Sleep apnoea and cardiac surgery: Screening, prevalence and postoperative outcomes

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Declaration

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Abstract

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Introduction: An excess of postoperative complications have been reported in patients with Obstructive Sleep Apnoea (OSA) following surgical procedures, however, studies reporting outcomes in patients with OSA following cardiac surgery are sparse and of limited quality. The cause of worse surgical outcomes in the OSA population is unknown but deleterious effects of opiates/opioids, common pain relieve medication following surgery have previously been proposed. There is a move towards pre-operative screening for OSA prior to surgery but the best screening methodology has not yet been established and more importantly the effect of treatment, in particular Continuous Positive Airway Pressure (CPAP), on surgical outcomes in patients with OSA is unknown.

Aim: This thesis examined the prevalence of sleep apnoea and its association with postoperative outcomes in patients undergoing major cardiac surgery. It also explored the usefulness of the STOP-Bang questionnaire, as a screening tool for OSA prior to cardiac surgery. In addition, current evidence regarding the effects of opiates/opioids and sedatives on patients with OSA was investigated and summarised in the Systematic Cochrane Review. The effect of morphine on severity of sleep apnoea in patients with moderate OSA was examined in a separate study.

Methods: The prevalence and association of sleep apnoea with postoperative outcomes in patients undergoing cardiac surgery and the usefulness of the STOP-Bang questionnaire in identifying patients at risk of OSA prior surgery was examined in a prospective, observational cohort study. The Systematic Cochrane review included randomised controlled trials examining the effects of opioids and sedatives, compared to placebo on severity of OSA in patients with established diagnosis of OSA. The effect of intravenous morphine

sulphate on the severity of sleep apnoea was examined in a prospective, paired design trial which recruited patients with moderate OSA.

Results: A high prevalence of sleep apnoea (47%) and a significant association between its severity and postoperative complications was found in 122 participants undergoing major cardiac surgery. The most significant risk factor for complications was found to be oxygen desaturations during the night reflecting the severity of sleep apnoea (OR=1.1 for each unit increase in oxygen desaturation index (ODI), 95% CI 1.02-1.17; p=0.014). It was found that the STOP-Bang scores between 0-2 would with high confidence exclude patients with at least moderate sleep apnoea prior surgery. The best diagnostic performance for diagnosis of at least moderate sleep apnoea was found at higher STOP-Bang scores of ≥6 which could identify those patients who might benefit from a sleep study before cardiac surgery. A systematic Cochrane review found that opiates/opioids, sedatives and hypnotics have no deleterious effect on the severity of OSA but most of the studies included in the review were of short duration, small size and with indiscernible methodological quality. The results of the Systematic Cochrane Review informed the development of my study, studying the effect of opiate, morphine sulphate, on patients with moderate OSA. This showed no change in Apnoea/Hypopnoea Index (AHI) where median difference (MD) was -12.95, IQR 9.45, p=0.173 but showed significant improvement in sleep apnoea indices including: obstructive apnoea index (MD -2.7, IQR 7.37, p=0.03), central apnoea index (MD – 0.35, IQR 0.83, p=0.04).However there was a fall in median nocturnal oxygen saturation.

Conclusion: This thesis reports high prevalence of sleep apnoea which was also found to be a risk factor for postoperative complications in patients undergoing major cardiac surgery. In this population, STOP-Bang score ≥6 could identify patients in need of a sleep study to identify those who may be at increased risk of postoperative complications. To date there is no strong evidence supporting deleterious effects of opioids/opiates on patients with OSA but larger studies are needed to clarify its effect.

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Glossary of Abbreviations:

AASM- American Academy of Sleep Medicine

ASA- American Society of Anaesthesiologists

AHI- Apnoea Hypopnoea Index

AU ROC- Area under Receiver Operating Curve

BMI- Body Mass Index (kg/m^2)

CABG- Coronary Artery Bypass Graft

CAD- Coronary Artery Disease

CO_2- Carbon Dioxide

CSA- Central Sleep Apnoea

CAI- Central Apnoea index

CSR- Cheyne–Stokes respiration

COPD- Chronic Obstructive Pulmonary Disease

CPAP- Continuous Positive Airway Pressure

EDS- Excessive Daytime Sleepiness

EEG- Electroencephalography

EMG- Electromyography

EOG- Electro-Oculography

EuroSCORE- European System for Cardiac Operative Risk Evaluation

HF- heart failure

kPa- Kilo Pascal

LOD- logarithm of odds

LV- Left Ventricle

LVF- Left Ventricular Function

MD- Mean Difference or Median Difference (specified in the text)

MIMOSA- Morphine in Moderate Sleep Apnoea

MSLT- Multiple Sleep Latency Test

NHS- National Health Service

NREM sleep- Non-Rapid Eye Movement

n- Number

OA- Oral Appliances

ODI- Oxygen Desaturation Index

OSA- Obstructive Sleep Apnoea

OAI- Obstructive Apnoea Index

OSAS- Obstructive Sleep Apnoea Syndrome

O_2- Oxygen

$PaCO_2$- Partial Pressure of Carbon Dioxide in Arterial Blood

PaO_2- Partial Pressure of Oxygen in Arterial Blood

PSG- Polysomnography

rPSG- Respiratory Polygraphy

p- Probability

RCT- Randomised Controlled Trial

REM sleep- Rapid Eye Movement

RERA's- Respiratory Effort Related Arousals

SE- Standard Error

SpO_2- Pulse Oximeter Oxygen Saturation

RSSC- Respiratory Support and Sleep Centre

>- Greater than

<- Less than

%- Percentage

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Overview

This thesis examines OSA in a very specific population of surgical patients presenting for major cardiac surgery. In particular, it examines the prevalence of OSA and the risks that OSA poses on surgical outcomes in these patients. It also looks at safety concerns associated with administration of intravenous opioid analgesia not only after surgery, but also on the severity of sleep apnoea when given to patients with previously diagnosed OSA. The body of work consists of a prospective observational cohort study looking at the association of OSA, expressed as ODI from nocturnal oximetry with postoperative outcomes, as well as prospective paired design trial looking at the effect of acute administration of morphine sulphate on the severity of OSA in patients with moderate OSA. One Chapter is dedicated to secondary research in the form of a Systematic Cochrane review examining extant evidence of the effect of opioids and sedatives on patients with known OSA.

OSA is common disease with complex and poorly understood pathophysiology. **Chapter 1** sumarises current evidence regarding the pathophysiology, epidemiology, diagnosis and treatment of OSA. More particularly, it appraises current knowledge of OSA in people undergoing surgery, including epidemiology, screening, the effect of OSA on surgical outcomes and the evidence for CPAP treatment affecting postoperative outcomes.

The first experimental study, a prospective observational cohort study (**S**leep **A**pnoea in **C**ardiac **S**urgery), is described in **Chapter 2 and Chapter 3** and investigates the prevalence of OSA in patients undergoing coronary revascularisation surgery. The null hypothesis tested was that there is no association between sleep apnoea and Intensive Care Unit lengths of stay, as an tangible impact of health care utilisation. The secondary outcomes included exploring for evidence of any association between OSA and postoperative complications in the Intensive Care Unit. As part of this study I have also explored the utility of the STOP-Bang questionnaire, a simple screening tool for sleep

apnoea, prior to surgery, and also looked for any association between the STOP-Bang scores and postoperative outcomes in the cardiac surgical population.

The results of the SACS study informed the development of secondary research examining the effect of opioids and sedatives on the severity of OSA in patients with a known diagnosis of OSA. The results are summarised in the Cochrane Systematic review reported as a precis in **Chapter 4.** Based on the result of this review, in particular the lack of evidence regarding any effect of opiates on patients with OSA I developed a prospective, paired design study examining the effect of intravenous morphine sulphate on the severity of OSA in patients with known diagnosis of moderate OSA (**M**orphine **I**n **M**oderate **OSA)**. This study along with its outcomes is described in **Chapter 5**.

Chapter 6 summarises findings of the thesis, considers the limitations of the research methodology, its usefulness and the possible impact of my results on clinical practice. Future directions of the research are also discussed.

Experimental protocols,research approval and ethics

All protocols involving new data acquisition in subjects received Papworth Hospital NHS Foundation Trust research approval and favourable ethical opinions from the local ethics committee with details in Appendix 3. Papworth Hospital NHS Foundation Trust sponsored the experimental protocols and funded the trials through the pump priming funds. Trials were conducted in keeping with recommendations for good clinical practice including the declaration of Helsinki. Written consent was obtained from all participants. All protocols were designed, ethical approval gained and funding secured by the author of this thesis.

Ethical approval for the prospective observational cohort study (SACS) was granted by The National Research Ethics Service East Midlands Northampton Proportionate Review Sub-committee (12/WM/0433). The local research committee, NRES Committee East of England, Cambridgeshire and Hertfordshire, gave ethical approval for the prospective, paired design study examining the effect of intravenous morphine sulphate on the severity of

OSA in patients with a known diagnosis of moderate OSA (MIMOSA) with further information

available in Appendix 3.

Chapter 1

Obstructive Sleep Apnoea in the surgical population and its implications for the post-operative care

Introduction

OSA, intermittent collapse of the upper airway in sleep, is very common in the adult population (Young et al. 1993; Duran et al. 2001) and it has been estimated that 80% of sufferers are undiagnosed (Young et al. 1997). It is inevitable that patients referred for surgery will include people with unrecognised and untreated OSA. There are conflicting data for the impact of undiagnosed OSA on the outcome of surgical procedures but at least some results suggest an association with poorer outcomes (Gupta et al. 2001; Hwang et al. 2008; Liao et al. 2009). Where an excess of postoperative complications has been associated with OSA it has been proposed that differences in sensitivity to the effects of opiates may be an explanation but the exact mechanism remains unknown (Catley et al. 1985; Esclamado et al. 1989). There is a move towards pre-operative screening for OSA but the best screening methodology has not yet been established and currently the evidence does not support routine preoperative screening for OSA (Vasu et al. 2012; Lockhart et al. 2013) and perhaps more importantly there is no evidence that screening for OSA pre-operatively affects surgical outcomes. OSA and coronary artery disease share some of the same risk factors (Mooe et al. 1996) and a high incidence of undiagnosed OSA and other forms of sleep disordered breathing might be predicted in patients undergoing coronary artery bypass grafting (CABG). This thesis aims to inform our understanding of any excess risk associated with undiagnosed OSA in patients undergoing major cardiac surgery and will explore the safety of morphine, a common post-operative analgesia, in patients with OSA.

This Chapter reviews the evidence base for OSA including the epidemiology, pathophysiology, investigation as well as treatment of OSA. In addition, it will also summarise our knowledge of OSA in surgical populations, including the epidemiology of

OSA in this subset of patients and current evidence regarding the value of pre-operative screening, peri-operative care and postoperative outcomes in patients with OSA.

<u>Historical perspective of Obstructive Sleep Apnoea</u>

Although humans spend one third of their life sleeping the full biological effects of sleep remain unknown. The perception of sleep has varied through history and many authors have portrayed sleep in their work. For example Macbeth in William Shakespeare's play described sleep as "chief nourisher in life's feast" (McNicholas et al. 2010). Some authors, however, including Tennyson, perceived sleep with fear and described it as "death's twin brother"(McNicholas et al. 2010). This idea resonates with Greek mythology where Hypnos, personification of sleep, was twin brother of Thanatos, personification of death, and images of Hypnos were often shown close to the images of death. In the last two decades sleep has attracted large interest and the field of sleep medicine has rapidly expanded.

OSA is one of the most prevalent sleep disorders and has, in the past, been described in classical literature including "The Tale of the Jack and the Beanstalk", where the giant slept soundly and was famous for his loud snoring and most likely suffered with OSA syndrome. Charles Dickens in the "Posthumous Papers of the Pickwick Club" described the cardinal feature of OSA in a fat boy, Joe who snored heavily as if "the roaring of cannon were his ordinary lullaby".

A closer description of the breathing pattern of patients with OSA was reported in paper by Broadbent (Broadbent 1877) in the late nineteen century but OSA was described as a clinical entity only in the late 1950's. In 1965 Gastaut et al. noted and described frequent apnoeas on polysomnographic assessment of obese, sleepy patients (Gastaut et al. 1965). The pathophysiology and clinical features of OSA were investigated and defined in the following decade. Early research focused on clinical and pathophysiological traits of OSA whereas the progress in understanding the OSA has lately been concentrating more on genetic and molecular aspects of OSA, association between OSA and other comorbid

conditions, including cardiovascular and metabolic, as well as on the effect of treatment on progress and prognosis of the conditions associated with OSA.

Understanding the pathophysiology of OSA has helped to develop the treatments, and this along with progress in development of appropriate diagnostic tools has informed the current practice of sleep medicine. Treatment of OSA remains mainly mechanistic and concentrates on bypassing or reducing upper airway obstruction. The first treatment used to bypass the obstruction was placement of a tracheostomy tube, reported in 1970 (Lugaresi et al. 1970). It was not until the advent of CPAP, delivered non-invasively via a mask, developed by Sullivan in 1981 (Sullivan et al. 1981), that we experienced the revolution in management of sleep disordered breathing and even today CPAP represents the cornerstone of treatment of patients with OSA.

Although our understanding of OSA has advanced considerably over the last few decades there is still much which remains unknown. This maintains research interest in OSA, comprising areas such as the basic mechanisms of OSA and its consequences, including after surgical procedures, genetic factors contributing to development of OSA as well as development of new innovative modalities of treatment.

Pathophysiology of OSA

Sleep Disordered Breathing is a term used to cover a range of breathing events, encountered during sleep and includes OSA, central sleep apnoea (CSA), Cheyne–Stokes respiration (CSR) and respiratory effort related arousals (RERA's). OSA is the most common form of SDB and when coupled with symptoms of excessive daytime sleepiness (EDS) it is described as OSA syndrome (OSAS). OSA is caused by recurrent episodes of partial or complete upper airway collapse with ongoing ventilatory effort during sleep, leading to intermittent reduction (hypopnoea) or cessation (apnoea) of air flow through the upper airway. These cause transient hypoxia and hypercapnia and intermittent activation of sympathetic drive. These events are usually terminated by the patient's arousal which

restores the airway patency and normalises the partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$).   Occasional nocturnal obstructive apnoea and hypopnoea are normal but when the frequency of these episodes increases to ≥5 per hour of sleep they can be associated with symptoms of excessive daytime sleepiness and un-refreshing sleep (Gottlieb et al. 1999) as well as adverse health outcomes including cardiovascular disease (Haas et al. 2005; Kuniyoshi et al. 2008), type 2 diabetes mellitus (Reichmuth et al. 2005) an increased risk of road traffic accidents (George et al. 1987; Findley et al. 1988; Wu et al. 1996) and mortality (Punjabi et al. 2009).

The pathophysiology of OSA is complex and not fully understood. OSA is a heterogeneous disease and underlying pathophysiological mechanisms vary between individuals creating different phenotypes of OSA. Various pathophysiological mechanisms for the development of OSA have been proposed and include contributions from: upper airway anatomy, upper airway dilator muscles activity, ability to wake during an apnoeic episode (arousal threshold), ventilatory control stability (loop gain) and lung volumes.

Upper airway anatomy

The human upper airway (UA) is a complex structure involved in various functions including breathing, swallowing and speech. It consists of four anatomical segments namely the nasopharynx extending from nares to hard palate, velopharynx ranging from the margin of the hard palate to the margin of the soft palate, oropharynx from the soft palate to the edge of the epiglottis and hypopharynx from epiglottis to vocal cords. Human pharynx contains of more than 20 muscles creating three main functional groups including muscles controlling hyoid bone (geniohyoid, sternohyoid muscles), muscles of the tongue (genioglossus, the major upper airway dilator muscle) and palatal muscles (palatopharyngeus, tensor palatine, levator palatine muscles).

The majority of the UA is a collapsible structure extending from soft palate to the larynx and its patency and stability depend on the relationship between collapsing and expanding forces. The forces supporting UA patency depend on the size and the shape of the UA as well as the dilator muscle activity. Forces promoting UA collapse consist of negative intraluminal pressure created during the inspiration and the mass load placed on the UA by intraluminal surface forces and external soft tissues (Shneerson 2005).

In patients with OSA, upper airway collapse and reinstatement of patency during sleep result from complex interactions (Berry et al. 1996; Mezzanotte et al. 1996; Wellman et al. 2004; Eckert et al. 2007). Generally, a narrow upper airway is more susceptible to collapse, compared to a larger one. Studies supporting this hypothesis, assessing cross-sectional area of upper airway during wakefulness using computed tomography and magnetic resonance showed that, compared to normal subjects, patients with OSA have a smaller UA, as well as altered alignment of the soft tissue adjacent to the UA, leading to anatomical compromise and increased propensity to UA collapse (Schwab et al. 1995). Increased propensity to UA collapse was confirmed by Isono et al. who observed more collapsible airway in patients with OSA undergoing general anaesthesia and muscle paralysis as evidenced by increased closing pressure (pressure inside the airway at which the airway collapses as described in the next paragraph) in patients with OSA (Isono et al. 1997).

The severity of OSA, duration of apnoeas and degree of oxygen desaturations have been negatively affected by supine compared to lateral recumbent position (Oksenberg et al. 2000). In some, this leads to positional OSA, defined as supine apnoea-hypopnoea index at least double of that in lateral position. One study reported prevalence of positional OSA at 50% of mild, 19% of moderate and 6.5% of severe OSA (Mador et al. 2005). This positional variability in OSA has been attributed to the effect of gravity on the shape of the UA, where the shape of UA changes from transverse elliptical in supine to circular in lateral position

potentially improving UA patency and reducing UA collapsibility in lateral position in patients with OSA (Gastaut 1965).

As already elaborated, the oropharynx is a collapsible structure and the relationship between pressure and flow has been studied using a Starling-resistor model (Smith et al. 1988), where the collapsible segment in the oropharynx has a critical closing pressure (Pcrit) defined as the pressure inside the airway at which the airway collapses, Pus is the atmospheric pressure at the nares and Pds is the tracheal pressure. When Pcrit exceeds Pus and Pds upper airway collapse follows. When Pcrit exceeds Pds but is less than Pus there is a flow limitation and when Pus and Pds are higher than Pcrit there is a free flow thorough the UA. Patients with normal breathing usually have Pcrit of $> -10 cmH_2O$, snorers without apnoeas a Pcrit from -10 to -5 cmH_2O and patients with obstructive hypopnoeas have Pcrit from -5 to 0 cmH_2O, whereas patients with obstructive apnoea had Pcrit $>0cmH_2O$ (Schwartz et al. 1988; Smith et al. 1988; Gleadhill et al. 1991). Patients with obesity have more collapsible airways and weight loss has been shown to be associated with reduction in Pcrit and improvement in OSA severity, supporting the importance of weight loss in treatment of obese OSA patients (Schwartz et al. 1991).

It has also been shown that UA anatomy and the severity of OSA can be affected by UA oedema reported to lead to narrowing of the UA lumen. Studies in healthy subjects have shown that displacement of fluid from legs to upper body leads to an increase in neck circumference (Chiu et al. 2006) and upper airway resistance and collapsibility (Su et al. 2008). These changes correlate with the severity of OSA, defined as apnoea-apopnea index in OSA patients (Redolfi et al. 2009). In another study diuresis of patients with severe OSA and diastolic heart failure led to a significant improvement in OSA, leading same support to the hypothesis of upper airway oedema influencing severity of OSA and diuresis as possible treatment option of OSA in patients who are fluid overloaded (Bucca et al. 2007).

Upper airway dilator muscles

It appears that during wakefulness patients with OSA compensate for reduction in UA diameter by increased UA dilator muscle activity, however, this compensatory mechanism is lost at sleep onset resulting in UA compromise. During wakefulness, the electromyogram (EMG) activity of genioglossus muscle, one of the most studied upper airway dilator muscles, is increased in patients with OSA, compared to healthy controls (Mezzanotte et al. 1992) but reduction in EMG activity occurs at sleep onset and the reduction is larger in OSA patients, when compared to healthy controls. Healthy individuals may experience breathing instability at sleep onset but patients with OSA are particularly vulnerable and develop an increased frequency of apnoeas and hypopnoeas during the transition from wakefulness to sleep (Trinder et al. 1992). As obstructive breathing events are terminated by arousals it is difficult for patients with OSA to enter deeper restorative slow wave sleep during which the upper airway dilator muscle activity is increased and it has been observed that the severity of OSA in this sleep stage improves (Basner et al. 1991).

One of the major components promoting UA patency is locally mediated negative pressure reflex based on the mechanoreceptive response to surges of negative intraluminal UA pressure (Horner et al. 1991). There are both excitatory and inhibitory components to this reflex, where the excitatory component remains stable during the sleep but the inhibitory component is more pronounced and may be responsible for reduced negative pressure responsiveness during sleep in healthy subjects (Eckert et al. 2007). This reflex has been less studied in OSA patients.

Another mechanism proposed as a possible cause for an impaired response of UA dilator muscles to negative pharyngeal pressure in patients with OSA is UA sensory neuropathy due to the mechanical trauma of snoring and hypoxia related oxidative stress causing inflammation. Pathological changes consistent with a neuropathic process and muscle denervation have been found in UA muscle specimens of OSA patients (Bergeron et

al. 2005; Svanborg 2005). The degree of sensory neuropathy correlates with OSA severity (Nguyen et al. 2005) and the duration of OSA and may lead to worsening OSA severity. It has also been shown that cortical evoked potentials reflecting the sensory processing of respiratory afferent information are impaired in patients with OSA during sleep but not during wakefulness (Gora et al. 2002). Further research in this area is needed to confirm the role of UA sensory impairment in the pathophysiology of OSA as well as its role in modulating disease severity.

Lung volumes

Studies in animals and humans suggest that lung volumes may play a role in the pathophysiology of OSA. A reduction in lung volume has been associated with increased UA resistance (Hoffstein et al. 1984). The mechanism is not well understood but one explanation in animal models is loss of caudal traction on the UA (Kairaitis et al. 2007). Further studies are necessary to inform the exact mechanism on pathophysiology of OSA.

