSG device assessments of supine sleep were still shown to be significantly reduced during supine-avoidance treatment. In future studies, more accurate device synchronisation and positioning strategies would be very useful to more directly and reliably compare supine-avoidance treatment effectiveness and relationships with PSG determined sleep outcomes.

Other methodological considerations

The population represented in this study were specifically selected on the basis of a supine AHI twice that of the non-supine AHI along with a clinically abnormal supine AHI (>10 /h) and a normal non-supine AHI (<10 /h) (Bignold et al., 2011; Mador et al., 2005a). Whilst it is unclear if selecting patients with somewhat different characteristics would change the study outcomes, this patient group remains one of the most relevant to supine-avoidance treatment given that supine-avoidance should effectively normalise OSA according to these criteria. Nonetheless, further investigations to

establish outcomes in supine-predominant snorers and perhaps less sleepy patients who could potentially exhibit more sleep disturbance to alarm-based treatments may be warranted.

The supine-avoidance alarm used in this study did not possess an internal clock. Developing methods to synchronise device recorded posture shift and alarm data with PSG events was challenging and has not been attempted previously (Levendowski et al., 2014; Van Maanen et al., 2013). However, the accuracy of synchronization was inevitably more limited than within PSG recorded data but where temporal alignment with alarm events was uncertain. The lack of an internal clock in the supine avoidance device meant that accurate synchronization with sleep data (i.e. PSG data) was ultimately not possible. Thus, analysis of posture shift behaviours was conducted independently on supine-avoidance and PSG device data. Thus, future studies would benefit from more reliable methods to align alarm events with PSG recordings.

In summary, the findings of this study support that most posture shifts during sleep are preceded by either wake or EEG arousal / awakening such that most supine alarm events occur around the time of brief cortical activation potentially needed for co-ordinated body movements with minimal effect on the time taken for sleep to resume. Further studies examining posture shifts and other activation responses such as heart rate and airflow may provide further understanding of physiological disturbances associated with position changes in sleep.

CHAPTER 4. A comparison of snoring changes with a supine-avoidance alarm device compared to constant positive airway pressure treatment in patients with supine-predominant OSA

Key points

Question: This study investigated the effectiveness of supine-avoidance therapy via a vibratory alarm device and CPAP therapy in reducing objectively measured snoring frequency in patients with supine-dependent obstructive sleep apnea (SDOSA).

Findings: Whilst CPAP therapy successfully reduced snoring, supine-avoidance therapy did not systematically reduce snoring. However, in a sub-group of patients who suffered from supine snoring as well SDOSA supine-avoidance therapy significantly reduced snoring as well as CPAP.

Meaning: Reducing supine sleep via supine-avoidance therapy may help a subgroup of patients who suffer from supine-mainly snoring and SDOSA to significantly decrease both their snoring and OSA.

Abstract

Snoring is one of the primary complaints from patients or their partners when they seek sleep physician advice. Snoring can substantially disrupt patient and particularly bed-partner sleep contributing to insomnia, psychosocial problems and reduced quality of life for both snorers and their bed partners. Despite this, snoring is not routinely assessed and is often largely ignored in clinical settings where the main focus is typically on other measures such as the apnea hypopnea index, oxygen desaturation index and arousal index. This study aimed to analyse, for the first time, snoring data from the SUPA trial objectively (Chapter 2) to quantify how much snoring occurs in clinical patients with supine-dependent OSA and the comparative effectiveness of supine-avoidance therapy versus CPAP to reduce objective measures of snoring. Snoring and treatment outcomes were also examined in a subgroup of patients with supine dependent snoring (defined on the basis of snoring frequency at least 2x higher in supine than non-supine postures). Baseline measurements showed snoring frequency was 48.9 [95% CI 16.7 to 188.7], 26.3 [95% CI 17.0 to 106.3], 57.5 [95% CI 16.8 to 190.7] snores/h for the whole group, supine snorer and non-supine snorers respectively. Supine sleep as a percentage of total sleep was almost completely abolished with supine-avoidance treatment (Baseline= 30.7% [95% 15.4 to 46.4], supine-avoidance= 0.2% [95% 0.0 to 15.7]). In the whole group, CPAP significantly reduced overall snoring frequency although some residual snoring remained. However, no treatment effect was observed with supine-avoidance therapy in reducing snoring frequency (frequency of snores ≥50 dBA; baseline= 48.9 [95% 16.7 to 188.7], supine-avoidance= 36.8 [95% 6.3 to 233.7], CPAP= 4.2 [95% 2.1 to 29.5] snores /h). However, in the sub-group of supine-dependent snorers supine-

avoidance therapy was effective snoring frequency (Baseline= 26.3 [95% 17.0 to 106.3], supine-avoidance= 14.3 [95% 3.0 to 18.1], CPAP= 4.6 [95% 2.6 to 8.9] snores/h). In conclusion, supine-avoidance therapy may not necessarily lead to a systematic reduction of snoring frequency in patients with supine-predominant OSA, but does appear to be effective in the subgroup of patients with supine-predominant snoring. This study supports that in suitably selected patients, supine-avoidance is a simple, feasible, effective and affordable approach well-suited to patients with supine-predominant OSA and/or snoring.