Arousal from sleep

Arousal from sleep at the termination of an apnoea or hypopnoea is a protective mechanism to restore UA patency during sleep. Arousal from sleep at the end of the breathing event is triggered by negative pleural pressure, generated by respiratory effort (Vincken et al. 1987) and leads to increased dilator muscle activity which restores airflow patency and normalised blood gas tensions (Jordan et al. 2003). Patients with OSA seem to have impaired arousal responses to breathing events compared to healthy subjects in that they either have a higher arousal threshold (more difficult to wake up) or require a higher negative pressure to trigger the arousal (Berry et al. 1996). It has been shown that CPAP in OSA patients lowers the arousal threshold which would suggest that other mechanisms associated with OSA such as hypoxia, hypercapnia or frequent arousals may be

responsible for impaired arousal rather than an inherent defect in arousal threshold (Haba-Rubio et al. 2015).

It was believed that arousal from sleep is necessary for restoring upper airway patency but in the study by Younes et al. 22 % of patients with OSA exposed to transient reduction in CPAP pressure during sleep had increase in UA flow before the arousal occurred and 17% had the flow restored without an arousal (Younes 2004). To understand the mechanism of restoring UA flow without an arousal Jordan et al. found that up to five minutes of transient CPAP pressure reduction during sleep leads to an increase in genioglossus muscle activity in both OSA as well as healthy individuals but patients with OSA were less able to restore flow without cortical arousal (Jordan et al. 2007). These findings may suggest that in a certain cohort of patients, with low arousal threshold, manipulating an arousal threshold may be beneficial, and would allow time to recruit UA dilator muscle and restore UA patency. This may also allow patients to consolidate sleep by entering deep, slow wave sleep during which the severity of OSA improves due to increased dilator muscle activity.

Manipulation of arousal threshold may open new therapeutic strategies for a phenotype of patients with low arousal threshold but caution has to be exercised as this approach may be deleterious for patients with severe sleep disordered breathing and high arousal threshold as these individuals may experience prolong duration of breathing events and worsening in blood gas tension (Dyken et al. 2004). Manipulation of arousal threshold by hypnotics has been explored by Eckert et al. who showed that eszopiclone increases the arousal threshold and lowers the AHI in obstructive sleep apnoea patients that do not have marked overnight hypoxaemia (Eckert et al. 2011). More recently the effects of zopiclone, temazepam and zolpidem were compared in randomised, double blind, placebo controlled trial (Carberry et al. 2017). The arousal threshold increased with zolpidem and zopiclone compared to placebo but not with temazepam. These drugs did not reduce upper

airway muscle activity or alter airway collapsibility during sleep but rather, muscle activity increased during airway narrowing with zolpidem (Carberry et al. 2017). These results suggest that contrary to common beliefs hypnotics do not reduce UA dilator muscle activity and may bring about new possibilities of treatment for a particular phenotype of OSA patients. Larger and longer duration studies are needed to reproduce and confirm these findings.

Ventilatory control stability

Although, an arousal from sleep can be beneficial in restoring UA patency, optimising ventilation and normalising arterial blood gas tension, it can also destabilise ventilatory control and exacerbate sleep apnoea severity (Eckert et al. 2007). Ventilatory control refers to a system that assures stability of breathing and responsiveness to a disruption in breathing. Ventilatory control is mediated by feedback loops and loop gain (Khoo et al. 1982), which in turn consist of controller gain and plant gain. Controller gain refers to ventilatory response to hypoxia and hypercapnia and plant gain is the ability of ventilation to excrete carbon dioxide (CO_2).

High loop gain refers to a system that overreacts to a respiratory stimulus and low loop gain to a system with a blunted response and under-reacts to the respiratory stimulus. Studies measuring loop gain such as proportional assist ventilation (PAV) techniques have demonstrated that some patients with OSA have elevated loop gain causing ventilatory instability which contributes to worsening of SDB (Wellman et al. 2004). An elevated loop gain may work through an elevated response to arousal, leading to reduction of $PaCO_2$ below the apnoeic threshold, causing obstructive or central apnoea, depending on the predominant mechanics of UA at the time.

Genetic factors

The different pathophysiological mechanisms for the development of OSA make OSA a heterogeneous disease and the complex phenotypes of OSA render establishment of a single genetic link for OSA most unlikely.

Different genetic approaches have been used to seek genetic predisposition to OSA, including linkage studies, case-control studies and genome wide association studies. Linkage studies are used for single gene disorders and usually use extended families. In these studies, a genetic marker may be identified, but this marker is not necessarily linked to phenotypic effect. Complex statistical methods expressed as a logarithm of odds (LOD) score is used to describe the association between genetic locus and phenotypic marker. A LOD score of 3 indicates significant association, where the genetic and phenotypic marker have a chance of <1/1000 not to be linked. Scores of <2 are not suggestive of linkage (Lander et al. 1995). There are 3 large genome wide association studies including European-American pedigrees and African-American pedigrees, where OSA was phenotyped on AHI alone, diagnosed on multichannel home polyghraphy. In all of these studies when AHI was adjusted for BMI there was no significant association between genetic markers and OSA (Palmer et al. 2003; Palmer et al. 2004).

Candidate gene association studies identify a gene of interest which is then sequenced in cases with disease in question and unrelated, disease free controls. In these studies common and variant genes can be detected. Several studies have been published with various genes of interest but a meta-analysis of 8 studies examining the apolipoprotein E gene epsilon 4 (APOE4), considered to be a precursor of atherosclerosis, reported ods ratio (OR) of 1.13 (95%CI 0.86-1.47) with significant heterogeneity in included studies and concluded that there was no significant association between this gene and OSA (Thakre et al. 2009). Studies examining various other genes have not been replicated, not properly controlled and variable phenotypes of OSA were used.

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There is some evidence for a heritable component to OSA taking into account familial predisposition to obesity (Pillar et al. 1995; Redline et al. 1995) but anatomic traits including UA soft tissue size, ventilator control and response to UA resistance during the sleep also appear to share a genetic predisposition (Pillar et al. 1997; Bhama et al. 2006). It appears that genetic traits may also be responsible for OSA in different racial groups such as Asians who have shorter maxillae and mandibles and lower BMI compared to Caucasians for a given degree of OSA severity (Redline et al. 1997) and African-Americans who have an increase in soft tissue load on the UA compared to Caucasians (Cakirer et al. 2001). It is likely that further meaningful genotyping of OSA will depend on more accurate phenotyping of OSA cohorts.

The consequences of OSA are in part mediated by chronic intermittent hypoxia, sympathetic activation, oxidative stress and inflammation. Assessing molecular signatures of the disease described as "pattern of gene or protein expression in cells or tissue related to the disease state" could assist with diagnosis and advice regarding the prognosis of OSA related comorbidities or development of new therapies (Arnardottir et al. 2009) and studies assessing gene expression in blood cells during sleep may provide important information regarding gene expression during the sleep and molecules affected by OSA. In this regard, there is one published study in adult OSA involving only 4 patients and 4 controls showing overnight upregulation of expression of oxidative stress responsive genes such as the antioxidant enzyme superoxidase dismutase 2 (SOD2) and over-regulation of superperoxidase desmutase 1 (SOD1), compared to controls (Hoffmann et al. 2007).

The main issue in identifying molecular signatures and biomarkers of OSA lies in separating the consequence of OSA and obesity which is an independent risk factors for many comorbidities associated with OSA and seems to activate the same molecular pathways (Arnardottir et al. 2009). One proposed strategy is to evaluate relevant molecular pathways during sleep and at the transition from wake to sleep as such changes may, at

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least partly, be related to chronic hypoxia and sympathetic surges occurring in OSA patients during the sleep.

Another expanding area looking at the molecular signature of OSA is proteomics providing information on true molecular phenotype of a disease as knowledge of gene variants and gene expression may not translate into actual changes in proteins. Proteomics is more complicated than genomics and the technology is not yet as developed as microarrays, the platform that allows automated analysis of high volume DNA at once. Two studies have been published assessing proteomic pattern in children (Krishna et al. 2006; Shah et al. 2006). One study reported increased expression of three proteins in children with OSA compared to simple snorers. One of the proteins was osteocalcin a precursor of gamma-carboxyglutamic acid containing protein, used as a biomarker as growth retardation (Shah et al. 2006). This exciting strategy may provide important details of the molecular signature of OSA and may lead to new diagnostic techniques using OSA biomarkers.

Risk factors for OSA

Various risk factors have been proposed in the development of OSA including: the male sex, age and obesity (Eckert et al. 2008).

Obesity

The link of obesity to OSA is supported by finding that modest reduction in weight results in improvement of OSA severity (Peppard et al. 2000). Proposed physiological mechanisms for the effect of obesity on the development of OSA include: deposition of fat around pharyngeal airways, reduction of functional residual capacity as well as low lung volumes leading to decreased oxygen reservoir and ventilatory control instability (Eckert et al. 2008). In one longitudinal study of 690 subjects assessed at 4 years intervals, Peppard et al. reported that 10% weight gain led to 32% increase in AHI (95% CI 20-45%) and a 6 folds increase in odds of developing moderate to severe OSA (AHI>15 events/hr) but 10 % weight

loss led to 26%(95% CI 18-34%) reduction of AHI (Peppard et al. 2000). This stresses the importance of implementation of weight reduction programmes in the management of OSA but also in the prevention of OSA. Although the relation to obesity has been demonstrated from these studies, it is not a sole risk factor in development of OSA as 1/3 of OSA patients are not obese and not all obese patients with large neck circumference suffer with OSA (Lecube et al. 2010).

Sex

Studies have confirmed that OSA is more common in males compared to females with male-female ration of 2:1 and a similar finding has been observed in simple snoring. The reason for male predominance is not clear but some mechanisms have been proposed. A longer pharyngeal airway in males and increased fat deposition around the UA could increase pharyngeal collapsibility (Whittle et al. 1999; Malhotra et al. 2002). In addition, hormonal differences between sexes, especially of testosterone, may be implicated, as the prevalence of OSA is higher in post-menopausal females. The role of hormones is not fully understood. Despite higher prevalence of OSA in postmenopausal women, it was shown that in the elderly population over 65 years, the same ratio of male to female distribution persists (Hader et al. 2005) and therefore clear mechanism remains unknown and more research is needed to provide further understanding.

Age

Most studies examining the prevalence of OSA have included populations up to 60 years old but studies which included older patients show continuous increase in prevalence which seems to plateau after 65 years (Young et al. 2002). Proposed mechanisms for developing OSA in the elderly include: increased pharyngeal fat deposition and reduced genioglossus negative pressure reflex with aging (Eckert et al. 2008). Ancoli-Israel et al. studied a sample of 427 elderly men and women, 65-95 years old, and found OSA (AHI>10)

in 70% of men and 56% of women, which is much higher than the prevalence found in middle age (Ancoli-Israel et al. 1991). Similar findings were reported in Sleep Heart Health study, where OSA (AHI>15) was 1.7 fold higher in older patients (60-99), compared to younger participants (40-60) (Young et al. 2002). In both studies the prevalence plateaus after the age of 65 years which may imply either increased mortality rate in people with OSA in this age group or remission of OSA with aging.

There has been a suggestion that OSA represents a different entity in the older age group as several studies have reported little or no association of OSA with sleepiness, hypertension or cognitive function impairment compared to patients in the middle age (Young et al. 2002). In one study, OSA syndrome defined as AHI≥10/hr and associated hypertension or sleepiness, was reported in 1.75% in those over 65 years and 4.7% in 45-64 years adults (Bixler et al. 2001). In an 18 years follow up study of older participants there was weak association of BMI and AHI (Ancoli-Israel et al. 2001) and similarly, the association of obesity and AHI was weaker in older compared to younger participants in the Sleep Heart Health study (Young et al. 2002). It has also been noted that self-reported snoring decreases past middle age (Bliwise et al. 1988; Wetter et al. 1994; Bixler et al. 1998) with possible explanations being that their bed partners are no longer alive to witness snoring in the elderly or they may suffer with central sleep apnoea not associated with snoring, reported to occur at 5 % in over 65 years old (Bixler et al. 1998). Although OSA syndrome may not be as prevalent as in middle aged patients those who are symptomatic benefit from CPAP similarly to younger adults (Launois et al. 2007; McMillan et al. 2014). With increasing longevity further studies are needed to investigate the nature and consequences of OSA in the elderly to inform the appropriate clinical management of the older patients.

Smoking and alcohol

Several studies report an association between cigarette smoking and snoring or OSA with one possible underlying mechanisms being upper airway inflammation. In a Swedish ten year longitudinal study smoking was a predictor of snoring in males below 60 years but not older males (Lindberg et al. 1998). Another study found a dose response relationship between smoking and AHI and current smokers (but not ex-smokers) were three times more likely to have OSA than never smokers [95% CI 1.4-6.4] (Wetter et al. 1994). However, the role of smoking as a risk factor for OSA is not clear as the Sleep Heart Health Study reported an inverse association of smoking and OSA in that that smokers less frequently had sleep apnoea compared to non-smokers (Newman et al. 2001). As such, although a plausible hypothesis exists for the effect of smoking on the development of OSA the role of smoking as a risk factor for OSA remains unknown and needs to be established.

Alcohol reduces UA dilator muscle activity leading to hypotonia and predisposition to UA collapse and therefore could potentially worsen OSA severity (Krol et al. 1984). Studies examining alcohol effect looked at acute administration of alcohol in relation to respiratory disturbance index and epidemiological studies have looked at the correlation between self-reported alcohol intake and OSA. Most, but not all studies where alcohol was administered to healthy subjects or patients with OSA before bedtime showed an increase in AHI (apnoea/hypopnoea index) and duration of apnoeas during the night (Young et al. 2002). Two CPAP titration studies examining the pressure needed to abolish apnoeas and hyponoeas during the night in patients who ingested a moderate amount of alcohol before bed time showed conflicting results (Mitler et al. 1988; Teschler et al. 1996). The association between chronic alcohol consumption and OSA severity was examined in longitudinal studies and again showed contradicting outcomes (Young et al. 2002).

Epidemiology of OSA

Understanding the disease prevalence, proportion of population with the condition in question, is paramount in planning health care needs and allocating healthcare resources. When comparing prevalence of disease by demographic factors, important hints regarding etiological factors or populations at risk may arise. It has to be remembered, however, that estimates of prevalence are vulnerable to many methodological concerns including: sleep diagnostics used, definition of OSA (which has changed over the years), sample size, participation bias and loss to follow up. For example, choosing a sample population from a sleep clinic with referrals directly from cardiac clinics would likely overestimate the association of OSA and cardiovascular disease. It is also important to note that even when recognised diagnostic methods such as polysomnography or respiratory polygraphy are used it is difficult to distinguish between central and obstructive hypopnoea. In addition, there is a lack of standardisation in quantifying airflow where methods such thermistry, and nasal cannula pressure transducer provide different levels of sensitivity to airflow.

Some reviews have addressed this issue by adjusting for differences in definition and comparing the results of studies with similar study designs. One study that analysed 12 studies of OSA prevalence in Western populations estimated that 1-5% of adults suffer OSAS (Davies et al. 1996). Lindberg and Gislason estimated the prevalence of OSA from nine studies using a two- stage sampling procedure (Lindberg et al. 2000). In this method sleep studies are undertaken on a sample of a population drawn from large surveys using questionnaires of symptoms such snoring to identify patients at risk for OSA and therefore these studies are vulnerable to selection bias and may overestimate the prevalence of OSA. The prevalence of OSAS in the studies ranged from 0.3% to 5%. Based on these results, it appears that up to 5% of Western, middle aged population suffers with OSAS and may be candidates for treatment with CPAP.

OSA without symptoms appears to be much more prevalent, and is not included in these estimates. More importantly, its clinical and public health significance remain

unknown. Taking into account large population based studies using in-laboratory polysomnography with a similar definition of OSA, and using cohorts from Wisconsin, Pennsylvania and Spain, prevalence of mild OSA in men ranges between 17-26% and women 9-28%, whereas moderate OSA has been described in 9-14% of men and 2-7% of women (Young et al. 1993; Bixler et al. 1998; Bixler et al. 2001; Duran et al. 2001). As reported by Peppard *et al.* this prevalence has risen in the last two decades (1993-2013) with relative increases of between 14% and 55%, depending on the subgroup, but moderate to severe OSA (AHI≥15) was present in 34% in men and 17 % in women aged 30-70 years (Peppard et al. 2013). The latest population based study (HypnoLaus study) in Switzerland showed that at least mild OSA (apnoea-hypopnoea index ≥5) was present in 84% of men and 61% of women and at least moderate disease (apnoea-hypopnoea index ≥15) was present in 50% of men and 23 % of women (Heinzer et al. 2015). The strength of this cohort is that the population was selected from the general population and not based on the result of sleep questionnaires, minimising selection bias. The high prevalence in this study, compared to earlier work, may be due to the more sensitive polysomnographic techniques developed over the years and a change in apnoea-hypopnoea definition. The 2012 American Academy of Sleep Medicine (AASM) guidelines defined hypopnoeas as a ⩾30% decrease in nasal flow with ⩾3% desaturation of arterial oxygen measured by pulse oximetry or electroencephalography (EEG) arousal (Berry et al. 2012). Duce et al. looked at the impact of applying this new definition on OSA prevalence in a retrospective set of 112 polysomnography (PSG) studies, where he compared prevalence with more stringent AASM 2007 criteria and not surprisingly found that the more liberal AASM 2012 criteria resulted in a markedly higher prevalence of OSA (Duce et al. 2015).

Given the fact that mechanisms by which OSA affect health consequences are still poorly understood, the most meaningful definition of OSA is unknown and the AHI does not distinguish between different aspects of OSA such as hypoxia or sleep fragmentation which may have distinctive consequences for the patient (Thomas et al. 2014). Although a higher

prevalence of OSA was reported in the HypnoLaus study, the prevalence of OSAS in this study seems to be in line with previous reports ranging from 0.07% to around 6.2 % across the severity of OSA spectrum from severe to mild OSA. Moreover, after variable adjustments, this study also reported that more severe OSA, with an AHI of over 20·6 events/hr, was independently associated with the presence of hypertension (OR1·60, 95% CI 1·14–2·26; p=0·0292), diabetes (OR 2·00, 95%CI1·05–3·99; p=0·0467), metabolic syndrome (OR 2·80, 95%CI1·86–4·29; p<0·0001) as well as depression (OR1·92, 95%CI1·01–3·64; p=0·0292).

The prevalence of OSA has been reported in only a few non Western populations and racial and ethnic prevalence patterns are poorly understood. Geographical distribution of the disease could generate important clues regarding the aetiology of OSA but it is difficult to distinguish between environmental and cultural influences such as diet from genetic factors. A few studies suggest that OSA prevalence is higher in African – Americans, compared with Caucasians (Ancoli-Israel et al. 1995; Redline et al. 1997), but data from over 6,000 participants in the Sleep Heart Health study did not confirmed this when adjusted for age, sex and BMI (Young et al. 2002). Only a few studies from Asian populations are available. In Hong-Kong, men, aged 30-60 years had a prevalence of OSA (AHI≥15) of 5% and OSA syndrome (AHI≥5 and excessive daytime sleepiness) of 4% (Ip et al. 2001). The prevalence of OSAS in Chinese women in Hong Kong was found to be 2% (Ip et al. 2004). Although the prevalence appears to be similar to that in the Western population, correlation of BMI and weight with OSA was weaker. It was therefore hypothesized that other risk factors such as craniopharyngeal features may be more influential in this population and this hypothesis was supported by other observational studies of Asian patients. Because genetic and environmental risk factors may vary between African, Asian and Western populations more studies on native population as well as migrants and their offsprings may offer more understanding.

There is considerable evidence about prevalence of OSA from Western populations but little is known about the incidence, defined as occurrence of new cases over time interval or progression or worsening over the time. Identifying the incidence comes with all the issues related to prevalence but moreover it is difficult to identify a disease free cohort. This can be further influenced by night to night variability in AHI, hence validity of an OSA free cohort. Only a few reports are available on the progression of OSA. Eight years follow up of 282 participants from the Wisconsin cohort showed an overall increase in mean AHI by 2.6 events/hr from baseline 2.5 to 5.1 and the progression was greater in obese, older and habitual snorers (Young et al. 2002). Similar findings were reported in a preliminary report from the Cleveland family study with an increase in AHI from a mean baseline of 2 (±1.4) to 6.2 (±7.9) at 5 years follow up with significant predictors of progression being BMI, central obesity, cardiovascular disease and diabetes (Tishler et al. 2003).

These results suggest that significant progression can occur within a relatively short period of time with obesity being the main risk factor. As the "obesity epidemic" increases it is likely that there will be a rise in incidence and prevalence of OSA and the public health effort should be aimed at weight reduction programmes to mitigate the risk on already over-streched healthcare systems.

Sleepiness

Sleepiness is the main symptom of OSAS but as recognised from clinical practice there is significant interpersonal variability in terms of sleepiness in patients with OSA regardless of severity of OSA. There is evidence that effective treatment of selected patients with OSAS with CPAP, compared to sham CPAP improves sleepiness (Engleman et al. 1994; Patel et al. 2003; Giles et al. 2006). In addition, large cross-sectional studies in the general population show evidence that snoring as well as OSA is associated with sleepiness.

For example, in the Wisconsin Sleep Cohort study 35% of women and 23% of men with AHI>5 reported excessive sleepiness compared to 29% of women and 24% of men who

snored with AHI<5 and 19% women and 6% men with AHI<5 who did not snore (Young et al. 1993). In another study of 850 randomly selected males snoring was associated with a 5 fold increase in the odds of excessive sleepiness adjusting for severity of OSA (Stradling et al. 1991). Young et al. reported that snorers with AHI of < 5/hr reported hyper somnolence more frequently than non-snoring controls (Young et al. 1993) and she also showed that habitual snores with AHI<5 had a 3 fold increased odds of experiencing road traffic collisions during a 5 year period, compared with subjects without habitual snoring (Young et al. 1997). In the Sleep Heart Health study there was a significant increase in excessive sleepiness assessed by Epworth Sleepiness Scale (ESS) score (Johns 1991) in patients with AHI<5 (ESS 7) to ESS of 9 in participants with AHI>15, independent of sex , age and BMI (Gottlieb et al. 1999).

However, the cause of sleepiness in patients with OSA is not fully understood. It was believed that arousals leading to sleep fragmentation may be responsible for this symptom but studies have failed to confirm this hypothesis (Stradling et al. 2000; Kapur et al. 2005). A multi-center cohort study published in 2008 suggested that apnoeas and sleep disruption were not the primary determinants of excessive sleepiness and patients with excessive sleepiness had longer sleep duration, increased slow wave sleep and more sleep fragmentation (Roure et al. 2008).

These studies suggest that snoring, independent of OSA is associated with excessive daytime sleepiness. The mechanism of this is not clear and validation of self-reported snoring is challenging. Although, there is night to night variability in measured AHI it is possible that one night assessment of patients diagnosed with simple snoring may miss the diagnosis of OSA. One possible mechanism for snoring related sleepiness is mechanical trauma to the pharynx, leading to an inflammation cascade and release of cytokines such as tumour necrosis factor α and interleukin-6. These are elevated in patients with OSA and associated with sleepiness, independently of obesity (Vgontzas et al. 2000). In a placebo controlled, double blind study treatment with tumour necrosis factor α antibody significantly

reduced day time sleepiness and AHI (Vgontzas et al. 2004). These data have to be interpreted with caution, but if this hypothesis of snoring related hyper somnolence is correct the burden of snoring related sleepiness on public health may well exceed that of OSA.

Diagnosis of OSA

When considering a diagnosis of OSA or OSAS it is important to establish a detailed clinical history and obtain objective evidence of respiratory disturbances during the night. The majority of the clinical evidence to date has focus on middle-aged, overweight men with the female phenotype of OSAS less clearly defined. Female OSAS patients may present differently with headache, insomnia and mood disturbances (Ye et al. 2009). Age at presentation may also determine clinical symptoms where for example in the elderly, co-morbidities and lifestyle adjustments such as diurnal napping could cloud symptomatology (McMillan et al. 2014).

Polysomnography

Clinical history is extremely important in raising the possibility of the diagnosis but confirming OSA requires objective clarification through overnight studies. The method considered by some as the gold standard, despite limited evidence, is overnight PSG which simultaneously monitors sleep architecture, nocturnal oxygen saturations, air flow, cardiac rhythm and thoraco-abdominal movements. The routine components of polysomnography include: EEG which differentiates sleep from wakefulness and sleep stages as well as establishes arousals from sleep, electro-oculography (EOG) which is necessary for scoring REM sleep and electromyography, another component of sleep staging, in particular for REM sleep.

Assessment of respiratory function is via the respiratory channels which include assessment of airflow, thoracic and abdominal effort and oxygenation with pulse oximetry. These measures are used to quantify apnoeas and hypopnoeas. An obstructive apnoea is

defined as a cessation or reduction by >90% of airflow with continued effort for at least 10 seconds. The hyponoea definition has changed over the years. It was defined previously as reduction in flow of 50% to 90% lasting ≥10 seconds accompanied by ≥3% decrease in oxyhaemoglobin saturation (SpO_2) or terminated by arousal from sleep [American Academy of Sleep Medicine Task Force (1999)]. The 2012 AASM guidelines defined hypopnoeas as a ⩾30% decrease in nasal flow with ⩾3% desaturation of arterial oxygen measured by pulse oximetry or EEG arousal. (Berry et al. 2012). OSA is defined as the presence of ≥5 episodes of apnoea and hypopnea per hour of sleep. An AHI cut off has been used to define the severity of OSA, defined as mild (AHI 5-15 events /hour), moderate (AHI 15-29 events/hour) and severe (AHI ≥ 30 events /hour). OSAS comprises of AHI≥5 episodes/hour and excessive daytime somnolence or at least two of the following: choking or gasping during sleep, recurrent awaking, unrefreshing sleep, daytime fatigue or impaired concentration or memory (1999). This constitutes a definition of the disorder with reasonable utility. It is important to note, that there are very few normative data for the general population, let alone more specific populations such as, the elderly or people with intellectual disability (Eckert et al. 2008).

Portable monitoring devices

As overnight in-laboratory PSG is labour and resource intensive other diagnostic tools have been developed and validated for home screening and diagnosis of OSA. These include home unattended PSG with portable devices which according to the Standards of Practice Committee of the American Sleep Disorders Association, are classified into several types (Collop et al. 2007).

- "Comprehensive portable PSG: minimum of seven channels monitored, including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort and oxygen saturation"

- "Modified portable sleep apnoea testing: minimum of four channels, including ventilation or airflow with at least two channels of respiratory movement, or respiratory movement and airflow; heart rate or ECG; and oxygen saturation"

- "Continuous single or dual bioparameters: one or two channels, typically including oxygen saturation or airflow"

As a minimum requirement it is recommended that portable home monitoring should comprise airflow, respiratory effort and blood oxygenation. Respiratory polygraphy (rPG) has become a useful and reliable method for the diagnosis of OSAS. PSG is frequently replaced by portable monitors a move driven by costs which was quantified in an economic analysis by *Kim et al* (Kim et al. 2015). Three hundred and seventy three patients with a high pre-test probability of OSA were randomly allocated to an in-laboratory PSG followed by CPAP titration or a portable assessment at home, followed by auto-titrating CPAP. From a payer perspective, the in-laboratory pathway was about 17% more expensive, compared to the home-based pathway. For providers, the costs of both pathways were comparable. A concern was raised that patient care may suffer if economics become the primary driver of OSA diagnostic pathways.

In terms of the diagnostic comparability, data are becoming more widely available. A multi-centre European cohort included over 11,000 subjects, of whom, approximately half underwent PSG and o half rPG ($\geqslant$4 channels of data, no electroencephalography). The AHI was lower by 30% in those who underwent rPG which may be explained, at least in part, by an overestimate of sleep time if EEG data are not available and inability of scoring respiratory events associated with arousals. The report of the Swiss respiratory polygraphy registry was based on 11,485 rPG's. In patients with clinical symptoms of OSAS (snoring, witnessed apnoea and hypersomnia, 4180 patients), 80% of rPG's confirmed OSAS, and only 3.5% were inconclusive and required PSG. According to the practice in Switzerland, PSG is rarely required in the diagnosis of OSA (Thurnheer et al. 2007).

Nocturnal oximetry

Ambulatory oximetry has been developed as a simple and inexpensive tool to screen for OSA. It works on the basis of diodes producing light in red and infrared regions and a photodetector which measures the amount of transmitted light through a body part, usually the fingertip. Pulse oximetry estimates the blood oxygen haemoglobin saturation on the principal that oxygenated and deoxygenated haemoglobin absorb different amounts of the red light. The accuracy of ambulatory oximetry depends on many factors such as body habitus, underlying pulmonary disease affecting baseline saturation, proportion of sleep/wake during the night, and technical qualities such as sampling rate and oximetry recording rate. The measurements are taken by performing a "running average" with a moving window that varies from 1 to 15 s in length and the speed of response to onset of oxygen breathing is on average 9 to 10 s with finger and ear probes.

The interpretation skill of overnight pulse oximetry begins with knowledge of normal oxygen saturation values during sleep. In a key validation study published in 1996, the authors noted normal overnight mean saturations of 96.5% in 350 healthy subjects (Gries et al. 1996). Nocturnal oxygen saturation decreased slightly with increasing age. The values ranging from 96.8% in the age group of 1- to 10-year-old patients to 95.1% in the age group >60 years (Gries et al. 1996). No uniform definition of an oxygen desaturation exists for a normal or abnormal oxygen desaturation index (ODI, oxygen desaturations per hour of sleep). There are generally three cut-off points for an abnormal ODI that mirror the severity definition of abnormal AHI.

Over the last decade, a debate in the literature has questioned whether or not pulse oximetry could effectively screen patients for SDB. Quoted values for sensitivity range from 31 to 98% and for specificity from 41 to 100% and several studies reported that sensitivity increases with severity of OSA (Netzer et al. 2001). In one study in patients with an AHI >25 events per hour, the sensitivity was 100% and the specificity 95%, in patients with AHI > 15

events per hour, these values decreased to 75% and 86% and in patients with AHI > 5 events per hour, to 60% and 80%, respectively. The authors concluded that pulse oximetry is an effective screening tool for patients with moderate to severe OSA (Cooper et al. 1991). A problem with interpreting these results reflecting sensitivity and specificity of oximetry which vary significantly between the individual studies is that authors looked only at a limited patient group in the spectrum of severity of OSA and findings from these studies may not be applicable to OSA patients with different levels of severity from those studied. It was suggested that the combination of a questionnaire and pulse oximetry doubles the specificity of oximetry as a screening tool for sleep apnea (Nuber et al. 2000) but this approach requires further validation.

Chiner et al. analysed how many PSG studies could be saved by overnight pulse oximetry in the initial diagnosis for patients with various severities of OSA. They found that in 275 suspected cases, 216 patients were confirmed to have OSA and pulse oximetry could have saved 140 PSG studies in the group with a respiratory disturbance index (RDI) >5, 119 in the group with an RDI >10, and 10 in the group with an RDI > 15 (Chiner et al. 1999). In addition, there is evidence that PSG is not superior to oximetry when identifying patients with OSA whose quality of life will improve with treatment with CPAP. This is an important consideration as the main purpose of screening and offering diagnostic tests to patients is to identify patients with OSA who will benefit from treatment rather than measure accurate AHI (Whitelaw et al. 2005).

Overnight pulse oximetry is a very useful tool for the diagnosis of SDB and establishing a final diagnosis is very difficult without oximetry data. As a screening tool for the diagnosis of OSA, pulse oximetry is cost-effective and shows substantial accuracy as described above. Sensitivity and specificity remain controversial and deserve further clarification through controlled studies. Technical limitations, limited user knowledge, and the lack of consensus on interpretation of data all play a role in diminishing the value of pulse

oximetry as a diagnostic tool. It has been proposed that patients with suspicion of OSA are screened with nocturnal oximetry and those with symptoms and ODI>15 are offered treatment and patients with an ODI<15 are assessed further by PSG (Netzer et al. 2001) .

Although pulse oximetry represents a useful tool for screening and diagnosis of OSA at the present time there is no internationally standardised technical specification or standardisation of signal processing of oximeters but the minimum standard criteria set by the AASM includes a sample rate of 25 Hz with an average of three values (Berry et al. 2012) and a resolution of 0.1% (Bohning et al. 2010). The current desaturation definitions usually revolve around a decrease of ≥4% from baseline saturations but, there is no unanimity in terms of what constitutes a normal or abnormal desaturation index (Netzer et al. 2001). Additional limitations of pulse oximetry include potential problems with blood flow and haemoglobinopathies, tissue optics in the very obese and an inability to detect other forms of sleep disordered breathing. Movement artefact needs to be taken into account as there can be significant measurement inaccuracies of ±2% in saturations (Bohning et al. 2010).

Assessment of sleepiness

Sleepiness has been very difficult to define and can range from normal sleepiness related to circadian rhythm to pathological sleepiness related to sleep scheduling or primary sleep disorders such as sleep disordered breathing. Cluydts et al. identified that sleepiness can be investigated using different tools including "i) assessment of behaviours such as yawning frequency, actigraphy, facial expression or assessment using performance tests such as driving simulators, psychomotor vigilance tests, or reaction time test; ii) self-evaluation using rating scales such as ESS, or Stanford Sleepiness scale and iii) direct electrophysiological measurements such as in multiple sleep latency test (MSLT) (Cluydts et al. 2002).

With respect to assessing sleepiness in patients with OSAS, the most widely used assessment tool is the ESS score developed in 1991. It is administered as a questionnaire and measures the tendency to fall asleep in 8 specific situations where the patient estimates the likelihood of falling asleep on a 3 point scale (0- never fall asleep to 3-high possibility of falling asleep) for each of 8 questions. The total score ranges between 0-24, with normal being ≤11(Johns 1991). The ESS aims to measure general level of sleepiness and has satisfactory test to retest reliability and helps to distinguish between normal and pathological sleepiness (Johns 1992). One limitation of the ESS is that it is subjective and some patients may not score high on the ESS scale despite feeling sleepy. The accuracy also depends on the awareness of falling asleep which may not always be present (Reyner et al. 1998). It has been shown that grading of one's sleepiness may be more precise by another person (Kingshott et al. 1995).

The Epwoth Sleepiness Scale score does not correlate strongly with more objective assessment of sleepiness such as MSLT's (Benbadis et al. 1999) but this is in keeping with the fact that these tests assess different aspects of sleepiness and supports the difficulty of a definition of sleepiness. The MSLT was developed in 1970 as an objective laboratory test to assess   sleepiness. It is performed during the day following an in laboratory PSG to evidence a good quality and quantity of sleep during the preceding night. It consists of 4 nap opportunities separated by 2 hours, lasting for up to 20 minutes and assesses the mean sleep time latency and presence of REM sleep during these naps (Carskadon et al. 1986). The MSLT is not routinely indicated for diagnosis of OSAS but can be useful in cases of persistent EDS despite adequate treatment of OSA.

Treatment of OSA

General therapeutic options including life style adjustments such as reduction in body weight, abstinence from both alcohol and sedatives and positional therapy should always be considered in all OSA patients (Shneerson et al. 2001). In addition, upper airway surgery in

patients with obvious anatomical abnormalities or bariatric surgery for patients with morbid obesity could be considered (Spicuzza et al. 2015). Oral appliances can be effective for patients with mild to moderate OSA and some patients prefer such treatment to CPAP (Ngiam et al. 2013). Oral appliances promote UA patency by holding the tongue forward and repositioning the mandible forward with the attached tongue.

The most effective treatment of OSA is CPAP. The CPAP acts as a pneumatic splint to prevent upper airway collapse. It has been shown to reduce nocturnal oxygen desaturations, excessive daytime sleepiness and improve cognitive function (Engleman et al. 1994; Giles et al. 2006). From the available evidence, CPAP therapy is indicated in patients with moderate/severe OSA (AHI≥15) associated with symptoms, including excessive daytime sleepiness with its established clinical and cost effectiveness (Giles et al. 2006). Although, various cardiovascular benefits of CPAP have been noted (Marin et al. 2005; Buchner et al. 2007; Duran-Cantolla et al. 2009) indication for treatment of asymptomatic, moderate/severe OSA patients with cardiovascular disease is not clear due to the lack of long term outcome studies and randomised controlled trials(McEvoy et al. 2016).

Treatment with CPAP may have less desirable metabolic effects. Quan et al. recently examined the effect of 6 months of therapeutic versus sham CPAP on weight, in 812 patients from the Apnoea Positive Pressure Long-term Efficacy Study (APPLES) (Quan et al. 2013). They found that subjects treated with therapeutic CPAP gained 0.35 kg while those treated with sham lost 0.70 kg, and greater adherence to therapy correlated with more weight gain. Consistent with this evidence, Drager et al. (Drager et al. 2015) published a meta-analysis of 25 CPAP studies confirming modest weight gain with CPAP treatment with proposed explanations including reductions in energy spent during sleep, elimination of hypoxia-induced anorexia, and decrease of lipolysis (Patel 2015).

<u>OSA and cardiovascular disease</u>

Mechanical effect

OSA causes increased ventricular preload and afterload and reduces cardiac output (Stoohs et al. 1992). This may contribute to cardiac remodelling, hypertrophy and development of cardiac failure over time by the proposed following mechanism. The increase in the negative inspiratory inthrathoracic pressure during an airway obstruction leads to increase in left ventricular (LV) transmural pressure, LV afterload (Bradley et al. 2001) and myocardial oxygen demand which is further impaired by apnoea/hypopnea related hypoxia which can precipitate myocardial ischemia (Bradley et al. 2001; Bradley et al. 2003; Bradley et al. 2003). There is an increase in venous return to the right heart (increased right ventricular (RV) preload) causing enlargement of the right heart and left septal displacement during diastole which can further diminish left ventricular filling and output (Brinker et al. 1980; Bradley et al. 2003). OSA related hypoxia leads to pulmonary vasoconstriction and thus increases RV afterload.

Autonomic effect

Patients with OSA have increased sympathetic neural activity during the night associated with apnoeas (Hedner et al. 1988). This sympathetic nerve activity is not limited to the night but persists during the daytime as evidenced by norepinephrine concentration in the blood and the urine and muscle sympathetic nerve activity (Somers et al. 1989; Narkiewicz et al. 2003). Compared to healthy controls, OSA patients have higher heart rates, blunted heart rate variability and higher blood pressure during the day (Fletcher 2003; Narkiewicz et al. 2003).

Oxidative, inflammatory and vascular endothelial effects

Intermittent hypoxia and reoxygenation leads to oxidative stress, development of reactive oxygen species and inflammation diminishing nitric oxide levels and endothelially mediated vasodilation contributing to hypertension and increased risk of cardiovascular

events (Carlson et al. 1996; Bonetti et al. 2003). Reactive oxygen species have been shown to activate nuclear transcriptional factors stimulating production of inflammatory mediators and adhesion molecules leading to endothelial damage and atherosclerosis (Garvey et al. 2009). Another proposed contributor to the development of atherosclerosis in OSA subjects is increased level of haematocrit, plasma fibrinogen and blood viscosity leading to increasing susceptibility to clot formation. Studies examining carotid artery intima-media thickness report an association of intima-media thickness with nocturnal desaturations and positive correlation with serum concentrations of inflammatory mediators (Minoguchi et al. 2005; Schulz et al. 2005).

Cardiovascular consequences of OSA

Cardiovascular and cerebrovascular disease

OSA and coronary artery disease share common risk factors including obesity, male sex and advanced age (Young et al. 1993; Young et al. 2002) and therefore a higher prevalence of OSA could be expected in patients with cardiovascular disease. How much OSA influences cardiovascular outcomes remains unknown. Moreover, it is unclear whether it is due to mechanisms other than hypertension which has been shown to be associated with OSA even after adjusting for excess weight and other potential confounding factors (Young et al. 2002). Proposed physiological mechanisms for the effect of OSA on cardiovascular health are described above in the paragraph "Cardiovascular effects of OSA".

There is evidence that nocturnal myocardial ischemia can be triggered by OSA, in patients with coronary artery disease (CAD) but there is no evidence for this in patients without CAD (Andreas et al. 1991; Hanly et al. 1993; Franklin et al. 1995). Several case control studies reported a high prevalence of OSA in patients with cardiovascular disease. OSA defined as AHI >10/h has been found in 37% of men with CAD diagnosed by angiography (Mooe et al. 1996). Other studies in patients with CAD reported prevalences between 31-50% (Mooe et al. 1996; Peker et al. 1999; Sanner et al. 2001). In addition,

about a quarter of patients with systemic hypertension (Schulz et al. 2006) and 83% of patients with drug resistant hypertension (Logan et al. 2001) have been found to have OSA.

The prevalence of OSA in patients with heart failure has been reported between 12% and 53% (Ferrier et al. 2005; Javaheri 2006; Vazir et al. 2007). OSA in patients with heart failure is more common in men (Yumino et al. 2009) and more are habitual snorers, compared to the general population. (Javaheri et al. 1998). However, the prevalence of OSA is likely to be higher than in the general population due to common risk factors, which may not have been adjusted for. The effect of heart function on sleep apnoea, in particular central sleep apnoea, as well as the effect of medications and myocardial infarction on OSA severity also need to be considered.

Cross-sectional studies have objectively measured OSA and its association with cardiovascular disease and report an association but of a lesser magnitude that case control studies. One study examining for an association of OSA with cardiovascular disease in 1,222 Hispanic Americans (Schmidt-Nowara et al. 1990) found a non-significant increase in the odds ratio of 1.8 (95% CI 0.9-3.6).

In the Sleep Heart Health study, with over 6000 participants, Shahar et al. reported that those with an AHI>11/hr had a 42% (95% CI 13-78%) greater risk of cardiovascular disease (coronary artery disease, stroke, congestive heart failure) than participants with AHI<1.3/hr after adjusting for multiple potential confounders (Shahar et al. 2001). This analysis was adjusted for hypertension, suggesting that hypertension is not the only mechanism by which OSA can influence cardiovascular outcomes and that treatment of hypertension does not fully protect patients against increased cardiovascular risk. More recently an odds ratio of 2.87 for fatal and 3.17 for non-fatal cardiovascular events was found in a severe, untreated OSA cohort, compared to healthy controls (Marin et al. 2005).

Similar findings came from large population based studies where Hu *et al* reported significant association between self-reported snoring and cardiovascular disease in nearly 72,000 women monitored for up to 8 years in Nurse's Health study (Hu et al. 2000) and

Koskenvuo surveyed 3,847 male participants on snoring status and found an odds ratio for ischaemic heart disease of 1.4 (95% CI 1.2-1.7) for regular *vs* infrequent snores adjusted for BMI, age, smoking, alcohol and hypertension 3 years later (Koskenvuo et al. 1987). A similar study, on 2,937 patients did not find significant association between snoring and cardiovascular disease assessed up to 6 years later (Jennum et al. 1995). It is interesting that the study by Jenum *et al,* although using similar methodsdiffers from the aforementioned Scandinavian studies. Jenum et al. sampled an older population of 54-74 years old compared to a population of 40-69 years in the study by Keskenvuo. This raises the hypothesis that the association of OSA and cardiovascular disease only exists in younger patients, less than 54 years old.

Stroke has been linked to OSA in case-control and cross-sectional studies. In the Sleep Heart Health study the odds ratio for stroke adjusted for multiple confounding factors was 1.6 (95% CI 1.02-2.46) for AHI >11/hr compared to AHI<1.3/hr (Shahar et al. 2001). In case control studies snorers have been found to have an odds ratio of 2 to 10 for developing a stroke compared to controls (Young et al. 2002). To clearly confirm the link, more prospective studies are necessary to confirm that the OSA precedes the stroke rather than being a consequence of acute stroke.

Cardiac arrhythmia and sudden cardiac death

There is some evidence for an association between OSA and ventricular arrhythmia and sudden cardiac death, especially in patients with concomitant structural heart disease. The Sleep Heart Health study showed that after adjusting for confounding factors, including coronary artery disease, patients with severe OSA were three times as likely to develop non sustained ventricular tachycardia and twice as likely to develop complex ventricular ectopy. In the same study, the odds ratio for developing atrial fibrillation compared to matched controlled subjects was 4.5 (Mehra et al. 2006). In one study, patients with OSA had a significant peak in sudden death during sleep, compared to patients without OSA (Gami et al. 2005). Studies on patients in sleep clinics have reported that patients with OSA treated

conservatively (advised weight loss) compared to patients treated with tracheostomy had significantly higher mortality (Partinen et al. 1988; Partinen et al. 1990).