4.1 Introduction

Snoring and obstructive sleep apnea (OSA) are part of a continuum of obstructed breathing in sleep and underpin the majority of referrals to a sleep physician for a sleep study (Larsson et al., 2003). Snoring reflects Starling resistor-like behaviour of the upper airway where dynamic partial airway collapse limits airflow irrespective of inspiratory driving pressures(Wellman et al., 2014). Consequently, a portion of often substantial inspiratory effort is converted into tissue vibration and snoring with reduced airflow (hypopnoea) instead of normal unimpeded airflow and ventilation. Although OSA can include apneas without snoring, and snoring can be sustained for long periods that fail to meet traditional hypopnea scoring criteria, most respiratory events in OSA reflect transient hypopneas (Ratnavadivel et al., 2009) likely to be directly associated with snoring. Thus, up to 95% of all OSA patients snore heavily most or every night (Viner et al., 1991) and snoring frequency and intensity are strongly associated with respiratory and arousal disturbances in sleep (Viner et al., 1991; Wilson et al., 1999).

Habitual loud snoring without OSA affects somewhere between 15%-54% of all middle-aged adults, potentially making it a more common problem than OSA (Young et al., 1993; Enright et al., 1996). In clinical settings, snoring is a clear sign of a collapsible airway, but is considered less of a clinical concern than frequent transient obstruction, desaturation and arousal events that contribute to an elevated apnea hypopnoea index (AHI) in OSA. Nevertheless, habitual loud snoring without

necessarily a high AHI may have important negative effects on the snorer and bed partner sleep quality and health.

Snoring can substantially disrupt patient and particularly bed-partner sleep contributing to insomnia, psychosocial problems and reduced quality of life for both snorers and their partners. Snoring has been linked to marital problems (Jones and Swift, 2000), occasional acts of violence including homicide (Pelausa and Tarshis, 1989), and is one of the primary reasons patients seek sleep treatments from ear, nose and throat (ENT) specialists (Marshall et al., 2007; Mcardle et al., 2001). Snoring could also contribute to increased cardiovascular disease risk due to vibration-induced vascular injury and effects of chronic cardiac exposure to large negative intrathoracic pressures known to be associated with right ventricular hypertrophy (Amatoury et al., 2006; Curry et al., 2002; Puig et al., 2005). Substantial vibration energy and the associated tissue stress caused by snoring is likely to be transmitted to the nearby carotid arteries, potentially contributing to endothelial tissue damage, inflammation and potentially plaque rupture risk (Curry et al., 2002). A dose-dependent relationship between snoring severity and carotid atherosclerosis but not femoral artery atherosclerosis is consistent with this hypothesis (Lee et al., 2008). Thus, chronic obstructed breathing and snoring in sleep could contribute to increased adverse cardiovascular outcome risk, including stroke.

Upper airway collapsibility, and thus snoring, during sleep is strongly body position dependent and both are typically higher during supine compared to non-supine sleep. Although the prevalence of supine-predominant snoring is not well-established,

approximately 50% of all patients diagnosed with OSA show strong supine-predominance of OSA severity, with an at least a 2-fold higher supine versus non-supine AHI (Adams et al., 2017). The majority of snorers without OSA also snore less in lateral compared to supine sleep (Loord and Hultcrantz, 2007; Miyamoto et al., 1997). If the prevalence of supine-predominant snoring follows a similar pattern to OSA, then around 20-30% of all adults potentially exhibit supine-predominant snoring and could potentially benefit from supine-avoidance therapy. Given a growing body of evidence to support that simple supine-avoidance devices can effectively reduce supine sleep time, nearly one third of OSA patients who exhibit clinically significant OSA only when supine, and a large number of snorers without OSA (Oksenberg and Gadoth, 2019; Berry et al., 2019), could potentially be treated through simple supine-avoidance treatment alone. Whilst promising, successful reduction of snoring through simple supine-avoidance device treatment remains to be demonstrated.

Despite the effectiveness of continuous positive airway pressure (CPAP) for reducing AHI, patient acceptance and adherence to treatment remains problematic (Rotenberg et al., 2016) and there remains a remarkable lack of objective data regarding effects on snoring, one of the key reasons for which patients may seek treatment. Chapter 2 reported that supine-avoidance via a simple non-discomfort vibration-based alarm device is effective in reducing sleepiness and showed substantially greater treatment adherence compared to CPAP over 6-8 weeks of treatment. Given a lack of data concerning OSA treatment effects on snoring, the primary purpose of this study was to compare anticipated snoring frequency, intensity and snoring-related complaint reductions between supine-avoidance therapy compared to CPAP. A secondary aim

was to examine the prevalence of supine-predominant snoring in patients selected on the basis of supine-predominant OSA, and to test for potential differences in snoring and treatment adherence outcomes in patients with versus without co-existing supine-predominant snoring.