An association between AHI and all-cause mortality has also been examined in several population based studies. In the earlier studies, Lindberg et al. looked at mortality of 3,100 men, 30-60 years old over a 10 year period and did not report an association between snoring and mortality but those less than 60 years of age with snoring and excessive sleepiness were twice as likely to die as those without these symptoms with relative risk 2.2, 95% CI 1.3-3.8 after adjusting for several confounding factors (Lindberg et al. 1998). Evidence supporting an association of OSA and increased risk of mortality comes from more recent population based studies (Marshall et al. 2008; Young et al. 2008).

The Wisconsin Sleep Cohort and the Busselton Sleep Cohort studies show an independent association between sleep disordered breathing and all-cause mortality. In the Wisconsin study, the fully adjusted hazard ratio for all-cause mortality comparing people with severe disease (AHI≥30 events/h) to those without disease (AHI<5 events/h) was 2.7 (95% CI: 1.3–5.7). Cardiovascular disease-related mortality in the Wisconsin study was also higher in people with severe disease than those without disease (hazard ratio: 5.2; 95% CI: 1.4–19.2) (Young et al. 2008), whilst the Busselton study found that moderate-to-severe sleep-disordered breathing was associated with all-cause mortality with an adjusted hazard ratio of 6.2 (95% CI: 2.0–19.4) (Marshall et al. 2008). The result from the Sleep Heart Health study complimented this finding and demonstrate that, independent of several confounding variables, sleep-disordered breathing was associated with all-cause and cardiovascular disease–related mortality (Punjabi et al. 2009). The association was most apparent in men aged 40–70 y with severe disease (AHI≥30 events/h). This study also reported that excess mortality was most apparent in men aged ≤70 years.

More persuasive evidence of causation might come from randomized controlled trials of treatment effect of CPAP. However, a recent, large randomised controlled trial looking at death from cardiovascular causes, myocardial infarction, stroke, hospitalisation for unstable

angiana, transient ischaemic attack or heart failure, as the primary end point, in patients with moderate to severe OSA, unexpectadly showed that treatment with CPAP and usual care versus usual care alone did not prevent cardiovascular events in patients with established cardiovascular disease (McEvoy et al. 2016). A potential limitation of the study was poor compliance in the treatment group with average compliance of 3.3 hours. Subgroup analysis of patients who used the CPAP for >4 hours (42%) showed trend towards slight reduction in primary endpoint but the samle size was too low to have sufficient statistical power to show the difference. In addition, factors like variable access to resources in some geographical areas, and power recalculation due to difficulty in recruiting may have led to type 2 error in this study. More importantly, the inclusion criteria for participation in this study was presence of coronary artery disease or cerebrovascular disease. Therefore this study did not assess the effect of CPAP on primary but secondary prevention of cardiovascular disease. In addition, the mean age of patients in this study was 61 years which is not representative of typical OSA population. Taken together, this largest RCT to date has multiple methodological flaws and the results remain inconclusive. Furher research is needed to answer the question regarding the true effect of CPAP on cardiovascular disease, both, in terms of primary and secondary prevention. Similarly, the Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular trial (MOSAIC), a randomised, 6-month controlled trial in minimally symptomatic patients with OSA reported that 6 months of CPAP therapy improved daytime sleepiness and self-assessed health status, but did not improve the calculated 5-year risk of a fatal cardiovascular event, or any of its component parts (Craig et al. 2012). The compliance in this trial was low (median compliance 2.8 hrs/night) but on subsequent analysis, there was no difference in primary outcomes in patients who complied with CPAP for >4 hours. It is also possible that the cardiovascular score used in this trial was not sensitive enough to pick up the improvement or 6 moths treatment was not long enough to effect cardiovascular score. Subsequent analysis on MOSAIC cohort, however, showed improvement in endothelial function but no arterial stiffness or inflammatory markers. It is possible that the negative outcomes in terms of reduction in cardiovascular risk and arterial

stiffness is due to selected population of more elderly patients with previous cardiovascular morbidity which could have dampened the effect of CPAP in this group. Similarly to above mentioned study by MacEvoy, this study recruited patients with established cardiovascular disease which could have reduced the effect of CPAP on cardiovascular disease and larger and longer trials are needed to show the effect. In addition, future trials should also concentrate on patients without pre-existing cardiovascular disease as it is possible that the effct of CPAP on cardiovascular risk in these patients may be greater. In a study by Ancoli-Israel conducted in 426 older people over 8 to 10 years no significant association between OSA and mortality was found in multiple regression models. However, the true association could have been underestimated as adjustment was made for cardiovascular disease, one of the most important mechanism by which OSA contributes to death (Ancoli-Israel et al. 1996). Negative findings for any association between AHI and mortality in elderly people was also reported by Mant et al. at the 4 year follow up (Mant et al. 1995).

Although clinic based studies report higher mortality in patients with untreated OSA without randomisation to treatment groups it is not possible to draw any definite conclusion (Young et al. 2002). In addition, it is possible that the patients with most severe OSA were treated, which could have confounded the presented results. The most convincing evidence comes from the aforementioned large population based studies. Studies by Lindberg and Punjabi showing an association in middle aged men only and in under 70 years old respectively suggest that elderly patients may be more resistant to the consequences of OSA represents a different disease in the older population. However, with increasing age the likelihood of death from other causes rises and therefore quantifying the potential association between sleep disordered breathing and mortality becomes more difficult. In conclusion, it is possible that OSA increases the risk of mortality but large population based studies where OSA is objectively assessed are needed to confirm this hypothesis and similarly, the evidence regarding the effect of OSA on cardiovascular outcomes, independent

of hypertension, as well as the evidence of treatment with CPAP on cardiovascular outcomes in patients with OSA is still awaited.

Arterial hypertension

OSA has been a recognised cause of hypertension in two large studies. The Sleep Heart Health Study analysed data on >6000 participants and reported an independent association between severity of OSA and hypertension (Nieto et al. 2000) and the Wisconsin Sleep Cohort Study showed an association between severity of OSA and hypertension (Peppard et al. 2000) with stronger association found in the younger subjects. Due to cross-sectional design, these studies were not able to establish causation or that OSA predated hypertension. In the Wisconsin sleep cohort even minimally elevated AHI of >0 and <5 was associated with 42% (95% CI 13-78%) increased odds of developing hypertension over 4 years follow up (Peppard et al. 2000). Stradling et al. reported attenuated night time blood pressure dipping in patients with OSA proportional to oxygen desaturation index (Stradling et al. 2000).

Stronger evidence for causation comes from randomised controlled trials. Meta-analysis of seven randomized controlled trials reporting 24-hour ambulatory blood pressure showed that CPAP was associated with significant reductions in 24-hour ambulatory systolic blood pressure (SBP) of -2.32 mmHg (95% CI -3.65 to -1.00) and diastolic blood pressure (DBP) of -1.98 mmHg (95%CI -2.82 to -1.14). CPAP led to a more significant improvement in nocturnal SBP than that in diurnal SBP (Hu et al. 2015). The clinical significance of these blood pressure changes is likely modest and whether the long term effect of CPAP on blood pressure in patients with OSA is greater remains unanswered.

Effect of CPAP on cardiovascular disease and mortality

CPAP has been reported to reduce nocturnal sympathetic activation, heart rate, variability in blood pressure (Sforza et al. 1992; Somers et al. 1995; Bonsignore et al. 2006) as well as pre-load and after-load in patients with chronic heart failure (Naughton et al. 1995;

Narkiewicz et al. 1999). In addition it has been found to reduce 24-h mean blood pressure by around 2mmHg, particularly at night, with the largest effect observed in patients with symptomatic and severe OSA (Duran-Cantolla et al. 2009). CPAP has been found to affect cardiovascular outcomes in patients with increased cardiovascular risk or presence of coronary artery disease with reduction in new cardiovascular events (Milleron et al. 2004) and death from cardiovascular disease (Doherty et al. 2005). The strongest evidence for an effect of CPAP on cardiovascular outcomes comes from (Marin et al. 2005). This observational study in 1651 participants over a 10 years period showed that the risk for fatal and non-fatal cardiovascular events was significantly increased in severe untreated or non-compliant OSA patients (OR 2.9 and 3.2 respectively), compared to healthy participants. In patients with mild to moderate OSA, CPAP has been associated with a 64% cardiovascular risk reduction, independent of age and pre-existing cardiovascular comorbidities (Buchner et al. 2007). However, there are no randomised controlled trials confirming this benefit and a recent, large, randomized controlled trial of adults with moderate to severe OSA and pre-existing cardiovascular disease showed that the use of CPAP had no significant effect on the prevention of recurrent serious cardiovascular events (McEvoy et al. 2016). It is possible that patients with compliance exceeding 4h/night may benefit in terms of cardiac outcomes but further research is needed to clarify this benefit (Abuzaid et al. 2017; Khan et al. 2017).

Obstructive sleep apnoea in surgical populations

Prevalence of OSA in surgical population

No epidemiological studies have been conducted to assess true prevalence of OSA in patients undergoing surgical procedures. Estimated prevalence varies and depends on surgical population, diagnostic criteria of OSA and the sleep diagnostic used. A large retrospective study examining 43,576 adult cases undergoing anesthesia and general surgery found a prevalence rate for OSA of 7-10% (Ramachandran et al. 2010). Higher prevalence, was reported in certain surgical populations (Auckley 2003). Using PSG as a screening method for OSA (defined as AHI>5/hour), it was found in 71% of patients

undergoing bariatric surgery, compared to 9.5% of patients undergoing general surgery, excluding cardiac surgery. High prevalence (85%) was recently reported in patients undergoing surgery for severe peripheral vascular disease, using an overnight polysomnography (Utriainen et al. 2013). As OSA and cardiovascular disease share common risk factors it is likely that higher prevalence is found in highly selected cardiovascular cohorts. In addition, not surprisingly, higher prevalence may be reported using tools with high sensitivity and low specificity. For example, Hwang et al. screened patients undergoing general surgery with nocturnal oximetry and found that 57% of patients had sleep apnoea defined as 4% ODI>5/hour (Hwang et al. 2008).

Assessing prevalence using tools such as questionnaires without objective assessment of respiratory disturbance may be misleading and high prevalence has been reported in such studies. Prevalence of sleep apnoea in patients undergoing CABG, screened using the Berlin Questionnaire estimated that 67% of patients were at high risk of OSA compared to 24% of patients undergoing general surgery (Chung et al. 2007). In another study of elective surgical patients, using STOP-BANG questionnaire, 41% were said to be at high risk of OSA (Vasu et al. 2010).

A major difficulty in assessing prevalence of OSA in surgical population is that PSG is labour and resource intensive and may cause delay to surgery and it is therefore difficult to recruit patients to such studies. One study reported that only 44% of patients identified as high risk for OSA prior surgery agreed to undergo PSG to confirm the diagnosis (Fidan et al. 2006). A high proportion, 78% of patients, who agreed to undergo PSG in this study, had a diagnosis of OSA, evidenced by AHI > 5/hour (Vasu et al. 2010). Currently, estimated prevalence may represent a conservative estimate as it has been shown that 60% of OSA patients assessed for OSA in preadmission clinics are not suspected to suffer with OSA based on simple clinical assessment (Finkel et al. 2009; Singh et al. 2013). Moreover, it has been estimated that 82% of men and 92% of females with moderate to severe OSA remain undiagnosed (Ancoli-Israel et al. 1991) and may be presenting for the surgery without

previous diagnosis or treatment posing a potential challenge to the anaesthetist in the perioperative period.

Screening tools for OSA prior to surgery

In view of the increasing prevalence of OSA in the last two decades and due to emerging evidence of its association with worse postoperative outcomes clinicians have sought to enable screening for sleep disordered breathing in various surgical populations. Methods include using a combination of clinical variables such as BMI, neck circumference, jaw structure, snoring, reports of nocturnal breathing disturbances and the presence of hypertension. The sensitivity of these methods is high (78-95%) but the specificity tends to be low (41-63%) (Rowley et al. 2000).

In terms of objective assessment, the use of PSG, due to its technical complexity, time requirement, cost and availability, is limited. Other multichannel portable sleep devices, although more accessible, also require a trained and experienced sleep physician or sleep technician to analyse the study. In UK clinical practice access to sleep diagnostics and assessment by sleep physicians are limited. Around two thirds of sleep studies in UK are oximetry alone and 20 % are limited multi-channel sleep studies with only 10% being PSG's (Flemons et al. 2004). A high resolution oximeter represents an economic and practical screening tool requiring little training for both patient and sleep clinician. The devices are available as a watch oximeter with a high sampling frequency detecting intermittent drops in oxygen saturations usually reported as 4% oxygen desaturation index. The data are analysed automatically by computer programs with an acceptable accuracy.

This method of screening has been validated in sleep centres and in a general surgical population, where the ODI >10 was found to have a sensitivity of 93% and specificity of 75% to detect moderate and severe sleep disordered breathing (Chung et al. 2012). When compared to PSG, oximetry has an accuracy of 86–94 % for detecting moderate to severe OSA in patients undergoing general surgery (Chung et al. 2012; Hang et al. 2015). Although OSA can be missed on nocturnal oximetry, there is emerging

evidence that ODI from high resolution nocturnal oximetry can be a useful tool for risk stratifying patients prior to surgery and identifying patients who are at risk of postoperative complications (Hwang et al. 2008; Chung et al. 2014). Nocturnal oximetry has been validated against portable monitoring in patients undergoing bariatric surgery where the 3% ODI measured by nocturnal oximetry could rule out or detect moderate to severe OSA with reasonable accuracy (Malbois et al. 2010).

A number of screening questionnaires, to identify patients who are at high risk of sleep apnoea, have been developed. These tools have been validated against full sleep diagnostics in preselected surgical populations. They should not be applied without validation in other cohorts. The accuracy of screening questionnaires has been examined in recent reviews. Most of the screening tools including: STOP questionnaire, STOP-Bang questionnaire, Berlin questionnaire, Sleep Apnea Clinical Screen (SACS) questionnaire, American Society of Anesthesiology (ASA) checklist have been found to have reasonable sensitivities (70–85 %) and positive predictive values (72–90 %) but poor specificities (40–55 %) and negative predictive values (40–60 %) (Ramachandran et al. 2009; Abrishami et al. 2010).

The review by Ramachandran found no clinical tool as an ideal pre-operative screening test (Ramachandran et al. 2009). Diagnostic odds ratio (DOR) which combines data on sensitivity and specificity and represents the ability of test to rule out or rule in the condition was used to interpret the data in this review. A DOR of >81 represents an excellent test because it indicates that both sensitivity and specificity are >0.9 (Deeks 2001). The STOP-Bang questionnaire with DOR of 142 was found an excellent questionnaire for predicting the presence of severe OSA (AHI>30). However the test accuracy for individual screening tools defined by DOR was poorly reproducible in multiple validation studies. Based on false negative rates and heterogeneity none of the questionnaires or clinical models were found to be satisfactory. A more recent review suggested that STOP and STOP-Bang questionnaires for screening of OSA in a general surgical population are

superior due to their higher methodological quality and easy-to-use features (Abrishami et al. 2010) and recent meta-analysis of the STOP-Bang questionnaire has confirmed its high performance in sleep clinics and surgical patients (Nagappa et al. 2015).

STOP-BANG questionnaire

The STOP-Bang questionnaire (Snoring, Tiredness, Observed apnoeas, high blood Pressure, BMI >35 kg/m^2, Age >50 years, Neck circumference >40cm, male Gender) is a scoring model consisting of 8 questions with yes/no responses. The total score can range from 0-8 according to the number of positive answers. Patients scoring >3 on STOP-Bang are perceived to be at high risk of OSA. The STOP-Bang questionnaire was developed and validated in a general surgical population (Chung et al. 2008) and has been adopted as a screening tool in surgical pre-assessment clinics for its easy use. In the original population the sensitivity and specificity for moderate OSA were found to be 93% and 43% respectively and for severe OSA 100% and 37% with a negative predictive value of 100% for severe OSA (Chung et al. 2008). In systematic reviews of screening questionnaires for OSA, the STOP-Bang questionnaire had the highest methodological validity, moderately high sensitivity and best negative predictive value for assessing the risk of moderate/severe OSA (Abrishami et al. 2010; Chiu et al. 2017). The high sensitivity means that STOP-Bang of 0-2 would with high accuracy exclude patients with OSA but low specificity means that significant number of patients with scores of ≥3 would screen falsely positive.

To deal with the issue of low specificity several aspects of STOP-Bang scoring have been explored. A relationship between STOP-Bang scores and the predicted probability of OSA was examined and found that the higher the STOP-Bang score the greater probability of OSA (Nagappa et al. 2015). In this pooled surgical population of 957 patients, the probability of moderate-to-severe OSA for a score of 3 was 40% and the higher the STOP-Bang score, the greater was the probability of OSA. The addition of serum bicarbonate level HCO3$^-$ to STOP-Bang scores has been explored and it was shown that the addition of serum HCO3$^-$ of at least 28 mmol/l to a STOP-Bang score of ≥3 improves the specificity to predict

moderate-to-severe OSA, but decreases significantly its sensitivity (Chung et al. 2016). The predictive performance of various individual items of STOP-Bang has been examined. Specificity in detecting moderate to severe OSA increased based on different combinations: 85% for a STOP score at least 2 + BMI more than 35 kg/ m^2; 79% for a STOP score at least 2 + neck circumference more than 40 cm and 77% for a STOP score at least 2 + male (Chung et al. 2014).

Based on these results a two step approach has been proposed (Chung et al. 2014) in that if patients score 0-2, there is a low risk of moderate to severe OSA. If a patient scores ≥5 they have high probability for moderate to severe OSA and further assessment by sleep physician may be needed. The intermediate risk are patients with scores 3, 4 can be further stratified as high risk of OSA based on STOP score at least 2 + BMI more than 35 kg/m2 or STOP score at least 2 + male or STOP score at least 2 + neck circumference more than 40 cm. In addition, patients with STOP-Bang score at least 3 can be further classified as high-risk for moderate-to-severe OSA if the serum HCO3$^-$ is at least 28mmol/L. However, this two-step algorithm makes the simple question more complex and needs further prospective validation.

The STOP-Bang questionnaire has been validated in different populations, but a selection bias such as referring patients with suspected sleep-related concerns from sleep clinics or in studies targeting surgical patients and, a self-selection bias from patients with preexisting sleep symptoms could exist in some of the validation studies. This, along with high prevalence of OSA in the studied population may have influenced the results and therefore validation in specific target populations is recommended (Chung et al. 2016).

Some studies have shown that the STOP-Bang score might predict increased risk of postoperative pulmonary and cardiac complications in patients undergoing various surgical procedures (Nagappa et al. 2017). Data from a large prospective study (n=3,452 patients) showed that patients with high risk of OSA, compared to low risk, on the STOP-Bang

questionnaire had a higher rate of postoperative complications in terms of difficult intubation (20% vs 9%) and difficult mask ventilation (23% vs 7%) (Corso et al. 2014).

Peri-operative risks in patients with of OSA

Surgery and the postoperative period may represent a vulnerable time for patients with OSA due to potential deleterious effects of sedatives and opioids, supine position following surgery as well as possible REM sleep rebound reported after surgery, all of which may worsen the severity of OSA (Kaw et al. 2006). It has been hypothesised that the worsening severity of sleep-disordered breathing after surgery may be responsible for an increased incidence of postoperative complications in patients with OSA and that understanding the mechanism of the postoperative deterioration of sleep-disordered breathing may help with the perioperative management of patients with OSA (Chung et al. 2014).

Several studies have reported worsening of OSA in the postoperative period with one study reporting peak worsening of sleep disordered breathing on postoperative night three which recovered to preoperative level of severity on postoperative night seven (Chung et al. 2014). Rosenberg et al. reported that postoperative rebound of nocturnal REM sleep might contribute to the development of sleep-disordered breathing and nocturnal episodic hypoxemia (Rosenberg et al. 1994). A prospective study of 376 patients undergoing various surgical procedures showed that factors associated with worsening of OSA after surgery were preoperative severity of OSA (as evidenced by AHI), age, and 72-h opioid dose. (Chung et al. 2014). The mechanisms by which sleep apnoea might affect postoperative outcomes are unknown but one study by Gögenur et al. demonstrated that postoperative nocturnal hypoxemia was associated with tachycardia and myocardial ischemia (Gogenur et al. 2004).

Impact of sedation, anaesthesia and opioid analgesia on OSA

The cardinal feature of OSA is recurrent UA obstruction due to imbalance between collapsing and dilating UA forces. It has been reported that general anaesthetics reduce UA dilator muscles activity and impair arousal responses to hypoxia (Vasu et al. 2012) leading to increased upper airway collapsibility and worsening OSA. A study of 12 healthy volunteers undergoing minor surgery showed that increased depth of propofol anaesthesia was associated with an increase in critical upper airway pressure and airway collapsibility due to reduced genioglossus activity (Eastwood et al. 2005; Hillman et al. 2009).

Opiates/opioids in OSA

The use of opioids is prevalent in Western societies and opioids are commonly used in the management of postoperative pain but use in patients with OSA may be limited by concerns regarding respiratory depression (Wang et al. 2007). Opiates are naturally occurring compounds whereas opioids are synthetic agents and both are widely used as analgesics following major surgery. Opiates and opioids bind to four different classes of receptors, namely δ, κ, μ and the nociception/orphanin receptor (Pattinson 2008). It has been shown that opioids inhibit brainstem arousal centres and could therefore cause reduced consciousness. Opiates/opioids exercise their negative effect on ventilation by reducing the respiratory rate and tidal volume as well as decreasing chemoresponsivness to hypoxia and hypercapnia and reducing UA muscle tone (Lalley 2008; Van Ryswyk et al. 2016) . Opioid receptors are located in the nuclei that are active in sleep regulation and opioids have been reported to impair basic sleep–wake mechanisms (Lydic et al. 2005) by inhibiting central cholinergic (Lydic et al. 1993) and adenosinergic (Nelson et al. 2009) transmission. Opioids with μ receptor stimulating action can lead to inhibition of REM sleep (Cronin et al. 1995).

The effects of opioids on respiration share common physiological pathways with OSA and thus could increase susceptibility to sleep disordered breathing. Patients suffering from

sleep-disordered breathing may be vulnerable to the central opioid effects such as sedation, diminished central respiratory drive as well as peripheral effects including increased airway collapsibility. Certain pathophysiological features of OSA including sleep fragmentation, intermittent hypoxemia, and systemic inflammation have been found to influence pain behaviour and/or increase sensitivity to opioids as described in the following paragraphs (Wang et al. 2007; Doufas et al. 2013).

The effect of opioids on sleep was not studied in surgical patients with OSA and there are only limited studies in non-surgical populations examining the effect of acute opioid administration on sleep apnoea. To date, there is only one randomised controlled trial examining the effect of the opioid, remifentanil. Nineteen subjects were studied and a reduction in obstructive apnoeic events along with an increase in central sleep apnoea frequency and significant reduction in minimal nocturnal oxygen saturation were observed (Bernards et al. 2009). This may be related to the REM-suppressing effect of the opioid. Caution is needed as discontinuation of opioids and REM rebound after the third postoperative night may worsen the severity of OSA in patients with REM-predominant apnea/hypopnea events and the obstructive events may recur with increased frequency and severity during an intense REM sleep rebound after the third postoperative night (Knill et al. 1990). The the clinical impact of this phenomenon is yet to be shown (Macintyre et al. 2011).

In one retrospective case series patients undergoing UA surgery for OSA treated with acutely administered opioids had increased extubation complications (Esclamado et al. 1989). Another case series described postoperative respiratory arrest in patients receiving epidural opioids (Ostermeier et al. 1997) and pronounced episodic oxygen desaturation in the postoperative period in patients with OSA treated with acute intravenous opioid analgesia has also been noticed (Catley et al. 1985). Apnoeas, respiratory depression and cyanosis were also described in patient with a history suggestive of OSA receiving postoperative epidural morphine (Lamarche et al. 1986). It has been described that

morphine can exacerbate upper airway obstruction in patients with established upper airway compromise due to enlarged tonsils or upper airway tumour with death reported after administration of morphine (Byard et al. 2005).

Considering the relatively high prevalence of OSA in the surgical population there are perhaps surprisingly few anecdotal reports of deleterious effects of morphine on patients with OSA after surgery. This may be due to careful monitoring of these patients following surgery or may support the hypothesis that only a small group of OSA patients are at increased risk for opioid-induced ventilatory compromise. Although, administration of oxygen (Hudgel et al. 1988; Mokhlesi et al. 2011) and sedatives(Eckert et al. 2011) may stabilise ventilatory control and benefit OSA patients with increased loop gain and low arousal thresholds, the same intervention could prolong the duration of airway obstruction, leading to severe hypoxemia, in patients with decreased ventilatory responses to hypoxia/hypercapnia and high arousal thresholds (Hudgel et al. 1988).

Although this group of patients with increased loop gain represents a minority amongst OSA cohort (Eckert et al. 2014) they might be at a greater risk of deleterious opioid-related respiratory events after surgery because they rely heavily on arousal to restore UP patency and normalise blood gas tensions. Opioids, by inhibiting chemical, behavioural, and motor control of respiration (Koo 2011), could further raise arousal thresholds, prolong airway obstruction, and precipitate hypoxemia. It was observed that fatal episodes were more likely to occur during the night-time in patients who were difficult to arouse (Ramachandran et al. 2011), which may suggest that OSA patients with high arousal thresholds, longer obstructive events, and potentially larger arterial desaturations may have a lower reserve to tolerate a significant respiratory event after surgery than patients with a different OSA phenotype presenting with frequent obstructive events and mild-to-moderate hypoxemia. In these patients the sedative effect of opioids may stabilise airway patency and breathing and improve OSA (Wang et al. 2013).

There is a growing body of experimental and clinical evidence supporting an association between OSA and/or intermittent hypoxia with increased sensitivity to the opioid analgesic effect. Children living at high altitude under conditions of chronic sustained hypoxia with resting oxyhemoglobin saturation of 92% consumed 40% less fentanyl peri-operatively, compared with children living at sea level (Rabbitts et al. 2010). Consistent with this report, in a retrospective cohort of 46 children undergoing adenotonsillectomy for OSA it was shown that recurrent nocturnal hypoxemia was associated with lower opioid consumption in the perioperative period (Brown et al. 2004) and in a prospective study in a paediatric population of 22 children it was reported that children with a nocturnal nadir SaO_2 <85% needed half of the total dose of morphine required to treat post adenotonsillectomy pain than children with a nadir SaO_2 ≥85% (Brown et al. 2006). These findings were also supported by independent experiments showing that intermittent hypoxia upregulated μ-opioid receptors in the developing rat (Laferriere et al. 2003) which may be responsible for an increased sensitivity to the analgesic and respiratory effects of opioids (Moss et al. 2006). Similarly, it was reported that in adult volunteers suffering OSA, both nocturnal nadir SaO_2 and insulin-like growth factor-binding protein 1, a serum marker of hypoxia, were significantly associated with increased sensitivity to the analgesic effect of remifentanil. (Doufas et al. 2013).A recent retrospective analysis of 218 obese adults with OSA, who underwent bariatric surgery, demonstrated that the percentage of total sleep time spent with SaO_2 <90% was inversely associated with total postoperative opioid consumption (Turan et al. 2015).

In addition, experimental and clinical evidence suggest that sleep disruption and nocturnal intermittent hypoxemia, cardinal features of OSA, could enhance pain either acting directly or via complex inflammatory pathways (Abrishami et al. 2010). In view of this evidence, both intermittent hypoxia and sleep disruption augment pain, and intermittent hypoxia may also potentiate opioid analgesic responses and OSA. This may complicate opioid-based perioperative management of pain by altering both pain processing and

sensitivity to opioid effects in OSA individuals. Given the variability of OSA phenotypes and pain/analgesia responses in humans, there is a need for large prospective trials examining the effect of the various OSA phenotypes on postoperative pain as well as the effect of opioid analgesia on these various OSA subtypes.

Opioid administration after surgery is often via patient controlled analgesia (PCA). A standard regime includes a 1mg bolus followed by 5-10 minutes of lock out period via the PCA device. Two retrospective reviews of over a thousand patients reported 1-2% risk of developing respiratory depression with PCA extending to 31 hours after initiation of analgesia, emphasising the importance of short and long term monitoring of patients with OSA. The American Society of Anaesthesiologist has issued practice guidelines regarding the management of patients with OSA, including use of opioids and other compounds suppressing respiration or having a negative impact on upper airway dilator muscles and advise that the smallest possible doses should be used (Gross et al. 2006).

Impact of REM sleep rebound on OSA

Although the exact mechanism for worsening of sleep apnoea in the postoperative period and effect of sleep apnoea on worse postoperative outcomes is unknown, the effect of REM sleep rebound has been proposed. Studies have shown that following surgery, patients have highly fragmented sleep during the second postoperative night with a reduction in REM sleep, slow wave sleep (SWS) and an increase in stage two sleep (Vasu et al. 2012). It appears that type of surgery plays an important role with more pronounced disruption in REM sleep and SWS noticed after major surgery for example gastrectomy as oppose to minor surgery such hernia repair (Vasu et al. 2012). Surgical trauma leads to increased levels of cortisol and pro-inflammatory mediators such tumour necrosis factor α , interleucin1 (IL-1) and interleukin 6 (IL-6), which have been shown to reduce REM sleep (Opp et al. 1992; Lin et al. 2000). REM sleep is mainly reduced on post-operative night 1

and 2 which is followed by REM sleep rebound during the postoperative nights 3-5 (Vasu et al. 2012).

It has been shown that during REM sleep pharyngeal muscle activity is minimal predisposing to upper airway closure and leading to intermittent hypoxia causing brief arousal leading to increase sympathetic surge, and causing tachyarrhythmia, haemodynamic instability and myocardial ischaemia (Gogenur et al. 2004). Episodes of hypoxaemia and complications, after surgery, have been described to occur mostly between night 3-5 after the surgery (Vasu et al. 2010). Episodic hypoxia has been previously linked to an increased risk of wound infections, cerebral dysfunction and cardiac arrhythmias (Kehlet et al. 1995). The incidence of myocardial infarction has been reported to peak on day 3 after the surgery (Tarhan et al. 1972) and delirium, nightmares, and psychomotor dysfunction have all been reported as increasing between nights 3 and 5 following surgery (Vasu et al. 2010). This anecdotal evidence supports the hypothesis of REM sleep rebound and its effect on worsening of sleep apnoea as well as worse postoperative outcomes in patients with OSA but more evidence needed to confirm this hypothesis.

Obstructive sleep apnoea and postoperative complications

Many factors have been shown to influence surgical outcomes including American Association of Anaesthesiology (ASA) class, age, type of paralytics, smoking status, low albumin, duration of surgery and presence of comorbidities such chronic obstructive pulmonary disease (COPD), renal failure and coronary artery disease (Vasu et al. 2012). It has also been reported that certain surgical procedures are associated with higher risks including cardiothoracic, abdominal, vascular and neck surgery (Vasu et al. 2012). A risk model have been developed to calculate the risk of mortality after cardiac surgery. EuroSCORE (European System for Cardiac Operative Risk Evaluation) is a risk model consisting of 17 items, developed between 1995 and 1999 to provide a simple, additive risk model of perioperative mortality (Geissler et al. 2000).

In the last decade, significant research effort has been placed on examining an association between OSA and postoperative outcomes with emerging evidence of worse outcomes in patients with unrecognised or untreated OSA. The evidence comes from studies of varied quality with perhaps the strongest evidence coming from studies of national databases of million patients. The accuracy of studies that use *International Classification of Diseases, Ninth Revision* (*ICD-9*) coding to identify patients with OSA may be criticised as coding systems may label a mixture of OSA and non OSA in study group and the control group may not represent a true negative control. However, considering the fact that patients with an *ICD-9* code of OSA are likely to have the disease, and many who remain undiagnosed are included in the control group as is likely the case in database studies, the associations found in these analyses could actually underestimate the true effects.

Memtsoudis et al. examined a database of over 6 million patients undergoing general and orthopaedic surgery and found the prevalence of sleep apnoea of 1.4% and 2.5% respectively. Sleep apnoea was associated with a significantly higher adjusted OR of developing pulmonary complications after both orthopaedic and general surgical procedures, respectively, with the exception of pulmonary embolus. The OR for aspiration pneumonia was 1.41 [95% CI 1.35, 1.47] and 1.37 [95% CI 1.33, 1.41], for ARDS: 2.39 [95% CI 2.28, 2.51] and 1.58 [95% CI 1.54, 1.62], and for intubation/mechanical ventilation 5.20 [95% CI 5.05, 5.37] and 1.95 [95% CI 1.91, 1.98] (Memtsoudis et al. 2011). In a similarly designed study, Memtsoudis et al. analysed entries of 530,089 patients undergoing total hip and knee arthroplasty and found the prevalence of sleep apnoea was 8.4%. Sleep apnoea was found to be an independent risk factor for major postoperative complications (OR 1.47; 95% CI 1.39-1.55) in particular pulmonary complications were 1.86 (95% CI, 1.65-2.09) times more likely and cardiac complications 1.59 (95% CI, 1.48-1.71) times more likely to occur in patients with sleep apnoea (Memtsoudis et al. 2014). In addition, sleep apnoea patients were more likely to receive ventilatory support, use more intensive care resource and have longer lengths of hospitalization (Memtsoudis et al. 2014). In line with these reports,

Mokhlesi et al. showed that sleep apnoea was independently associated with cardiopulmonary complications (Mokhlesi et al. 2013).

These studies have several limitations that are mainly related to the analysis of large administrative databases including the inability to ascertain the presence or absence of sleep apnoea and its severity, lack of information about home CPAP therapy or CPAP use/compliance during the postoperative period. In addition, information on all potential confounders, such as BMI was not available and therefore it is impossible to be sure that the worse postoperative outcomes are independent of obesity, one of the most significant risk factors for OSA.

Along with these large scale studies several single centre studies have been performed and outcomes analysed in 2 meta-analyses, including 13 and 17 studies (Kaw et al. 2012; Hai et al. 2014). The meta-analysis of 13 studies where the majority of patients were confirmed to have OSA by polysomnography, showed increased risks of post-operative cardiac events OR 2.07, acute respiratory failure OR 2.43, desaturations OR 2.27 and ICU transfers OR 2.81(Kaw et al. 2012). Data from several large studies, described above, using a diagnosis of OSA based on international code system were not included in these meta-analyses (Memtsoudis et al. 2011; Mokhlesi et al. 2013; Mokhlesi et al. 2013). The conclusions from these meta-analyse s suggest that due to heterogeneity of settings, sleep diagnostic used, definition of OSA and the outcomes measured it is not possible, with confidence, to determine that OSA is an independent risk factor for worse postoperative outcomes.

Although, the majority of studies reporting an association between OSA and postoperative outcomes were observational and given the limitations described, there is moderate evidence for an association between OSA and deleterious pulmonary and cardiovascular outcomes in patients undergoing general surgery. It is, however, impossible

to conclude the causation and to be certain that this association is independent of obesity and other cardiovascular comorbidities often found in these patients.

The literature regarding an association between OSA and mortality is less clear with some of the current evidence supporting improved 30 day mortality in patients with OSA. The evidence comes mainly from large population database analysis based on ICD-9 code diagnosis and confirming causality is therefore not possible (Nguyen et al. 2011; Mokhlesi et al. 2013; Mokhlesi et al. 2013). One possible mechanism for reduction in mortality in patients with SDB may be ischaemic preconditioning. Studies have reported that in patients with acute myocardial infarction, those with SDB and intermittent hypoxemia during sleep have better coronary collateral circulation and less severe cardiac injury (Shah et al. 2013). The majority of other studies report no association between OSA and postoperative mortality (Opperer et al. 2016) and one study suggests increase mortality in patients with OSA (D'Apuzzo et al. 2012).

Data in patients undergoing cardiac surgery are inconsistent with some results suggesting an association between OSA and postoperative complications and others not supporting this association (Foldvary-Schaefer et al. 2015; Uchoa et al. 2015). A study of 67 prospectively recruited participants, assessed for OSA by PSG showed no association between OSA and short term complications but reported that the OSA was independently associated with a higher rate of long-term cardiovascular events after CABG (Uchoa et al. 2015). Another study by Foldvary-Schaefer et al. recruited prospectively 107 patients and showed that OSA was not significantly associated with worse postoperative outcomes but the authors commented that the relatively small study sample could have influenced results (Foldvary-Schaefer et al. 2015).

A recent meta-analysis reported a positive association between OSA and postoperative complications in patients undergoing cardiac surgery (Nagappa et al. 2017). It included 11 studies and showed a higher chance of adverse cardiac and cerebrovascular

events with an odds ratio (OR) of 2.4; 95% CI 1.38-4.2; p=0.002, as well as newly documented postoperative atrial fibrillation OR = 1.94; CI 1.13-3.33; p=0.02 in patients with OSA compared to non OSA patients (Nagappa et al. 2017). There was no significant difference in the number of Intensive Care Unit readmissions, infection or sepsis, Intensive Care Unit lengths of stay, and hospital lengths of stay. The majority of patients in this meta-analysis were newly diagnosed, untreated patients with OSA. The studies included were of mixed quality. Only five out of 11 of the studies were prospective and used recognised sleep diagnostic (PSG or watch-PAT) to diagnose OSA (Mooe et al. 1996; Bhama et al. 2006; Foldvary-Schaefer et al. 2015; Uchoa et al. 2015; Zhao et al. 2015) whilst the rest were either retrospective cohort assessments or used questionnaires to estimate the risk of OSA. Out of the five higher quality studies, two reported no association between OSA and postoperative outcomes (Foldvary-Schaefer et al. 2015; Uchoa et al. 2015), two reported an association between OSA and post-operative atrial fibrillation (Mooe et al. 1996; Zhao et al. 2015) and one showed prolonged ventilation, tracheostomy duration, Intensive Care Unit and hospital duration of stay (Bhama et al. 2006).

A reason why studies reach different conclusions may be inconsistency in definition of OSA, sleep diagnostic used, small sample size for given outcomes and number of various reported outcomes. Overall, there is currently no compelling evidence for an increased risk of postoperative complications in patients with OSA independent of obesity and other comorbidities in patients undergoing cardiac surgery.

Perioperative management of patients with OSA

In 2006 the American Society of Anaesthesiologists and in 2016 the Society of Anaesthesia and Sleep Medicine published guidelines on perioperative management of patients with OSA with the following recommendations (Gross et al. 2006; Chung et al. 2016):

1. Perioperative evaluation

"A thorough clinical and sleep history should focus on symptoms associated with OSA including snoring, witnessed apnoeas, disrupted sleep, nocturnal chocking, morning headaches, and excessive daytime sleepiness. Physical examination including neck circumference, BMI, tongue size, tonsillar size and nasopharyngeal assessment should be undertaken." A screening questionnaire can be administered with clear plan for further investigation if felt appropriate by surgeon or anaesthetist but at present there is limited evidence to support the use of preoperative screening tools as a routine practice to reduce postoperative complications (Lockhart et al. 2013). Identifying patients at risk of OSA prior to surgery may allow perioperative precautions and interventions which may mitigate patients' risks, for example avoidance of general anaesthesia in patients with OSA undergoing joint arthroplasty (Memtsoudis et al. 2013). Local services should decide the threshold for screening test taking into account implications of missed diagnosis and cost of care. There is currently insufficient evidence for cancelling or delaying surgery to perform a sleep test to diagnose OSA in those with suspected disease. The best opportunity for diagnosis of OSA would come with earlier diagnosis such as in the surgical pre-assessment clinics to allow time for diagnosis and optimisation of treatment. Although AHI is the most commonly used metric for OSA other parameters such as ODI or % of time of oxygen saturation<90% from nocturnal oximetry may improve prediction of postoperative complications (Chung et al. 2014) and nocturnal oximetry may represent a useful tool for screening for OSA before surgery.

2. Intraoperative management

"Surgical stress and duration of surgery should be minimised as these have been shown to be associated with increased risk of postoperative complications. Use of regional anaesthesia when possible is preferable to general anaesthesia. Patient should be extubated when fully awake, preferably in the semi-erect position."

3. Postoperative management

"Patients with OSA at increased perioperative risk should be closely monitored at the post anaesthesia care unit for hypoxaemia with continuous pulse oximetry and other complications. Patients should be placed in non-supine position. Use of opioids and benzodiazepines should be minimised and other analgesia such NSAID's, tramadol, regional anaesthesia and dexmedetomidine for its opioid sparing effect and the lack of respiratory depression should be used preferably. CPAP should be used after the surgery in patients with known OSA. "

Use of peri-operative CPAP

CPAP acts as a pneumatic splint and prevents upper airway collapse, maintains airway patency, improves functional residual capacity, nocturnal oxygen saturations and reduces work of breathing, resulting in reduction in OSA severity with reduction in excessive daytime sleepiness and improvement in cognitive function (Engleman et al. 1994; Giles et al. 2006). It is apparent, from the presented evidence, that OSA is common in the cardiac surgical population and that it is associated with worse postoperative complications (Kua et al. 2016; Mason et al. 2017; Nagappa et al. 2017). Although CPAP is the conventional treatment for patients with OSA syndrome with established clinical and cost effectiveness (Giles et al. 2006) its effect for patients with OSA in perioperative settings has yet to be demonstrated.

A reduction in pulmonary complications, in patients without a diagnosis of OSA, undergoing thoraco-abdominal and cardiac surgery has been reported (Kindgen-Milles et al. 2005; Zarbock et al. 2009) but the evidence supporting the application of perioperative CPAP to patients with OSA is currently lacking. A recent meta-analysis of 6 studies including 904 patients showed no significant difference in post-operative adverse events between CPAP and non-CPAP treatment groups in patients undergoing general surgery (Nagappa et al. 2015). There is some evidence for improvement in cardiovascular morbidity in a retrospective cohort of 26,842 patients with OSA undergoing vascular surgery where those

not treated with positive airway pressure preoperatively were at increased risks for cardiopulmonary complications including unplanned reintubations (OR 2.5) and myocardial infarction (OR 2.6) compared with treated OSA patients (Abdelsattar et al. 2015). In one study it was noted that OSA patients who were compliant with CPAP had a reduced rate of postoperative complications (Gupta et al. 2001) and similarly in another study patients non-compliant with CPAP had a higher rate of postoperative complications (Liao et al. 2009). The effect of CPAP on patients with OSA undergoing cardiac surgery has not been examined in randomized controlled trials.

OVERALL RESEARCH AIM

The studies proposed in this thesis have examined:

1. The prevalence of undiagnosed sleep apnoea in patients attending for cardiac surgery

2. Whether undiagnosed sleep apnoea is associated with worse post-operative outcomes in patients attending for cardiac surgery

3. Whether the STOP-Bang questionnaire reliably identifies pre-operative patient with sleep apnoea attending for major cardiac surgery

4. Effect of opiates on postoperative outcomes following cardiac surgery in patients with and without sleep apnoea

5. Whether acutely administered intravenous morphine sulphate, changes the severity of OSA in patients with known moderate OSA

6. The extant literature regarding the effects of opioids/opiates and other sedative and hypnotic drugs on the severity of sleep apnoea in patients with established diagnosis of OSA.

Taken together, this thesis will inform our understanding of any excess risk associated with undiagnosed OSA in patients undergoing major cardiac surgery and of the safety of morphine, a routine post-operative analgesia, in patients with OSA.