4.2 Method

Participants were from a previously reported randomised-controlled cross-over trial (see Chapter 2 – SUPA trial) selected on the basis of polysomnography (PSG) confirmed supine-predominant OSA defined on the basis of a total apnea-hypopnoea index (AHI) > 10 events per hour and a supine AHI at least twice that of non-supine AHI measured from at least 4 hours of recording with at least 30 min in supine and non-supine postures. All available data from the full SUPA cohort were examined including a subgroup of patients who were also classified as supine-predominant snorers based on a snoring frequency of at least twice that in supine compared to non-supine positions. A total of 56 patients completed the SUPA trial and were available for this analysis. Following screening and consent, each participant completed a 1-week in-home assessment of sleep posture (inactive supine-alarm device) and a full in-home PSG study at baseline prior to randomisation to receive either CPAP or supine-avoidance therapy as their initial treatment. Patients then remained on each allocated treatment for a total of 6-8 weeks before crossing over to the other treatment for a further 6-8 weeks, with a full in-home PSG on allocated treatment repeated within the last week of each treatment arm of the study.

Baseline and follow up questionnaires including Snoring Severity Scale (SSS) (Lim and Curry, 1999), assessment of quality of life (AQoL-8D) (Richardson et al., 2014) and Epworth Sleepiness Score (ESS) (Johns, 1992) were used to assess the effects of snoring on quality of life and sleep quality.

4.2.1 Supine-avoidance treatment

As described in more detail in Chapter 2, supine-avoidance treatment was achieved using a simple battery-operated supine-alarm device (Buzzpod, Gorman ProMed Pty. Ltd).

4.2.2 Sleep and snoring assessments

PSG studies (Embletta MPR, Pleasanton, California, United States) included all standard recording cannels according to the AASM rules. For further detail see Chapter 2.

All PSG signal data were exported to EDF for sleep scoring and analysis, including snoring assessment using Compumedics software (Profusion4, Compumedics, Melbourne Australia). The primary study outcome was based on discrete snore events detected algorithmically (Profusion4, Compumedics) and categorised as soft (≥50 to <60dBA), medium (≥60 to <70 dBA) or loud (≥70 dBA) (Bignold et al., 2011) from which snoring frequency per hour of sleep was calculated based on sleep time in each stage and posture for each category of snoring and overall for all events ≥50 dBA.

Treatment adherence was determined using device recorded usage time per night during the course of each treatment. Blood pressure was measured before bedtime on PSG nights using a standard automatic digital sphygmomanometer.

4.2.3 Statistical analysis

Analysis was performed on all available data from a previously reported randomised controlled trial (RCT) of supine-avoidance therapy vs CPAP (SUPA trial). Given the count-based nature of the primary snoring frequency outcome, negative binomial regression analysis was used to test for effects of treatment condition (baseline, supine-avoidance and CPAP), including treatment order, on snoring frequency and intensity (mild, moderate and severe) in-line with recommendations for zero inflated count data (Yau et al., 2003; Alexander, 2012). All other comparisons between conditions in normally distributed continuous outcomes were examined using linear mixed effects model analysis using an auto-regressive covariance structure and subjects as a random effect, each with their own intercept, to account for the repeated measures design and expected inter-individual variability. IBM SPSS (Version 25) was used to perform all statistical analysis. All data are reported as mean ± SD or median and interquartile range as specified in the results. p-values <0.05 were considered statistically significant.

4.3 Results

The characteristics of the study population are shown in Table 4.1. A total of 10 patients dropped out of the study, 5 patients during supine-avoidance and 5 during CPAP and one further patient had missing snoring data due to technical failure (faulty

microphone) so was excluded from further analysis. Of the 66 participants in the SUPA-OSA trial, 56 completed both treatment arms, and 15 (26.7%) met the predefined supine-predominant snoring criteria of at least double the snoring frequency in supine compared to non-supine sleep. The study sample was comprised of predominantly middle-aged overweight men, as is typical in an OSA clinic sample and, by study selection criteria, exhibited at least mild through to severe supine-predominant OSA.

During PSG at baseline, patients slept on their back for almost 30% of sleep and showed supine-predominant OSA consistent with the study entry criteria applied to the pre-study diagnostic PSG. There were no significant differences in any baseline characteristic between the supine-predominant snorer sub-group compared to the remaining group.

Table 4.1 Baseline characteristics of the study population.

Parameter	Whole Group	Supine snorer	Non-supine snorer
N Total	64	15 (23.4%)	49 (76.5%)
N Females:Males (%)	23:41 (36:64%)	4:11 (27:73%)	19:30 (39:61%)
Age (yr)	52.8 ± 11.9	52.7 ± 10.9	54.6 ± 12.3
Height (cm)	171.9 ± 9.1	172.1 ± 9.2	171.9 ± 9.2
Weight (kg)	93.8 ± 21.4	87.3 ± 17.1	95.8 ± 22.3
Body mass index (kg/m²)	31.9 ± 7.8	29.7 ± 7.3	32.5 ± 7.9
Supine sleep time (%)	33.0 ± 24.6	45.4 ± 22.0	25.9 ± 22.0
Total AHI (/h)	14.2 ± 13.2	10.9 ± 10.5	13.4 ± 11.1
Supine AHI (/h)	25.4 ± 24.4	19.1 ± 14.8	24.5 ± 24.9
ESS	10.3 ± 3.9	9.9 ± 2.9	10.5 ± 4.2
AQoL – 8D	69.6 ± 13.6	74.1 ± 10.2	68.3 ± 14.3
SSS	6.1 ± 2.6	6.4 ± 2.6	6.0 ± 2.6
Systolic blood pressure (mmHg)	127.8 ± 12.9	128.4 ± 14.6	127.2 ± 13.2
Diastolic blood pressure (mmHg)	79.0 ± 9.5	81.1 ± 8.0	78.1 ± 9.9
Total snoring frequency (snores ≥50 dBA/h).	48.9 [16.7 to 188.7]	26.3 [17.0 to 106.3]	57.5 [16.8 to 190.7]

Values are mean±SD or median [interquartile range]. Apnea hypopnea index (AHI), Epworth sleepiness scale (ESS). Snore severity scale (SSS), Assessment of Quality of Life (AQoL-8D).

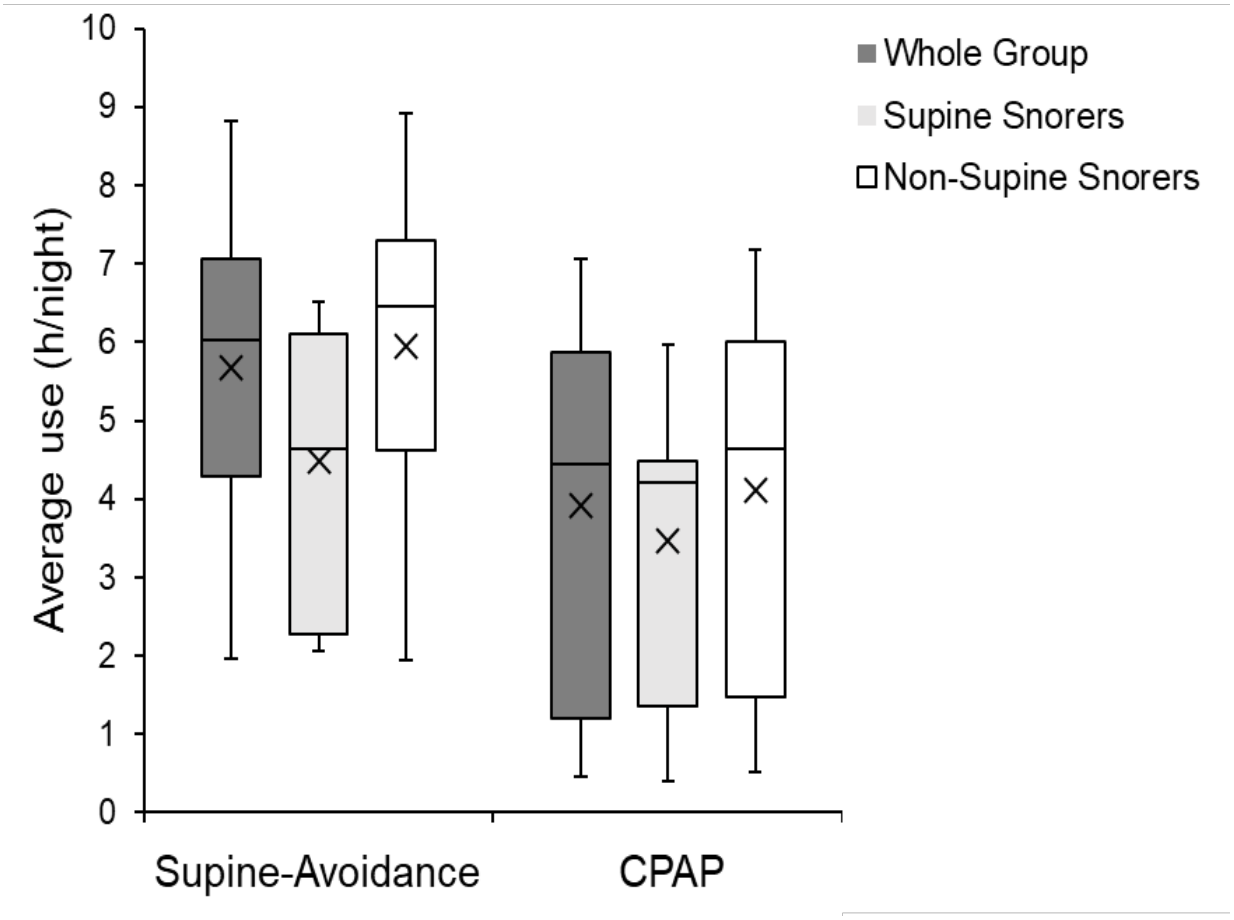
Table 4.2 shows snoring frequency in the full study sample at baseline and during repeat PSGs in the last week of each treatment. Compared to baseline, supine sleep time was significantly reduced with supine-avoidance treatment ($p<0.001$) but remained unchanged with CPAP. There were significant treatment by posture ($p<0.001$), posture by snoring intensity ($p=0.017$) and treatment by snore category ($p<0.001$) effects on snoring frequency. Over the whole night there was a reduction in snoring frequency with CPAP ($p<0.001$) but not supine-avoidance treatment ($p=0.651$). CPAP also significantly reduced snoring frequency and intensity compared to baseline and supine-avoidance therapy, in both supine and non-supine sleep.