Chapter 2

An association of sleep apnoea with postoperative outcomes in patients undergoing cardiac surgery; observational cohort study (SACS)

My personal involvement in this study includes: developing the research hypothesis as well as writing up the protocol and application for ethical approval. I have screened patients suitable for participation as well as recruited patients to the study. In addition, I have reviewed results from overnight oximetry and made decision regarding the need for CPAP treatment. Following completion of the study I have collected data on postoperative complications from patient's case notes. Statistical analysis was performed by Dr Jules-Fernandez-Sanches and Dr Linda Sharples. Dr Ian Smith helped with developing of the research hypothesis and protocol and was overlooking the whole project. I have published these results in the following papers (attached in Appendix 4):

1. Mason M, Hernandez-Sanchez J, Vuylsteke A, Smith I. Association between severity of untreated sleep apnoea and postoperative complications following major cardiac surgery: a prospective observational cohort study. Sleep Med.2017 Sep; 37:141-146

2. Mason M, Hernandez-Sanchez J, Vuylsteke A, Smith I Usefulness of the STOP-Bang questionnaire in a cardiac surgical population. J Cardiothorac Vasc Anesth. 2018 Dec;32(6):2694-2699

Null Hypothesis

Undiagnosed sleep apnoea is not a risk factor for a prolonged stay on ICU and postoperative complications in patients undergoing cardiac revascularisation surgery with and without valve surgery.

Introduction

The prevalence of OSA in the adult population has been increasing (Peppard et al. 2013). Severe OSA has been associated with increased risk of fatal and non-fatal cardiovascular events (Marin et al. 2005). OSA shares some risk factors with coronary artery disease (Mooe et al. 1996) and so while the exact prevalence of OSA among people undergoing coronary artery bypass surgery is unknown we might expect it to be higher than in the general adult population.

Association between OSA and postoperative complications in patients undergoing cardiac surgery has previously been reported in retrospective reviews and studies using screening questionnaires to diagnose OSA (Bhama et al. 2006; Kaw et al. 2006; Mungan et al. 2013; Amra et al. 2014; van Oosten et al. 2014; Zhao et al. 2015; Kua et al. 2016). Two prospective studies reported an association between OSA and postoperative atrial fibrillation and delirium in patients undergoing cardiac surgery, using respiratory polygraphy to diagnose sleep apnoea (Mooe et al. 1996; Roggenbach et al. 2014). Two subsequent prospective observational studies using polysomnography as a sleep diagnostic showed no association between OSA and adverse short term postoperative complications (Foldvary-Schaefer et al. 2015; Uchoa et al. 2015). These studies were conducted before the current study but published in 2015 shortly after completed recruitment but are also smaller than the current study.

Central sleep apnoea is characterised by pauses in breathing along with reduced or absent respiratoty effort and no apparent occlusion of the airway. It can be associated with symptoms including excessive daytime sleepiness, frequent nocturnal awakenings, or both. The International Classification of Sleep Disorders (ICSD)– 2 identifies 6 different forms of central sleep apnoea: Primary Central Sleep Apnea, Central Sleep Apnea Due to Cheyne Stokes Breathing Pattern, Central Sleep Apnea Due to Medical Condition (Not Cheyne Stokes), Central Sleep Apnea Due to High-Altitude Periodic Breathing, Central Sleep Apnea Due to Drug or Substance, and Primary Sleep Apnea of Infancy (Aurora et al. 2016). The

underlying pathophysiology of central sleep apnea is due to hyperventilation such as in congestive heart failure, high altitude sickness, and primary central sleep apnoea or hypoventilation in patients with central nervous system disease, neuromuscular disease, or severe abnormalities in pulmonary mechanics, for example kyphoscoliosis. Cheyne-Stokes respiration is characterized by an absence of air flow and respiratory effort which is followed by hyperventilation (a crescendo-decrescendo pattern). Cheyne-Stokes respiration most often occurs in patients with congestive heart failure. The prevalence is estimated to be approximately 30% to 40% in patients with congestive cardiac failure (Aurora et al. 2016). However, this respiratory pattern can also be seen in patients with stroke or renal failure. There are no published data on its impact on surgical outcomes though it has been implicated in adverse outcomes for patients with cardiac disease (Aurora et al. 2012).

There is currently limited evidence specifically linking OSA or central sleep apnoea, to postoperative complications. Moreover, there are currently no data showing that the application of perioperative continuous positive airway pressure therapy to patients with sleep apnoea reduces the risk of perioperative complications (Nagappa et al. 2015). Despite this lack of robust evidence screening pre-operatively for OSA is now the norm in some parts of the United Kingdom, leading to additional National Health Service cost and a potential delay in surgery. I designed a prospective observational study to examine whether untreated sleep apnoea is associated with prolonged ICU stay and increased frequency of postoperative ICU complications, in patients undergoing major cardiac surgery.

Methods

Design

This prospective observational cohort study recruited patients who were undergoing elective CABG with or without cardiac valve surgery at Papworth Hospital, a specialist cardiothoracic centre. Patients were screened for sleep apnoea the night before their

surgery. The primary aim of the study was to assess whether sleep apnoea was associated with a prolonged stay in ICU.

Ethical approval was granted by The National Research Ethics Service East Midlands Northampton Proportionate Review Sub-committee on 20 December 2012 (12/WM/0433). All participants who agreed to enter the study gave signed, informed consent.

This study was conducted at Papworth Hospital NHS Foundation Trust. Papworth Hospital is cardiothoracic hospital with a 32 bedded critical care area and eight cardiac recovery beds dedicated to the care of patients for the first 24 hours following cardiac surgery. The Respiratory Support and Sleep Centre (RSSC) is a Tertiary Centre with specialist expertise in various sleep disorders including the diagnosis, treatment and follow up of patients with OSA. Patients in this study were recruited from the adult patients population attending surgical preadmission clinics and undergoing elective surgical coronary artery revascularisation with or without cardiac valve surgery. The majority of surgical procedures undertaken at Papworth Hospital cardiothoracic unit include coronary artery revascularisation surgery with or without valve surgery. To minimise recruitment bias it was felt essential to recruit patients from the homogeneous surgical cohort and as many patients undergoing CABG surgery will simultaneously undergo cardiac valve surgery and vice versa and as the complexity of these surgical interventions was considered similar, patients undergoing such surgical interventions were chosen.

Population

Inclusion Criteria

- Age >18 years

- Listed for elective surgical coronary revascularisation with or without cardiac valve surgery

<u>Exclusion Criteria</u>

- Inability to give informed consent or comply with the protocol

- Emergency surgical coronary revascularization or valve surgery

- Tracheostomy before surgery

- Enrolment in another concurrent interventional research study likely to impact of study outcomes

Eligible participants were admitted on the night before surgery and had medical history and clinical measurements recorded including weight, height, body mass index and neck circumference. All participants completed the STOP-Bang questionnaire and Epworth Sleepiness Scale. The EuroSCORE, a mortality risk score developed for patients undergoing cardiac surgery, was calculated for all patients (Nashef et al. 1999). It is an additive score of predicted post-operative mortality, where scores of 1-2 determine low risk group with predicted post-operative mortality rate of 0.8%, scores of 3-5 put patients in medium risk group with predicted mortality of 3% and scores of >6 reflect high risk group with predicted mortality of 11%. The risk factors incorporated in the additive EuroSCORE include: age, gender, presence of chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction disease, previous cardiac surgery, serum creatinine >200 micromol/Lilitre preoperatively, active endocarditis, critical preoperative state, unstable angina, LV dysfunction, recent myocardial infarct, pulmonary hypertension, emergency procedure, other than isolated CABG, surgery on thoracic aorta, post-infarct septal rupture.

The STOP-Bang questionnaire has been developed and validated as a pre-operative screening tool for assessing the risk of OSA in general surgical population in 2008 by Chung *et al* (Chung et al. 2008). It is a self-administered and easy to use tool comprising eight questions with yes/no responses, each positive response scoring one point. A high risk of sleep apnoea has been defined as a score of ≥3 and a low risk as a score 0-2. (Figure 2.1)

Figure 2.1 STOP-Bang Questionnaire

STOP-BANG Questionnaire

S – Snoring: Do you snore loudly?

T – Tired: Do you feel tired, sleepy during daytime?

O – Observed: Has anyone observed you stop breathing during sleep?

P – Blood Pressure: Are you being treated or had you been treated for hypertension?

B – BMI: Body mass index > 35

A – Age: Age over 50 years

N – Neck: Neck circumference greater than 40 cm

G – Gender: Male gender

The Epworth sleepiness scale was introduced in 1991 by Dr Murray Johns of Epworth Hospital in Melbourne, Australia. The ESS in an internationally accepted scale used to assess patient's subjective daytime sleepiness. It estimates the chance of falling asleep in eight different situations where subjects rate their tendency to fall asleep on a scale of 0 to 3. 0= no chance of dozing, 1=mild chance, 2=moderate chance and 3 a high chance of dozing. A score of <11 is considered to be normal and a value of ≥ 11 suggests excessive daytime sleepiness (Figure 2.2).

Figure 2.2. The Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male=M, Female=F): _____

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

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

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

It is important that you answer each question as best you can.

Situation   **Chance of Dozing (0-3)**

Sitting and reading _____ ____

Watching TV _____ ____

Sitting, inactive in a public place (e.g., a theatre or a meeting) _____ ____

As a passenger in a car for an hour without a break _____ ____

Lying down to rest in the afternoon when circumstances permit _____ ____

Sitting and talking to someone _____ ____

Sitting quietly after a lunch without alcohol _____ ____

In a car, while stopped for a few minutes in the traffic _____

THANK YOU FOR YOUR COOPERATION

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Outcome measures

A range of objective outcome measures were used.

Pulse Oximetry: Patients were screened for the presence of sleep apnoea with nocturnal oximetry (Konica-Minolta PULSOX-300i) while self-ventilated on room air the night before surgery. Finger probes were used (Figure 3.1) with a wristwatch oximeter with a 300 hour memory capacity, resolution of 0.1% SpO2, stored at 1Hz and 30 hr battery life. These data are downloaded to and stored centrally by the RSSC on a single server and analysed using an automated system (Download 2000, Stowood Scientific instruments, Oxford, UK). Calculated values for the period monitored include a 4% desaturation index (number of desaturations of 4% or over per hour), mean heart rate, mean and minimum SpO2 values.

Sleep apnoea was defined as an arterial oxygen desaturation index (ODI=dips of oxygen greater than 4% or more, per hour sleep) of greater than 5 measured using nocturnal oximetry. Records without at least 4 hours adequate recording time were excluded as per our local practice.

Figure 2. 3. Nocturnal oximetry (Konica-Minolta PULSOX-300i)

Figure 2.4. An example of recording from nocturnal oximetry

Intermittent oxygen desaturations during the night consistent with sleep apnoea
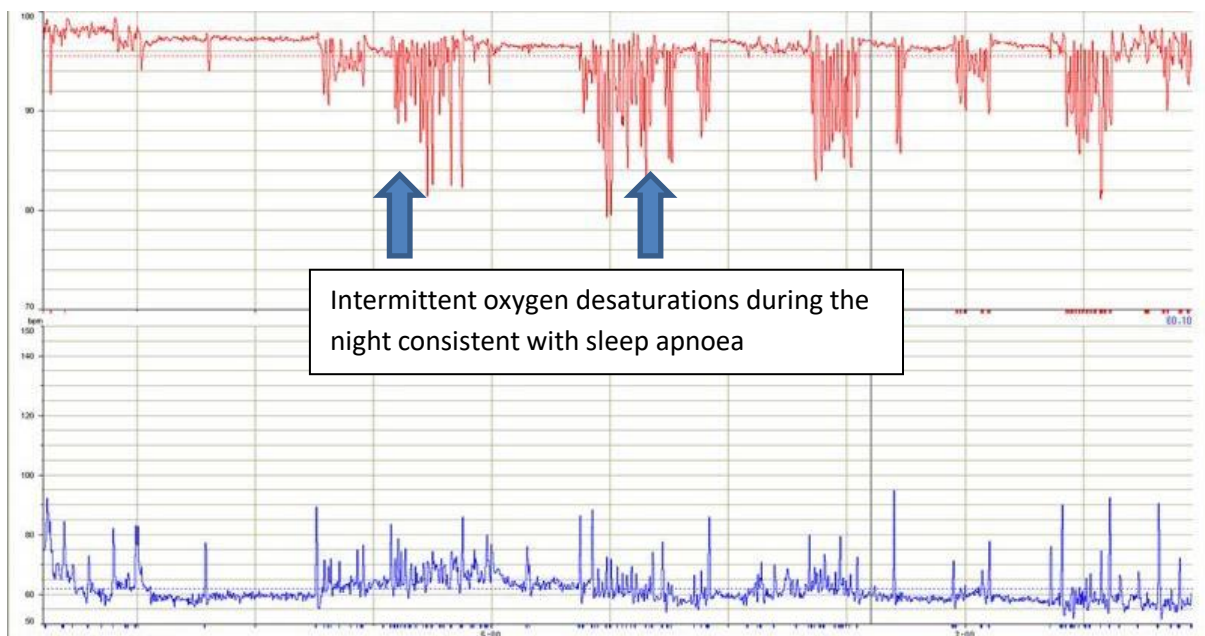
The primary outcome variable was length of stay (LoS) in the ICU, measured from arrival to ICU to discharge. Secondary outcomes included:

- duration of invasive ventilation (from intubation in theatre until extubation on ICU),

- need for continuous positive airway pressure (CPAP)/bi-level positive pressure ventilation after extubation,

- need for re-intubation,

- occurrence of new arrhythmias necessitating further monitoring or drug treatment or other intervention,

- need for additional organ support (intra-aortic balloon pump/ haemofiltration),

- major organ complication requiring further monitoring, treatment or other intervention including: cardiovascular, respiratory, renal, neurological, hepatic, coagulation,

- readmission to ICU

- 30 days mortality.

Recruitment

We recruited patients over 18 years of age, undergoing elective cardiac surgery and excluded patients who were participating in other interventional studies, those not able to give informed consent or comply with the protocol and patients with a tracheostomy before surgery. In addition, patients requiring emergency CABG/valve surgery and those admitted on the day of surgery (thereby not allowing in hospital overnight oximetry the night before surgery) were excluded. Some patients were subsequently excluded as intraoperative events or findings led them to have a different operation which did not meet our entry criteria. Patients with a previous diagnosis of OSA treated with CPAP were excluded from the final analysis (Figure 2.5).

Figure 2.5. Study Consort diagram

```
┌─────────────────────────┐          ┌─────────────────────────────┐
│ 332 patients assessed   │          │ 4 ineligible (enrolment in  │
│ for eligibility         │          │ other studies)              │
│                         │          │                             │
│                         │          │ 44 ineligible (not meeting  │
│                         │          │ inclusion criteria due to   │
│                         │ ───────▶ │ type of surgery)            │
│                         │          │                             │
│                         │          │ 132 did not wish to         │
│                         │          │ participate                 │
└───────────┬─────────────┘          └─────────────────────────────┘
            │
            ▼
┌─────────────────────────┐          ┌─────────────────────────────┐
│ 152 patients enrolled   │          │ 16 excluded (insufficient   │
│ in the study and        │          │ sleep study, technically    │
│ underwent preoperative  │          │ poor or less than 4 hours   │
│ evaluation and          │          │ recording)                  │
│ overnight sleep study   │          │                             │
│                         │          │ 7 excluded from final       │
│                         │ ───────▶ │ analysis as not meeting     │
│                         │          │ inclusion criteria due to   │
│                         │          │ type of surgery, changed    │
│                         │          │ ad hoc according to         │
│                         │          │ clinical needs              │
│                         │          │                             │
│                         │          │ 7 patients with previous    │
└───────────┬─────────────┘          │ diagnosis of OSA and using  │
            │                        │ CPAP                        │
            ▼                        └─────────────────────────────┘
┌─────────────────────────┐
│ 122 patients included   │
│ in final analysis       │
└─────────────────────────┘
```

Data Collection

Patients underwent inpatient overnight oximetry (Konica-Minolta PULSOX-300i) while self-ventilating in room air on the night prior to their surgery. The oximetry results were automatically analyzed (Visidownload, Stowood Ltd, Oxford UK) and reviewed by a sleep physician, blinded to all clinical data. The anesthetic and surgical teams had no access to the results of preoperative nocturnal oximetry. Since oximetry alone cannot differentiate obstructive from central apnoea, the results are reported as sleep apnoea, which was diagnosed in patients with an arterial oxygen desaturation index (ODI) ≥ 5. The ODI was defined as the number of dips in oxygen saturations of greater than 4% relative to the moving average, per hour of sleep. The oximeter was programmed to average measurements over 1 second. As per our usual clinical practice, oximetry records without at least 4 hours of adequate data were excluded. Demographic variables, co-morbidities and the Epworth Sleepiness Scale (ESS) score (Johns 1991) were recorded on the night of

admission for surgery. The EuroSCORE, a mortality risk score developed for patients undergoing cardiac surgery, was calculated for all patients (Nashef et al. 1999).   Data regarding postoperative complications were collected from the digital Clinical Information System in the ICU.

Outcomes

The primary outcome was length of stay (LoS) in ICU (days) a key performance indicator for assessing impact on resources. The secondary outcome was a composite measure of post-operative complications in ICU that included: use of continuous positive airway pressure/bi-level positive pressure ventilation via a mask after extubation, re-intubation, occurrence of new arrhythmias necessitating drug treatment or intervention, need for additional organ support (intra-aortic balloon pump/ haemofiltration), major organ complication (defined as those requiring treatment or intervention for cardiovascular, respiratory, renal, neurological, hepatic, coagulation issues), readmission to ICU and 30 days mortality.

Predictor variables

The primary predictor in all models was ODI analysed as a continuous variable. In view of its clinical relevance, sleep apnoea was divided into categories according to the ODI: mild if ODI ≥ 5 but <15, moderate if ODI was ≥ 15 but <30 and severe when ODI ≥ 30. Additional predictor variables thought to be risk factors relevant to the outcomes included EuroSCORE, age, body mass index, surgery type, administration of intravenous opioid analgesia (either intravenous morphine sulphate or fentanyl) during the ICU stay, comorbidities and mean nocturnal oxygen saturations from the pre-operative oximetry. Although the euroSCORE has been reported to be the best predictive score of mortality for patients undergoing cardiac surgery, certain risk factors within the euroSCORE may have different statistical weight for predicting morbidity and thus individual components of the euroSCORE were used as additional predictor variables (Geissler et al. 2000).

Administration of opioids was selected as a predictor due to previously reported effects including suppression of ventilatory drive and reduction of upper airway dilator muscle activity, potentially exposing patients with sleep apnoea to additional risk (Kaw et al. 2006).

Sample size

Through discussion with the Critical Care Team we determined a watershed LoS in ICU at 36 hours. Unpublished historical clinical data showed LoS<36 hours for approximately 75% of patients. The null hypothesis was that patients with sleep apnoea (ODI≥5) did not remain on ICU for >36 hours more frequently than patients without sleep apnoea. Fifty seven patients with sleep apnoea, and the same number without, were required to achieve 80% power at 5% significance with a 2-sided test for proportions, assuming the proportion of individuals staying longer than 36 hours at ICU was 40% in the presence of sleep apnoea compared to 15% in its absence (based on unpublished internal preliminary data).

Statistical analyses

A parametric accelerated failure time model (Weibull regression) was used to analyse LoS as a continuous response to preselected predictor variables.

Postoperative complications were dichotomised (yes/no) and analysed with a binary logistic regression. The same predictors used to analyse LoS (except complications) were used.

For all regressions, parsimonious models were developed using a combination of, removing predictors, step-wise and manually, and interactions that did not reach 5% significance level.

Results

All patients older than 18 years, between March 2013 and July 2014, were screened and contacted by letter prior to surgery. A total of 152 patients consented to participate in the study, of whom 30 were subsequently excluded (Figure 2.5). Of the 122 patients remaining,

57 (47%) had a new diagnosis of sleep apnoea. Table 2.1 shows characteristics of study

participants.

Table 2.1 Baseline characteristics of study subjects

Demographics	All n=122	No Sleep Apnoea (ODI<5/hr) n=65 (53%)	Sleep Apnoea (ODI≥5/hr) n=57 (47%)	p
Age yrs	70.3 (0.80)	70.6 (1.08)	69.9 (1.19)	0.69[a]
BMI kg/m^2	29.0 (0.42)	28.0 (0.52)	30.1 (0.64)	0.01[a]
ODI	6.2 (0.49)	3.0 (0.16)	11.3 (0.94)	<0.001[a]
Mean SpO$_2$	94.4 (0.29)	94.4 (0.43)	93.5 (0.39)	0.12[a]
ESS	6.5 (0.32)	6.2 (0.43)	6.7 (0.49)	0.47[a]
EuroSCORE	4.7 (0.27)	4.5 (0.36)	4.9 (0.41)	0.52[a]
LVEF	55.7 (1.31)	58.0 (1.37)	52.7 (2.3)	0.05[a]
Male	107 (88%)	57 (88%)	50 (88%)	1[b]
Smoking				0.88[b]
Non smoker	44 (36%)	24 (37%)	20 (35%)	
Ex-smoker	69 (57%)	37 (57%)	32 (56%)	
Smoker	9 (7%)	4 (6%)	5 (9%)	
Habitual snorers				0.78[b]
Never	20 (16%)	12 (18%)	8 (14%)	
Sometimes	75 (61%)	40 (62%)	35 (61%)	
Most Nights	23 (19%)	11 (17%)	12 (21%)	
Diabetes mellitus II	38 (31%)	17 (26%)	21 (37%)	0.24[b]
COPD	12 (10%)	6 (9%)	6 (11%)	1[b]
IOA	70 (57%)	39 (60%)	31 (54%)	0.58[b]
CABG	84 (69%)	43 (66%)	41 (71%)	0.56[b]

Continuous variables: mean (standard error); Categorical variables: total (% out of 122 patients); IOA: Intravenous Opiate Analgesia (administration of morphine sulphate in terms of patient controlled analgesia (n=66) or intravenous fentanyl (n=4)); CABG: Coronary artery bypass grafting without valve replacement/repair (the other interventions included CABG and valve); BMI: body mass index; ODI: 4% oxygen desaturation index; ESS: Epworth Sleepiness Scale score; LVEF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease. a: t-test, b: Fisher's exact test

Primary Outcome Analysis

The ICU LoS varied from 0.6 to 27 days with 88 patients (72%) remaining on ICU for 36 hours or less. The median LoS in ICU was 0.95 days (95%CI 0.91-1 days) [Figure 2.6]. There was no significant association between ODI and ICU LoS (HR 1.0, 95% CI 0.99-1.02;

p=0.12). The most significant association with ICU LoS was the presence of postoperative complications in ICU (HR 3.7, 95% CI 2.8-4.8; p<0.001). Multivariate analysis showed that the effect of complications on LoS was the same across both surgical interventions (CABG and CABG/valve surgery).