Table 4.2 Snoring frequency (snores/hour) of snoring by treatment group and snoring intensity separated by sleep posture and whole group.

Treatment	Baseline (N=56)	Supine-avoidance (N=56)	CPAP (N=56)
Supine Sleep time (%)	30.7 [15.4 to 46.4]	0.2 [0.0 to 15.7]*^	36.7 [12.2 to 70.2]
AQoL – 8D	69.5 [64.4 to 77.8]	71.3 [61.2 to 81.6]	73.4 [64.7 to 81.0]
SSS	6.0 [3.5 to 8.0]	5.5 [3.8 to 7.0]	6.0 [4.0 to 8.0]
Soft (≥50, <60 dBA)	27.0 [7.7 to 87.8]	14.7 [3.8 to 99.2]	1.9 [0.7 to 5.7]*
Medium (≥60, <70 dBA)	6.1 [1.4 to 40.9]	4.4 [0.3 to 55.4]	0.6 [0.3 to 2.6]*
Loud (≥70 dBA)	4.5 [1.6 to 26.0]	4.6 [0.8 to 42.5]	1.2 [0.5 to 6.2]*
Total (≥50 dBA)	48.9 [16.7 to 188.7]	36.8 [6.3 to 233.7]	4.2 [2.1 to 29.5]*^
During Supine Sleep			
Soft (≥50, <60 dBA)	38.1 [10.9 to 79.2]	2.2 [0.0 to 19.1]*	3.5 [0.9 to 8.5] *
Medium (≥60, <70 dBA)	9.2 [3.4 to 33.0]	0.0 [0.0 to 13.6]	1.0 [0.0 to 3.3] *
Loud (≥70 dBA)	5.3 [1.8 to 30.8]	1.3 [0.0 to 16.1]*	1.1 [0.0 to 12.1] *
Total (≥50 dBA)	66.3 [22.9 to 186.7]	13.2 [0.7 to 67.1]*	8.5 [1.6 to 44.3] *
During Non-Supine Sleep			
Soft (≥50, <60 dBA)	19.8 [2.3 to 71.3]	13.7 [1.1 to 100.3]	1.5 [0.6 to 4.5] *
Medium (≥60, <70 dBA)	3.4 [0.6 to 31.1]	2.6 [0.3 to 54.0]	0.5 [0.0 to 1.4] *
Loud (≥70 dBA)	3.4 [0.8 to 29.8]	2.4 [0.7 to 42.5]*	1.2 [0.5 to 4.8] *
Total (≥50 dBA)	33.8 [8.7 to 190.9]	36.8 [4.6 to 231.9]	4.0 [1.8 to 14.7] *^

Values are median [interquartile range], N=56. * indicates $p<0.05$ vs baseline, ^ $p<0.05$ vs CPAP.Snore severity scale (SSS), Assessment of Quality of Life (AQoL-8D).

Figure 4.1 Average hours of use per night.



Median and inter-quartile ranges, 10-90% whiskers, X indicates group mean over 6-8 weeks of treatment with supine-avoidance compared to CPAP in the whole group (N=56) and in supine-predominant snorers (N=15) compared to the remainder (N=41) of the group.

Table 4.3 shows snoring frequency findings in the sub-group of participants with supine-predominant snoring expected to benefit most from supine-avoidance therapy. As in the full study sample this sub-group showed a reduction in supine time with supine-avoidance but not CPAP treatment. However, in contrast to the full group, these participants showed a significant reduction in total snoring frequency (treatment effect $p<0.001$) and a shift to less severe snoring with both CPAP and supine-avoidance therapy (posture effect $p<0.001$, snoring intensity $p<0.001$). However, snoring reductions were larger and more consistent with CPAP compared to supine-avoidance which, unlike CPAP ($p=0.026$), did not significantly reduce soft and medium snoring. In addition, compared to baseline, non-supine snoring was significantly reduced with CPAP ($p<0.001$) but not supine-avoidance ($p=0.299$). Treatment type had no significant effect on AQoL or SSS scores in either the whole group ($p=0.294$ and 0.327, respectively) or the supine snorer sub-group ($p=0.345$ and $p=0.896$, respectively).

Table 4.3 Snoring frequency at baseline and on supine-avoidance compared to CPAP treatment in patients with both supine-predominant OSA and supine-predominant snoring.