Fig 2.6. **Kaplan-Meier cumulative probability of being discharged from ICU alive ("recovery") over time, with 95%CI**
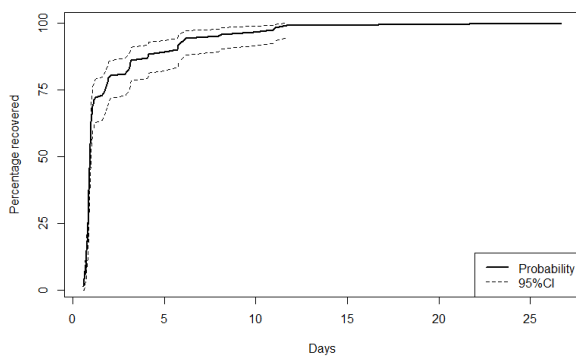
All patients stayed in the ICU for one night of observation, irrespective of the time of day they were admitted after surgery. Patients operated on earlier in the day were more likely to stay in the ICU over 24 hours than those admitted to ICU at the end of the day but no association between finishing time of surgery and LoS in ICU was found among patients who stayed in ICU 36 hours or less, using a simple linear regression of LoS in ICU onto finishing time of surgery (R^2=46%, p=0.24).

An association between opioid use and LoS in ICU was examined. There was no significant association between intravenous opioid analgesia and LoS on ICU. The hazard ratio for intravenous opioid analgesia (yes/no) on ICU LoS was 0.866 with CI=(0.693 to 1.083), p=0.205.

Secondary Outcome Analysis

Thirty six patients (30%) met our criteria for postoperative complications. Of these, 21 (58%) had sleep apnoea. The frequency and type of encountered complications are

described in Table 2.2. Patients with sleep apnoea were found to have significantly higher frequency of cardiovascular (p=0.05) and renal (p=0.02) complications, compared to patients without sleep apnoea. The majority of cardiovascular complications consisted of shock requiring treatment including fluid resuscitation and/or inotropic support and the majority of renal complications included acute kidney injury requiring treatment.

Table 2.2 Frequency and type of ICU complications in patients with and without sleep apnoea

Complication	No Sleep Apnoea ODI<5/hr (n=65)	Sleep Apnoea ODI≥5/hr (n=57)	p
Cardiovascular	3 (3%)	9 (7%)	0.05
Respiratory	7 (6%)	12 (10%)	0.14
Neurological	2 (2%)	2 (2%)	1
Renal	2 (2%)	9 (7%)	0.02
Coagulation	2 (2%)	2 (2%)	1
Arrhythmia	12 (10%)	8 (7%)	0.63
Infection	4 (3%)	2 (2%)	0.68
Reintubation	3 (3%)	2 (2%)	1
CPAP/bi-level PAP	8 (7%)	9 (7%)	0.61
30 days mortality	3 (3%)	2 (2%)	1
ICU readmissions	3 (3%)	1 (0%)	0.62

There was a significant association between ODI and postoperative complications in the ICU (OR=1.1 for each unit increase in ODI; 95% CI 1.02-1.17; p=0.014), that is the probability of developing complications rose with increasing ODI, hence severity of sleep apnoea (Figure 2.7). As an example of 100 patients with euroSCORE=5 and ODI of 20 we would predict approximately 1/3rd would have a post-operative complication. The other independent predictors of postoperative complications were administration of intravenous opioid analgesia, in particular morphine sulphate and fentanyl, (OR=3.6; 95% CI 1.41-10.06; p=0.010) and euroSCORE (OR=1.3; 95% CI 1.15-1.61; p<0.001) [Table 2.3]. BMI was not found to be an independent predictor of complications.

Table 2.3 Independent predictors for development of ICU complications

Variable	OR	95% CI	p
IOA **(Intravenous opioid analgesia)**	3.6	1.41-10.06	P=0.010
euroSCORE	1.3	1.15-1.61	p<0.001
ODI **(4% oxygen desaturation index)**	1.1	1.02-1.17	P=0.014

Sleep apnoea was found to have the strongest effect on postoperative complications. Patients with sleep apnoea, but also those without who received intravenous opioids during their stay in ICU, had a higher probability of suffering postoperative complications with little difference in the absolute risk increase (Table 2.4). In the same table, the relative risk appears higher for patients without sleep apnoea reflecting low baseline risk of suffering complications in patients without sleep apnoea. No significant association was found between dose of intravenous opioids and the risk of postoperative complications (OR=1; 95% CI = 0.98, 1.04; p=0.62). This could be due to the loss of statistical power as only 70 out of 122 patients received intravenous opioids. Compared to patients without sleep apnoea those with received more intravenous opioid, 17.5mg vs 21mg, but this difference was not statistically significant (p=0.51).

Figure 2.7. Predicted probabilities of suffering a complication at Intensive Care Unit in patients with a euroSCORE=5, according to sleep apnoea severity and administration of intravenous opioid analgesia
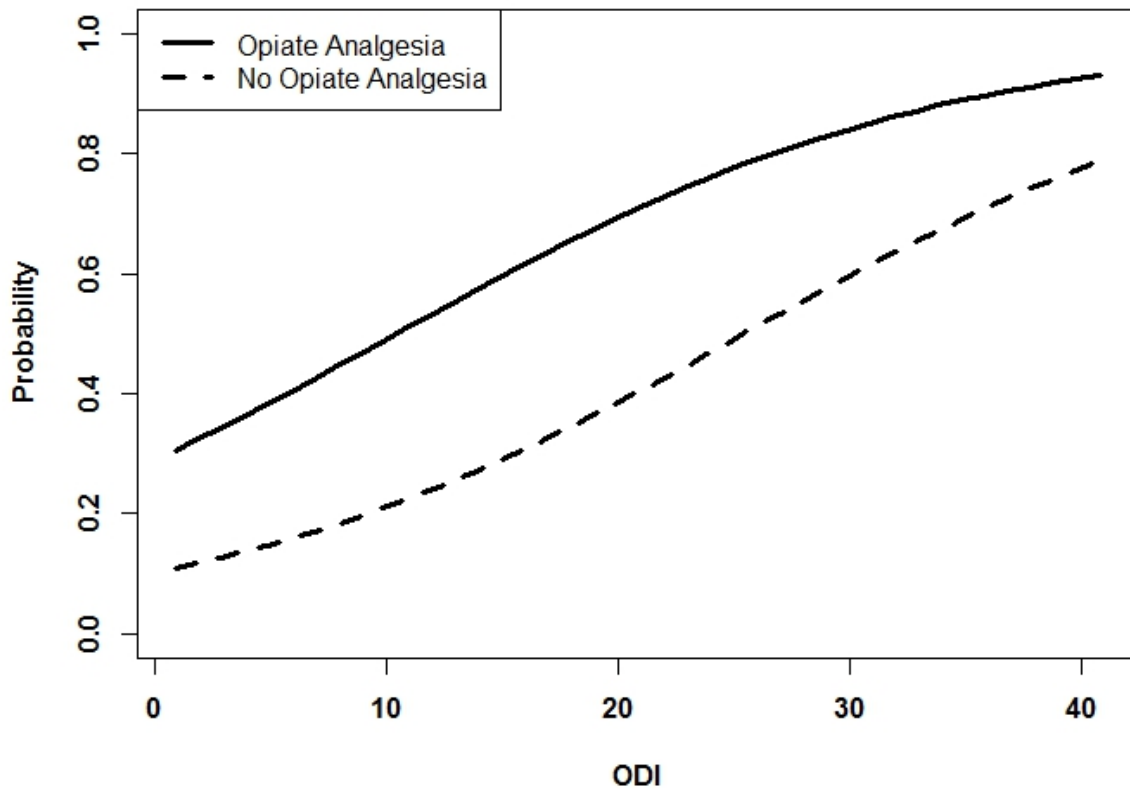
Table 2.4 Predicted percentage of patients with postoperative complications according to sleep apnoea severity and administration of additional intravenous opioid analgesia (IOA), in patients with euroSCORE 5

	No SA (ODI 3/hr)	Mild SA (ODI 8/hr)	Moderate/Severe SA (ODI 22/hr)
No IOA / IOA	13% / 35%	19% / 45%	44% / 74%
ARI / RRI	0.22 / 2.7	0.26 / 2.4	0.30 / 1.7

Predicted proportions are representative of patients with euroSCORE of 5 and ODI of 3/hr, 8/hr and 22/hr. These values were the observed mean euroSCORE and mean ODI in each SA severity class in our study population. ARI: absolute risk increase; RRI: relative risk increase

Discussion

The results of this study show that untreated sleep apnoea in a population of patients undergoing major cardiac surgery at Papworth Hospital is associated with an increased risk of postoperative complications, even though no significant association was found with LoS in ICU. The LoS in ICU was chosen as the primary outcome for the study, due to its tangible impact on healthcare cost and resources. In contrast a previously reported study, of retrospective national database data for 530,089 patients undergoing orthopaedic surgery, found a significant association between sleep apnoea and utilization of critical care resources and lengths of stay (Memtsoudis et al. 2014). In that study sleep apnoea had been previously diagnosed, which may indicate a different degree of physiological impact compared to the largely asymptomatic patients found on screening in the currentstudy. In addition, asymptomatic sleep apnoea was not excluded in the comparator group. Both of these points are relevant in any discussion of the value of screening surgical patients for sleep apnoea. However it is possible that the negative finding in the current study may be

due to the smaller cohort size. It may also reflect a difference due to surgical procedure and patient cohort.

ICU discharge is a complex process and depends on local policies and the availability of beds on the receiving ward over and above the clinical condition of the patient. It has previously been reported that institutional polices regarding ICU discharge affect ICU LoS (Widyastuti et al. 2012). Although there was no significant correlation between finishing time of surgery and LoS in ICU among patients who stayed in ICU 36 hours or less, for future studies the incidence of complications may represent a more appropriate study primary outcome.

Previous retrospective analyses reported a relationship between OSA and postoperative complications in patients undergoing cardiac surgery. Three studies demonstrated an increased risk of atrial fibrillation following CABG surgery (Mooe et al. 1996; Mungan et al. 2013; van Oosten et al. 2014), two studies reported prolonged mechanical ventilation (Bhama et al. 2006; Amra et al. 2014), three prolonged ICU and hospital length of stay (Bhama et al. 2006; Kaw et al. 2006; van Oosten et al. 2014) and one, post-operative infection and encephalopathy (Kaw et al. 2006). In contrast, 3 studies found no association between OSA and post-operative complications in patients undergoing CABG (Netzer et al. 1999; Foldvary-Schaefer et al. 2015; Uchoa et al. 2015), two of which were of prospective design and used polysomnography to screen for OSA. A possible reason why Foldvary-Schaefer did not show positive association between OSA and postoperative complications could have been small sample size as due to difficulty in recruitment the study was terminated earlier before reaching target sample size (Foldvary-Schaefer et al. 2015). Another possible explanation is that enhanced care and observation after major cardiac surgery mitigates the impact of OSA on postoperative outcomes. The study of Uchoa et al. was negative for short term, 30 days, postoperative complications, but in the longer term (mean follow up of 4.5 years) OSA was associated with increased risk of a need for new revascularization (19% vs 0%, p=0.01), episodes of typical angina (30% vs 7%, p=0.02) and

atrial fibrillation (22% vs 0%, p=0.007). As described in Chapter 1, OSA has been associated with endothelial dysfunction, increased inflammation, oxidative stress, and surges in sympathetic drive which may contribute to progression of atherosclerosis in the longer period following cardiac revascularisation surgery. Furthermore, the majority of patients in the current study as well as in the previous studies (Foldvary-Schaefer et al. 2015; Uchoa et al. 2015) were found to have impaired ejection fraction and it is possible that longer term impact of OSA on heart remodelling may be a contributory factor in triggering AF in these patents following cardiac surgery. The results of the current study raise an important question of the longer term clinical and economic impact of OSA, beyond the postoperative period as well as the role of screening for OSA in this high risk population and more importantly the role of treatment, on both, short and long term outcomes. Further research is needed to answer these important clinical and economic questions.

A recent prospective study reported that OSA may be a risk factor for postoperative delirium (Roggenbach et al. 2014). Other studies reporting an association between sleep apnoea and atrial fibrillation show conflicting results. Two studies (Mungan et al. 2013) and (van Oosten et al. 2014) used sleep questionnaires to diagnose sleep apnoea and reported a positive association. Mooe et al. who recorded prospective pre-operative sleep studies (Mooe et al. 1996) also reported a relationship between ODI and post-operative atrial fibrillation. Interestingly, no association was found between AHI and AF which raises the possibility that intermittent nocturnal hypoxiaemia is the main contributor to postoperative arrhythmia in this patient cohort. Other studies, (Uchoa et al. 2015) and (Unosawa et al. 2012), however, found no significant difference in the risk of developing postoperative AF in patients with, compared to patients without sleep apnoea. Similarly, there was not a significant difference in frequency of postoperative arrhythmia in patients with sleep apnoea, compared to those without such a diagnosis in the study reported in this thesis. The reason for this disagreement is not obvious and may require further, larger studies to settle the question.

There was an association of sleep apnoea with postoperative complications, in particular cardiovascular, and renal (AKI) in the current study. An association between sleep apnoea and postoperative AKI was reported in a recent retrospective analysis of prospectively collected data in a multi-ethnic Asian population. In this study sleep apnoea was defined as AHI≥15, diagnosed using a monitor of peripheral arterial tone, and as in our study no distinction between obstructive and central sleep apnoea was made (Kua et al. 2016). Although different mechanisms of OSA may predominate in Asian and Caucasian populations, our study, in a Caucasian population complements this previous evidence.

I have extended this evidence showing that even patients with mild sleep apnoea in my series presenting for CABG or CABG and valve surgery had a higher risk of postoperative complications and that this risk increased with the severity of sleep apnoea. Up until now, only one previous retrospective study reported an association between severity of sleep apnoea and risk of postoperative outcomes in patients undergoing various general surgical procedures (Mutter et al. 2014). In view of the observational nature of my study it must be noted that it is not possible to confirm the causal relationship between sleep apnoea and the risk of postoperative complications reported in this thesis.

Another predictor which associated with postoperative complications in our patients was the administration of intravenous opioids on ICU. It is proposed that opiates/opioids could worsen the severity of OSA in perioperative settings due to their effect on ventilatory drive and upper airway dilator muscles (Kaw et al. 2006) but it is also reported that in the majority of OSA patients, with frequent obstructive events and mild-to-moderate hypoxemia, the sedative effect of opioids may stabilise airway patency and breathing and paradoxically improve OSA (Wang et al. 2013). In my cohort of patients the majority had mild or moderate sleep apnoea.

In the current study, patients with sleep apnoea, but also those without were found to be at higher risk of postoperative complications when given postoperative opioids and the

absolute risk increase did not differ significantly between the diagnostic groups, that is patients with and without sleep apnoea. I have not found that intravenous opioids lengthened overall LoS but they did lengthens LoS in the CABG+valve type surgery. Although speculative, it is possible, that patients requiring intravenous opioids were a generally more vulnerable sub-population. As described in Chapter 1 in paragraph "Opiates and opioids in OSA", both intermittent hypoxia and sleep disruption augment pain, but intermittent hypoxia may potentiate opioid analgesic responses. Contrary to this hypothesis when I assessed the dose of opioids required for postoperative analgesia, patients without sleep apnoea compared to those with received on average less intravenous opioid, 17.5mg vs 21mg, a not significant difference. Clearly we failed to show lower doses in sleep apnoea patients.

The result of my study complements the evidence for high prevalence of sleep apnoea (47% for ODI≥5/hr) amongst patients undergoing cardiac revascularisation procedures. In the two prospective studies in patients undergoing CABG surgery, undiagnosed OSA (AHI ≥5/hr) was found in 74% and 87% of patients on nocturnal polysomnography (Foldvary-Schaefer et al. 2015; Uchoa et al. 2015). The majority of breathing events in one study were reported as hypopneas and although polysomnography was used the authors comment on the inability to distinguish between obstructive and central hypopneas (Foldvary-Schaefer et al. 2015). It is possible that patients with central sleep apnoea were included in the quoted prevalence. The higher prevalence in these studies, compared to prevalence in the current study, may be explained by the diagnostic methods used. The severity of sleep disordered breathing recorded on polysomnography is likely to be higher than oximetry as the presence of apnoea or hypopnoea can be scored against 3% ODI and nocturnal arousals.

With regards to patients' demographics, the current study showed that patients with sleep apnoea had significantly higher BMI, which is the strongest risk factor for OSA (Peppard et al. 2000) but there was no significant difference between the sleep apnoea and

non-sleep apnoea groups, in terms of other conventional risk factors for OSA such as age or sex. One possible explanation for this finding may be that patients presenting for cardiac revascularisation surgery in general (but also in this study) do not represent a typical OSA cohort but are older (mean age 70yrs) and more predominantly male (88%).

One demographic factor found in this patient cohort undergoing CABG surgery which has also previously been reported in aforementioned studies by Uchoa et al and Foldvary-Schaefer etal. is that patients with sleep apnoea have lower left ventricular ejection fraction compared to those patients without sleep apnoea. An association of OSA and heart failure has previously been reported in the Sleep Heart Health Study of 6424 participants where OSA (defined as AHI ≥11/h) conferred a 2.38 relative increase in the likelihood of having heart failure, independent of other known risk factors (Shahar et al. 2001). In the two large case series of patients with heart failure undergoing polysomnography, OSA was identified in 37% of 450 participants (Javaheri et al. 1998) with the prevalence of OSA greater in men (38%) than in women (31%) (Sin et al. 1999). The reported risk factors for OSA differed between men and women with the main risk factor in men being obesity, whereas in women it was older age. Patients with OSA and concomitant heart failure and peripheral vascular disease have previously been shown to have asymptomatic OSA (Somers et al. 2008; Utriainen et al. 2013). Similarly, the current cohort of patients, with significant ischaemic heart disease, presents in the main with asymptomatic sleep apnoea. There was no significant difference in mean ESS between patients with sleep apnoea and those without: 6.2 (0.43) vs 6.7(0.49).

This study has limitations. Firstly, it is not possible to distinguish between central and obstructive sleep apnoea with nocturnal oximetry alone. In the UK, around two thirds of respiratory sleep studies do employ just oximetry (Flemons et al. 2004). A high resolution oximeter represents an economical and practical screening tool prior surgery and an ODI >10 was previously found to have a sensitivity of 93% and specificity of 75% against respiratory polygraphy to detect moderate and severe OSA in patients undergoing general

surgery (Chung et al. 2012). For the current study we were not able to perform respiratory polygraphy for practical reasons, mainly as respiratory polygraphy was felt to be more disruptive to the patient's sleep on the night before major surgery. In addition, relying on Electronic Medical Records as the main source of postoperative complications is opened to recording bias as not all of the complications may have been strictly recorded. There was a high rate of non-recruitment from potentially eligible participants which may affect the generalisation of our results.

Conclusion

Despite its limitations, this study is the first prospective study using recognised a sleep diagnostic that reports an association of increasing severity of sleep apnoea with postoperative complications in patients undergoing CABG and CABG/valve surgery. Interestingly, even patients with ODI 5-15/hr , often regarded as clinically insignificant, had a higher probability of developing post-operative complications than patients with no desaturations overnight preoperatively. There was no association between sleep apnoea and ICU LoS. This negative finding may be due a relatively small sample size in the current study or local discharge policy in ICU and larger future studies may clarify this finding. We also found that intravenous opioids administered after surgery were independently associated with postoperative complications both in patients with and without sleep apnoea.

Future directions

Acknowledging the study's limitations, my results raise an interesting question worth further research. Examining the literature, the effect of opiates and opioids on post-operative outcomes in patients with sleep apnoea has to date been described in case reports and one retrospective review only (Esclamado et al. 1989; Ostermeier et al. 1997). The results of this study complement existing literature on the importance of sleep apnoea as a predictor of postoperative morbidity. There are currently no randomised controlled trials reporting any effects of perioperative continuous positive airway pressure on postoperative complications

in patients with OSA and the results of this study strengthen the case for further research to assess the clinical and economic impact of perioperative treatment with continuous positive airway pressure.

Chapter 3

Utility of the STOP-Bang questionnaire in cardiac surgical cohort

Null Hypothesis

The STOP-Bang questionnaire cannot reliably identify patients at high risk of sleep apnoea and postoperative complications in pre-operative setting, in patients presenting for major cardiac surgery.

Introduction

In Chapter 2, I have reported a significant association between sleep apnoea (defined as continuous variable of ODI) and post-operative complications, in particular cardiovascular and renal, in patients with newly diagnosed, untreated sleep apnoea. The aim of the study reported in this Chapter was to examine if the STOP-Bang questionnaire is a useful tool to identify patients who may benefit from a sleep study, such as oximetry, which in turn might identify those patients who are at higher risk of developing postoperative complications. I have also examined if the STOP-Bang score can predict those patients with worse postoperative outcomes.

The STOP-Bang questionnaire was developed and validated in a general surgical population (Chung et al. 2008) and has been adopted as a screening tool in surgical pre-

assessment clinics for its ease of use. In systematic reviews of screening questionnaires for OSA, the STOP-Bang questionnaire had the highest methodological validity, moderately high sensitivity and best negative predictive value for assessing the risk of moderate/severe OSA (Abrishami et al. 2010; Chiu et al. 2017). It was found that the higher the STOP-Bang score the greater the probability of OSA (Nagappa et al. 2015) and a high risk STOP-Bang score could predict an increased risk of postoperative pulmonary and cardiac complications in patients undergoing various surgical procedures (Nagappa et al. 2017). In the STOP-Bang validation studies, selection bias and high prevalence of OSA in the studied population may have influenced the results and therefore validation in specific target populations has been recommended (Chung et al. 2016). To my knowledge, the STOP-Bang questionnaire has not previously been validated in a surgical cohort undergoing cardiac bypass and valve surgery.