Treatment	Baseline (N=15)	Supine-avoidance (N=15)	CPAP (N=15)
Supine Sleep time (%)	42.0 [35.3 to 54.3]	12.2 [0.0 to 22.6]*^	32.6 [27.5 to 40.6]
AQoL – 8D	75.2 [68.4 to 81.6]	70.2 [65.2 to 85.8]	78.0 [64.2 to 82.3]
SSS	6.5 [4.0 to 7.8]	6.0 [5.0 to 7.0]	7.0 [4.0 to 7.5]
Soft (≥50, <60 dBA)	22.9 [12.8 to 71.6]	11.4 [2.1 to 15.0]	1.4 [0.7 to 3.7]*
Medium (≥60, <70 dBA)	4.5 [2.4 to 15.9]	0.9 [0.2 to 2.6]	0.3 [0.2 to 0.9]*
Loud (≥70 dBA)	2.7 [1.5 to 4.6]	0.9 [0.3 to 3.0]	2.4 [0.7 to 3.7]
Total (≥50 dBA)	26.3 [17.0 to 106.3]	14.3 [3.0 to 18.1]*	4.6 [2.6 to 8.9]*
During Supine Sleep			
Soft (≥50, <60 dBA)	48.7 [19.5 to 139.2]	7.8 [0.7 to 13.3] *	4.8 [1.8 to 5.5] *
Medium (≥60, <70 dBA)	8.5 [5.2 to 43.9]	1.5 [0.0 to 3.0] *	0.9 [0.4 to 1.1] *
Loud (≥70 dBA)	3.9 [1.8 to 7.8]	2.1 [0.3 to 13.4] *	1.8 [0.4 to 3.5] *
Total (≥50 dBA)	57.8 [33.0 to 202.5]	11.1 [1.6 to 29.4] *	9.8 [4.4 to 10.2] *
During Non-Supine Sleep			
Soft (≥50, <60 dBA)	4.2 [2.0 to 11.5]	5.9 [0.6 to 11.6]	0.7 [0.4 to 1.2]
Medium (≥60, <70 dBA)	0.9 [0.3 to 1.7]	0.5 [0.2 to 1.4]	0.3 [0.2 to 0.4]
Loud (≥70 dBA)	0.9 [0.3 to 3.0]	0.9 [0.3 to 1.3] *	2.9 [0.8 to 5.1]
Total (≥50 dBA)	8.3 [3.3 to 17.1]	11.4 [3.3 to 17.1]	4.3 [2.4 to 5.7] *

Values are median [interquartile range], N=15. * indicates $p<0.05$ vs baseline, ^ $p<0.05$ vs CPAP**. Snore severity scale (SSS), Assessment of Quality of Life (AQoL-8D).**

4.4 Discussion

This is the first study to assess supine-avoidance compared to CPAP treatment effects on objectively recorded snoring frequency and intensity in supine-predominant OSA patients, and in a sub-group of participants who also exhibited supine-predominant snoring. These are amongst the most relevant patient groups for targeting supine-avoidance device treatments. This is also one of very few studies to have examined the effects of CPAP on snoring, one of the most common symptoms and complaints for which patients seek sleep physician assessment and treatment (Krieger, 1992; Guzman et al., 2017).

By study design patients were selected on the basis of supine-predominant OSA, but with a normal non-supine AHI; the OSA patient group most likely to benefit from supine-avoidance treatment. In this group, successful supine-avoidance should theoretically normalise the AHI and OSA specific symptomatology. However, although snoring and OSA are clear signs of a collapsible airway in sleep (Gleadhill et al., 1991), the frequency of transient partial or complete airway obstruction events, measured on the basis of AHI, may show little if any relationship with the frequency and intensity of snoring. Thus, problematic snoring could potentially occur throughout much of the sleep period despite a normal AHI and potentially despite treatments designed to improve airway function. In this study, only 23% of supine-predominant OSA participants also exhibited supine-predominant snoring, with markedly reduced (by a factor of at least 2) snoring in non-supine sleep. Thus, successful supine-avoidance in individuals with supine-predominant OSA clearly does not necessarily translate into

parallel improvements in snoring. This is an important finding and supports that more specific attention to snoring measurements and outcomes is clearly warranted in patients attending sleep clinic services, particularly when patients attend clinic on the basis of bed-partner reported problem snoring. Nevertheless, snoring may be a strong sign of OSA, and given the importance of gravitational effects on the upper airway (Bilston and Gandevia, 2014), supine-avoidance is clearly worth considering as a treatment option in patients with supine-predominant OSA or with a history of supine-predominant snoring as the primary complaint.

By pneumatically splinting the upper airway to render partial and complete airway collapse less likely, CPAP might be expected to largely abolish snoring altogether. Whilst CPAP clearly did markedly reduce snoring in this patient group, some residual snoring remained, including loud snoring, particularly in supine sleep. Residual snoring potentially reflects periods of mask leak, and more challenging periods during the night such as supine and REM sleep where higher pressures could potentially achieve further reductions in snoring. CPAP was clearly superior compared to supine–avoidance at reducing snoring. However, in the sub-group of patients with supine-predominant snoring, supine-avoidance was of similar effectiveness compared to CPAP. These findings support the need for careful patient-selection and consideration of primary symptom complaints before selecting supine-avoidance versus CPAP treatment. Of further note is the finding of considerably greater treatment adherence with supine-avoidance compared to CPAP treatment, but not in the sub-group of patients with supine-predominant snoring. Whilst these findings are potentially confounded by multiple factors, including issues of statistical power given sub-group

analysis, these findings are strongly suggestive of important clinical trade-offs between patient acceptance, comfort and perceived symptom relief.

There are no widely accepted standards for assessing and defining problematic snoring. Given that classic definitions of supine-predominant OSA are based on an at least 2:1 ratio of supine vs non-supine respiratory events (Cartwright et al., 1985), and perhaps clinically more usefully include a normal AHI in non-supine sleep (Mador et al., 2005a), we used a similar 2:1 ratio basis to define supine-predominant snoring. This group could potentially benefit most from supine–avoidance, particularly when snoring is a primary complaint and given substantially poorly CPAP compared to supine-avoidance use. However, what constitutes problematic snoring remains very poorly defined and alternative definitions with a more specific focus around bed-partner complaints and what might constitute acceptable residual snoring appear to be needed. Furthermore, in supine-predominant snorers, treatment adherence was not different compared to CPAP despite significant reductions in snoring, supporting the need for further studies to clarify what problems are most concerning to patients and/or their partners, balanced against treatment choices most likely to be efficacious and to be accepted and used by patients.

Given that this study analysed snoring in patients with supine-predominant OSA, it is possible that outcomes may be different in participants with simple snoring alone without OSA. Alternative supine-avoidance device approaches might also achieve different outcomes (Ha et al., 2014; Levendowski et al., 2015; Levendowski et al., 2014), although similar outcomes appear likely as long as the selected approach

effectively achieves supine-avoidance with minimal discomfort and sleep disruption. Nevertheless, improved outcomes might be possible through smarter devices able to detect and more specifically respond to posture-dependent respiratory events or problem snoring without unnecessary alarm events during wake or quiet supine sleep without respiratory events that could potentially negatively impact patient acceptance and use.

In summary, this study showed that simple vibration alarm based supine-avoidance treatment in patients with supine-predominant OSA does not necessarily translate into systematic reductions in snoring in sleep clinic patients with supine-predominant OSA. Although CPAP clearly achieves superior OSA and snoring reduction outcomes, patient use over 6-8 weeks of treatment is substantially inferior, and some residual snoring remained even with CPAP. Yet in patients with both supine-predominant OSA and supine-predominant snoring, supine-avoidance not unexpectedly achieves relatively effective treatment outcomes comparable to CPAP, including comparable treatment usage. Thus, there appear to be important and potentially quite complex trade-offs between patient characteristics and treatment outcomes for which careful treatment selection is clearly warranted. These data support the principles of precision medicine and that in well-selected patients, supine-avoidance is a simple, viable and low-cost approach well-suited to patients with supine-predominant OSA and/or snoring. Thus, comfortable non-mask based treatments better targeted to specific abnormalities such as supine-dependant snoring could help to manage a significant fraction of the community burden of sleep breathing disorders, and help to achieve improved long-term treatment outcomes which are often poor.

CHAPTER 5. Thesis conclusions

The overall objective of this thesis was to advance new knowledge regarding a very simple but potentially clinically useful treatment option for patients with supine-predominant sleep apnea for which objective data on treatment efficacy, adherence, effectiveness and symptom relief were previously lacking. Although it is already well known that supine sleep significantly impacts OSA severity and that one of the simplest approaches to treat OSA is to avoid sleeping supine, very poor treatment acceptance and use of traditional discomfort-based supine-avoidance treatment approaches render this approach non-viable. Thus, avoiding supine sleep based on physician's recommendations, from almost a century ago, to attach a bulky object to person's back (e.g. tennis ball treatment) to discourage supine sleep is too inherently uncomfortable to achieve effective treatment outcomes for patients long-term. The introduction of more recent new generation non-discomfort based vibratory supine alarm devices show significant promise in this area and could potentially represent a clinically effective, acceptable, easier to use and lower cost treatment alternative to CPAP in appropriately selected patients. However, given much poorer treatment acceptance and use of traditional TBT therapy, the hypothesis that new generation devices can achieve non-inferior treatment outcomes compared to CPAP clearly requires sufficient high quality evidence before any new form of treatment can become a recommended treatment for any specific sub-group of patients. Thus, the systematic investigation of supine-avoidance treatment outcomes with direct comparison to usual

care with CPAP within this thesis work makes a major contribution to the field of sleep medicine.

Very few studies have addressed key questions surrounding supine-avoidance therapy via new generation vibratory devices (Chapter 1). The work presented in this thesis has provided objective evidence to help fill important knowledge gaps regarding the comparative effectiveness of a simple vibratory supine alarm device compared to current standard treatment for OSA using CPAP.

The primary focus was to investigate whether supine-avoidance therapy via a vibratory alarm device is non-inferior compared to CPAP in reducing daytime sleepiness, the primary symptom complaint of greatest clinical concern in patients with OSA (Chapter 2). Through a randomised controlled cross-over trial design it was shown that the lower bound of the reduction in sleepiness following 6-8 weeks of supine-avoidance alarm device treatment was within a conservative predetermined margin of non-inferiority (ESS difference < -1.5) when compared CPAP. Adherence to therapy was also shown to be significantly and substantially (almost 2 hours per night) greater with supine-avoidance therapy such that the estimated overall effectiveness at reducing AHI was similar with both treatments (Chapter 2).

The following chapter (Chapter 3) examined the temporal relationship between EEG and posture shifts during sleep, specifically seeking to examine the frequency and duration of posture shifts, if overnight posture shifts are initiated from wake or following brief arousal and to examine what impact supine-avoidance alarms have on post-

alarm sleep onset latency. Supine sleep time was markedly reduced supporting the efficacy of supine-avoidance alarms for discouraging supine sleep, although there were occasional “sleep through” events followed by prolonged periods of supine sleep. Around 50-60% of overnight posture shifts were initiated from prior wake and the majority of posture shifts initiated from prior sleep were preceded by a brief arousal or awakening event. Consequently, most device alarm events appeared to occur very shortly after a period of established wake or brief cortical activation potentially needed for coordinated body movements associated with posture shifts themselves. In combination with the finding of no difference in the time-course of sleep onset following alarm events, these data support that supine-alarms do not interfere with the attainment of sleep in the post-alarm period (Chapter 3). Sleep onset following posture shifts to supine that were initiated from wake were also not different compared to a baseline sleep study without treatment or another night with CPAP treatment. These findings further support that supine-avoidance alarms do not interfere with the attainment of sleep following posture shifts from either sleep or prior wake.

In the final study (Chapter 4), snoring frequency and loudness changes with CPAP compared to supine-avoidance therapy were investigated in patients with supine-predominant OSA and a subgroup of patients who also showed supine-predominant snoring. This study showed that a simple supine-avoidance alarm device is less effective than CPAP in reducing snoring frequency, and that even with CPAP there is substantial residual snoring. However, there was a significant and likely to be a clinically more useful reduction in snoring in a subgroup of patients with both supine-predominant OSA and supine-predominant snoring. These data support that simple

supine-avoidance treatments are likely to be clinically useful in appropriately selected patients, and that greater attention to snoring outcomes and their supine-dependence is likely warranted in clinical practice.

One of the main limitations of all three experimental studies presented in this thesis was the lack of an internal clock in the supine avoidance device, which logged posture at approximately 1 Hz, but with somewhat variable sampling rates and thus “clock drift” over time between devices. This made it particularly difficult to reliably and accurately synchronise posture shift data recorded by the supine-avoidance device to home PSG data from which sleep quality and respiratory disturbances were primarily assessed. Several approaches were attempted to minimise uncertainty surrounding time synchronisation between devices, including manual logging of device button-push events against accurate local time when posture devices are setup and returned. This allowed for direct assessment and adjustment for variable sampling rates between devices. Custom algorithms were also developed to minimise reliance on subjective bedtime/sleep onset reported by patients using a sleep diary, although these provided very useful confirmatory data when patients reliably used them. For the most part these methods demonstrated high levels of agreement between supine-avoidance device versus PSG recorded posture data. However, given some further inevitable uncertainty regarding correct patient placement of supine-avoidance and PSG devices in the home environment a degree of uncertainty remains regarding posture recording and classification accuracy. Further potential limitations that warrant consideration include some lost data associated with home PSG, potential interference associated

with bed-partner snoring and the inevitable open-label nature of these studies for which study blinding of inherently different interventions was not possible.

The novel data and analysis presented in this thesis make an important contribution to sleep medicine towards establishing the evidence-base needed to support direct clinical translation and uptake of new generation supine-avoidance alarm devices to treat supine-predominant OSA and potentially snoring. Nevertheless, several unanswered questions remain for which further studies remain needed, especially given prior work clearly demonstrating that assumptions regarding treatments which in theory would be expected to benefit patients may not be sufficiently acceptable or beneficial to patients for long-term use. Although other similar devices might be expected to show similar performance, the treatment effectiveness and patient acceptance and use may not necessarily be comparable between devices and deserve cautious interpretation and sufficiently favourable comparative treatment outcomes for all specific new device treatments. This work showed substantially superior supine-avoidance compared to CPAP acceptance and use over 6-8 weeks. Nevertheless, longer-term effectiveness and adherence to therapy remains unknown and will require longer-term comparative effectiveness and outcome studies.

The current generation of vibration based supine-avoidance alarm devices rely only on posture signals alone to trigger an alarm. A substantial fraction of posture shifts to the supine position occurred during established wake and potentially include nuisance alarms when the wearer is not necessarily attempting to sleep and may prefer to lay supine and awake without the need to intervene to suppress alarms. Furthermore, supine sleep does not necessarily always lead to respiratory events or snoring.

Consequently, future work appears likely to benefit from signal integration towards a new generation of “smarter” supine-avoidance alarms triggered not simply from posture shifts alone, but with additional consideration of respiratory effort, snoring and/or potentially oxygen desaturation signals. Despite a strong vibration stimulus, not all alarm events resulted in supine-avoidance. Thus, further device improvements to minimise alarms that fail to effectively discourage supine sleep may also be warranted.

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