In this study of patients undergoing elective coronary artery bypass grafting (CABG) with or without cardiac valve surgery, I examined the diagnostic performance of the STOP-Bang questionnaire against an arterial oxygen desaturation index (ODI = number of dips of greater than 4% or more, per hour sleep), from nocturnal oximetry. I also explored associations between STOP-Bang scores and post-operative outcomes.

Methods

Ethical approval for this prospective observational cohort study was granted by The National Research Ethics Service East Midlands Northampton Proportionate Review Sub-committee (12/WM/0433). All participants who agreed to enter the study gave signed, informed consent.

Population cohort

Population

<u>Inclusion Criteria</u>

- Age >18 years

- Listed for elective surgical coronary revascularisation with or without cardiac valve surgery

<u>Exclusion Criteria</u>

- Inability to give informed consent or comply with the protocol

- Emergency surgical coronary revascularization or valve surgery

- Tracheostomy before surgery

- Enrolment in another concurrent interventional research study likely to impact of study outcomes

Eligible participants were admitted on the night before surgery and had medical history and clinical measurements recorded including weight, height, body mass index and neck circumference. All participants completed the STOP-Bang questionnaire and Epworth Sleepiness Scale.

Sleep apnoea assessment and data collection

All participants included in this prospective observational cohort study completed the STOP-Bang questionnaire (Figure 2.1) (Chung et al. 2008) which consists of 8 questions scored as yes/no response. The total score can range from 0-8 according to the number of positive answers. From previous data, patients scoring ≥3 on STOP-Bang have been perceived to be at high risk of OSA (Chung et al. 2008).

In addition to the STOP-Bang score, all participants underwent nocturnal oximetry on the night before surgery while self-ventilating on room air. The oximetry results were automatically analysed (Visidownload, Stowood Ltd, Oxford UK) and reviewed by a sleep

physician, blinded to all clinical data. The anaesthetic and surgical teams had no access to the results of preoperative nocturnal oximetry. Sleep apnoea was diagnosed in patients with an ODI greater than 5. The oximeter was programmed to average measurements over 1 second. Nocturnal monitoring without at least 4 hours of adequate data was excluded as per our usual accepted practice. The results are reported as sleep apnoea since nocturnal oximetry cannot distinguish between obstructive and central sleep apnoea. Demographic information, comorbidities, ESS (Johns 1991) and the EuroSCORE were recorded prospectively, on the night of admission. The EuroSCORE, a mortality risk score developed for patients undergoing cardiac surgery, was calculated for all patients (Nashef et al. 1999). Data regarding postoperative complications were collected from the digital Clinical Information System in the ICU.

Outcomes

The primary outcome was to assess the diagnostic performance of the STOP-Bang questionnaire against ODI from nocturnal oximetry by calculating sensitivity, specificity, positive predictive value, negative predictive value and area under receiver operating characteristic curve.

The secondary outcome was length of stay (LoS) in ICU (days) and a composite measure of post-operative complications in ICU that included: use of continuous positive airway pressure (CPAP)/bi-level positive pressure ventilation via a mask after extubation, re-intubation, occurrence of new arrhythmias necessitating drug treatment or intervention, need for additional organ support (intra-aortic balloon pump/ haemofiltration), major organ complication (defined as those requiring treatment or intervention for cardiovascular, respiratory, renal, neurological, hepatic, coagulation), readmission to ICU and 30 days mortality.

Predictor variables

The primary predictor variable was the STOP-Bang score analysed as a continuous variable. Additional predictor variables thought to be risk factors relevant to the outcomes included EuroSCORE, age, body mass index, surgery type, administration of intravenous opioid analgesia (either intravenous morphine sulphate or fentanyl) during ICU stay, comorbidities and mean nocturnal oxygen saturations.

Statistical analysis

Descriptive statistics are shown for the variables used in this study (Table 3.1). Continuous variables are reported as mean (SE), categorical variables as percentages. The severity of SA according to ODI was defined as follows: no SA if ODI<5, mild SA if ODI≥5 and <15, moderate SA if ODI≥15 and <30 and severe SA when ODI≥30. The prevalence of SA according to severity was calculated.

The area under receiver operating characteristic curves (AUC-ROC) was calculated to assess discriminating ability of different STOP-Bang scores for sleep apnoea. The ROC curves were used to identify the best STOP-Bang discriminating score in terms of sensitivity and specificity for predicting sleep apnoea. The STOP-Bang diagnostic performance for mild and moderate/severe sleep apnoea, at both the conventional cut off value ≥3, and at the best discriminating value was assessed using multiple 2x2 contingency tables and expressed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

A parametric accelerated failure time model (Weibull regression) was used to analyse LoS as a continuous response to preselected predictor variables. Postoperative complications were dichotomised (yes/no) and analysed with a binary logistic regression using the same predictors used to analyse LoS. For all regressions, parsimonious models were obtained with a combination of step-wise and manually removing predictors and interactions that did not reach 5% significance level.

Results

A total of 322 patients were screened for eligibility of whom 152 underwent preoperative evaluation with STOP-Bang questionnaire and nocturnal oximetry. Of these, 30 patients were excluded (Figure 2.5). A total of 122 patients were included in the final analysis. Of those, 6 patients (5%) scored low risk for OSA using the STOP-Bang score whilst 116 (95%) scored high risk (STOP-Bang ≥ 3). Sleep apnoea was diagnosed by nocturnal oximetry in 57 patients (47%). Table 2.1 shows the demographics of individuals included.

Diagnostic performance of STOP-Bang against ODI from nocturnal oximetry

It was found that the STOP-Bang score poorly predicted patients with mild SA [AUC-ROC 0.57 (95% CI 0.47-0.67)] but was better for patients with moderate SA [AUC-ROC 0.82 (95% CI 0.69-0.95)]. Setting the STOP-Bang score at ≥6 improved the accuracy in terms of sensitivity (75%) and specificity (77%) in detecting moderate/severe SA (Figure 3.1).

Figure 3.1. Receiver operating curves (ROC) for STOP-Bang to predict ODI≥5 and ODI≥15. The AU ROC curve was 0.57(CI: 0.47-0.67) for ODI≥5 and 0.82 (CI: 0.69-0.95) for ODI≥15
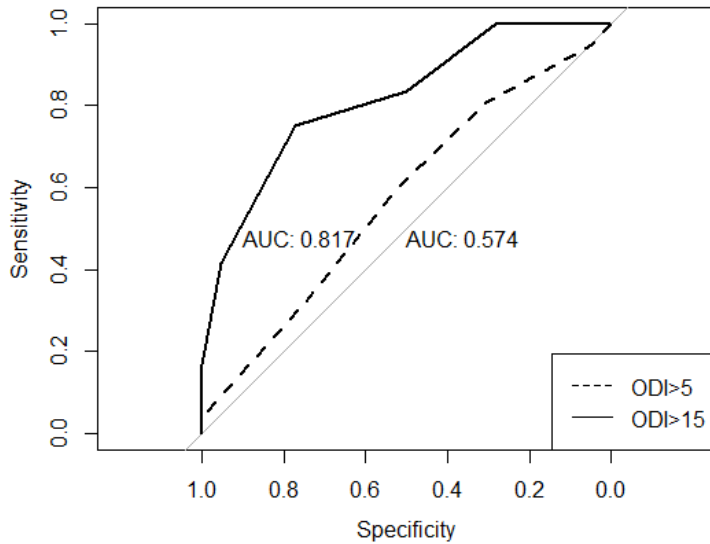
At the conventional cut off value of ≥3, the STOP-Bang score demonstrated high sensitivity for mild (95%) and moderate/severe sleep apnoea (100%), but the specificity was very low (5% and 6% respectively). In view of 100% sensitivity and 100% NPV for moderate/severe sleep apnoea, STOP-Bang scores of 0-2 would confidently exclude patients with at least moderate sleep apnoea, in the cardiac pre-operative settings. However, in our population only 6/122 (5%) scored low risk for sleep apnoea.

Assessing predictive value for severe sleep apnoea was not possible due to the lack of severe sleep apnoea cases. The sensitivity, specificity, NPV and PPV for STOP-Bang at cut off values ≥3 and ≥6 are summarised in Table 3.1.

Table 3.1 Sensitivity, Specificity, positive predictive value and negative predictive value of STOP-Bang questionnaire for predicting mild (ODI≥5) and moderate/severe SA (ODI≥15)

STOP-Bang ≥3	Mild SA (ODI ≥5-14 /hr)	Moderate/Severe SA (ODI ≥15/hr)
Sensitivity (%)	95	100
Specificity (%)	5	6
PPV (%)	47	10
NPV (%)	50	100
STOP-Bang≥6	Mild SA (ODI ≥5-14 /hr)	Moderate/Severe SA (ODI ≥15/hr)
Sensitivity (%)	32	75
Specificity (%)	75	77
PPV (%)	53	27
NPV (%)	56	97

NPV: negative predictive value; ODI: 4% oxygen desaturation index; PPV: positive predictive value; SA: sleep apnoea

Secondary outcome analysis

The median LoS in ICU was 0.95 days (95%CI 0.91-1 days). In the multiple logistic regression models we found that there was no significant association between STOP-Bang scores and LoS in ICU (HR 1.1, 95% CI 0.99-1.19; p=0.08) and no significant association between STOP-Bang scores and postoperative ICU complication (OR 1.0, 95% CI 0.59-1.72; p=0.98).

Discussion

In our study population of predominantly men, all with cardiac disease, the STOP-Bang questionnaire had poor diagnostic accuracy in detecting sleep apnoea. Many patients would be falsely positive when using the generally accepted cut off value of ≥3, leading to inappropriate utilization of sleep diagnostics and potentially delays in surgery. However, STOP-bang scores lower than 2 would allow confident exclusion of moderate/severe sleep apnoea in patients, but as only 5% of patients scored at that level, only a small proportion of patients not suffering from OSA would be excluded.

The poor performance of the STOP-bang score in my patient cohort is explained by the inherent characteristics of the cardiac surgical population (male, older, majority suffering hypertension) that are common to the traits detected by the STOP-Bang questionnaire.

The STOP-Bang questionnaire was introduced as a scoring model in the general surgical population to identify patients at risk of undiagnosed moderate/severe OSA prior to surgery. In the general surgical population, at a cut-off level of ≥3, it showed sensitivity and specificity for moderate OSA of 93% and 43% respectively and for severe OSA of 100% and 37% (Chung et al. 2008). The NPV for moderate and severe OSA was 90% and 100% respectively and therefore scores of 0-2 would, with high confidence, exclude patients with moderate to severe disease in patients presenting for general surgery. In view of its low specificity for moderate and severe OSA in the general surgical cohort, its predictive probability was examined at the higher scores and it was found that scores over 5 identified patients with high probability of moderate/severe OSA (Chung et al. 2012).

In contrast to previous reports, where patients undergoing general surgery scoring high on STOP-Bang questionnaire had higher odds of developing post-operative complications (Nagappa et al. 2017) I have not shown a significant association between STOP-Bang scores and ICU LoS or risk of developing post-operative complications which

may be due to low specificity of the questionnaire at the conventional cut of value ≥ 3, falsely identifying patients with the disease.

In the current patient cohort, I found that the best discriminating score for moderate/severe sleep apnoea was at ≥6. This score would decrease the false positive rates for predicting sleep apnoea, but at the expense of lower sensitivity and up to 25% of patients with moderate/severe sleep apnoea will still have either a falsely positive or negative results. In Chapter 3 I reported a significant association between sleep apnoea, defined as the continuous measure of ODI, with postoperative complications (Mason et al. 2017) which adds to the evidence of a positive association between untreated sleep apnoea and postoperative complications in patients undergoing cardiac surgery (Nagappa et al. 2017). The results of the current study suggest that a STOP-Bang score ≥6 in the cardiac surgical population could identify those in need of further screening for sleep apnoea. As ODI ≥5 from nocturnal oximetry identified patients who had higher probability of developing cardiovascular and renal complications, using nocturnal oximetry in all patients scoring ≥6 on the STOP-Bang score could help with planning of perioperative care. Data from randomised controlled trials are still needed to define the clinical effectiveness and cost implications of screening and treatment of OSA prior surgery (Nagappa et al. 2015) but whilst this is awaited identifying patients with untreated sleep apnoea before cardiac surgery may help with perioperative precautions and airway management. In addition, it has been reported that patients with untreated OSA have increased risk of long term cardiovascular complications and therefore identifying and treating these patients may have long term benefits but further research is necessary to confirm this.

The limitations of the current study include the lack of patients with severe SA and therefore the utility of STOP-Bang in such patients remains unknown. The STOP-Bang was not compared to formal polysomnography but in the UK around two thirds of respiratory sleep studies use oximetry alone (Flemons et al. 2004). It is possible that some of the patients with raised ODI had central sleep apnoea but in view of previously reported positive

association between oxygen desaturations from nocturnal oximetry (ODI) and worse postoperative outcomes in cardiac surgical cohort (Mason et al. 2017), identifying patients at risk of sleep apnoea with help of STOP-Bang questionnaire may help to recognise patients in need of nocturnal oximetry and subsequently those who may be at risk of postoperative complications. Patient selection bias may be responsible for the high prevalence of OSA found in our study.

In conclusion, the STOP-Bang questionnaire had limited diagnostic value in identifying patients at high risk of SA prior to major cardiac surgery at the conventional cut of ≥3, but scores ≤2 were highly predictive of the absence of SA. A STOP-Bang score ≥6 would be more accurate but still be falsely positive or negative in up to 25% of patients. Due to its high specificity, a STOP-Bang score ≥6 in the cardiac surgical population could identify some people for further screening for sleep apnoea using nocturnal oximetry. STOP-Bang scores were not significantly associated with worse post-operative outcomes in this cohort, contrary to previous reports in patients undergoing general surgical procedures.

Future directions

As described in Chapter 1 to deal with the low specificity issue of the STOP-Bang questionnaire specific aspects of STOP-Bang score have been evaluated in the general surgical population and found to increase the specificity including BMI more than 35 kg/m2, male sex and neck circumference more than 40 cm. In addition, serum HCO_3^- of at least 28mmol/L has also been reported to increase the specificity of STOP-Bang questionnaire (Chung et al. 2013). In this study, I have not evaluated the impact of these aspects on the sensitivity and specificity of STOP-Bang questionnaire as when planning my research these results were not available. To increase the diagnostic value of the STOP-Bang questionnaire in a cardiac surgical population and to rationalise the use of sleep diagnostics before surgery these additional aspects may deserve further research. Based on the results of my study reported in this Chapter and previously proposed 2 step approach of screening for OSA in general surgical cohort, this approach may warrant validation in cardiac patients in that if

patients score 0-2, low risk of moderate to severe OSA is suspected. If patient scores ≥6 they have high probability for moderate to severe OSA and further assessment by a sleep physician may be needed. The intermediate risk would represent patients with scores 3, 4 and who could be further stratified as high risk of OSA based on the validation of aforementioned additional aspects of the STOP-Bang, namely: BMI more than 35 kg/m^2, male sex, neck circumference more than 40 cm along with the serum HCO3$^-$ of at least 28mmol/L. It has to be remembered that before universal screening is adopted the effect of treatment needs evaluation. If no improvement in postoperative outcomes is achieved by treating OSA in surgical patients there may be no need for screening for this condition in preoperative setting.

Chapter 4

Systematic Cochrane review: Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea

My personal involvement in this research includes: Developing the idea for the review and writing up the protocol with help and overview of Dr Ian Smith. The electronic searches were performed by the Cochrane Airway group. I have assessed the abstracts for eligibility along with Dr Kate Chong (KC). I and KC independently screened the full text, identified studies for inclusion and recorded reasons for exclusion of ineligible studies. I have extracted the data and transferred it into data manger (RevMan). I have analysed the data with the help of Dr Chris Cates from Cochrane Airway Group and written the review with help from Dr Ian Smith.

The review was published in July 2015 (Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep- disordered breathing in adults with obstructive sleep apnoea. *Cochrane Database Syst. Rev.* 2015 Jul 14;7:CD011090

Introduction

The observational cohort study described in Chapter 3 showed an association between intravenous opioids and postoperative complications in patients undergoing cardiac surgery. This gave grounds for examining the current evidence base for the effect of opioids and sedatives on patients with OSA. Patients with OSA and those at risk for OSA along with the rest of population are likely to have conditions such as anxiety and chronic pain and may be presenting for surgery and may be in need of these pharmacological agents. Administration of such drugs to patients with OSA may exacerbate nocturnal hypoxaemia and the severity of SDB (Walker et al. 2007; Yue et al. 2010). It is proposed that opiates/opioids could worsen the severity of OSA in perioperative settings due to their effect on ventilatory drive and upper airway dilator muscles (Kaw et al. 2006). In the SACS study, described in Chapter 3, not only patients with sleep apnoea, but also those without were found to be at higher risk of postoperative complications when given postoperative opioids. The British National Formulary (BNF) advises physicians not to prescribe hypnotics to patients with severe OSA and/or OSAS and to avoid opioids in patients suffering acute respiratory depression. Caution is also advised when administering such drugs to patients with OSA peri-operatively (Gross et al. 2006). This review examines the evidence concerning the safety of sedatives and hypnotics in patients with pre-existing OSA, especially regarding their effect on the frequency and/or severity of apnoeas and/ or hypopnoeas during sleep and addresses whether the anxieties regarding prescribing these drugs to patients with OSA are justified. This review was constructed using the Cochrane methodology with the assistance of Cochrane airway group and published in the Cochrane library (Mason et al. 2015) .

Description of conditions for which prescription of hypnotic or sedative drugs may be desirable

Opiates and opioids

Opiates and opioids are used to treat acute and chronic pain, as well as respiratory distress. Morphine is a strong opiate and is a valuable analgesic for severe pain including during palliative care. Codeine is a weak opiate that is used for the treatment of mild to moderate pain. Alfentanil, fentanyl and remifentanil are used intravenously to treat pain during surgery, and fentanyl is also available in a skin patch preparation to treat chronic intractable pain. Other opiate and opioid drugs are used during and after surgery.

Sedatives and hypnotics

Benzodiazepines (BZDs) are indicated for short-term relief of severe anxiety, behavioural disturbance or agitation, as well as panic disorders when antidepressants do not control symptoms. Furthermore, some BZDs are used to control and prevent seizure activity, to relieve chronic muscle spasm, in some sleep-related disorders including insomnia (difficulty initiating or maintaining sleep) and in conditions in which an increase in motor activity during sleep occurs, including REM behaviour disorders. Non-BZD gamma-aminobutyric acid A (GABA$_A$) receptor agonists (novel hypnotics and 'Z drugs') are licensed for treatment of sleep-onset insomnia (difficulty falling asleep) and sleep-maintenance insomnia, to be taken in the middle of the night should waking occur. Gabapentin and pregabalin are used for the treatment of seizure activity and neuropathic pain. Pregabalin is also licensed for the treatment of anxiety. Sodium oxybate (SXB) is used in narcolepsy with cataplexy. People with narcolepsy and cataplexy experience periods of extreme daytime sleepiness and sudden loss of voluntary muscle tone in emotionally charged situations (cataplexy), which SXB can reduce.

Melatonin and melatonin-related drugs

Melatonin is licensed for the short-term treatment of insomnia and can help to promote regular sleep-wake cycles with adaptation to time zone changes (jet lag).

<u>**Description of intervention**</u>

Opiates and opioids

The term 'opiates' refers to the alkaloids found naturally in the opium poppy; examples include morphine, codeine and thebaine. Synthetic and semi synthetic drugs with opium- or morphine-like pharmacological action are referred to as opioids and include hydrocodone, hydromorphone, oxycodone and oxymorphone among others. Opiates and opioids bind to four different classes of receptors, namely δ, κ, μ and the nociception/orphanin receptor. These receptors mediate and regulate pain, stress responses and respiration. Ligands that stimulate κ and μ receptors suppress respiratory pattern generation, leading to a decrease in respiratory rate and tidal volume (Lalley 2008). Opiates and opioids are widely used for treatment of acute and chronic pain

Sedatives and hypnotics

Agents described in this review include BZDs, non-BZD $GABA_A$ receptor agonists (novel hypnotics and 'Z drugs'), gabapentin, pregabalin and SXB. Most hypnotics work as GABA receptor modifiers. BZDs interact with $GABA_A$ receptors and enhance the effects of GABA, leading to hypnosis, anxiolysis, muscle relaxation, amnesia and anticonvulsant effects. The pharmacokinetics of BZDs vary. They can be divided into short-, intermediate- and long-acting agents. Non-BZD $GABA_A$ receptor agonists also bind to the $GABA_A$ receptor complex but at a different site than BZDs. These agents also cause sedation but less prominent muscle relaxation and anxiolysis. They have rapid onset and a short to intermediate duration of action. Examples include zolpidem, zaleplon, zopiclone and

eszopiclone. They are used mainly for sleep-onset and sleep-maintenance insomnia. Gabapentin increases the GABA content of neurones, and pregabalin has an effect on GABA transmission. Both of these drugs increase deep sleep and thereby improve the subjective quality of sleep (Holsboer-Trachsler et al. 2013).Sodium oxybate is used in the treatment of narcolepsy with cataplexy. Its mechanism of action is uncertain, but it has some affinity for gamma-aminobutyric acid B ($GABA_B$) receptors and is a potent hypnotic (Huang et al. 2009).

Melatonin and melatonin-related drugs

Melatonin is synthesised within and secreted from the pineal gland. Oral administration of melatonin induces drowsiness, particularly if administered during the day, when naturally produced melatonin levels are low. The melatonin receptor-agonist, ramelteon, has been developed with the advantage of a longer half-life and increased bioavailability.

The pharmacological substances described in this review might affect the pathophysiology of OSA in many different ways but are largely thought to be deleterious (Younes 2004; Jordan et al. 2007). Caution, which is based on low-quality evidence, has been advised when such substances are prescribed for people with OSA.

Many other agents have been noted to have soporific effects, including tricyclic antidepressants, antihistamines, antipsychotic drugs and alpha-adrenoceptor blockers. These agents are not approved sedatives or hypnotics and are beyond the scope of this review. The effects of antidepressants on OSA has been addressed in the Cochrane review, "Drug therapy for obstructive sleep apnoea in adults" (Mason et al. 2013).

How the intervention might work and what effects it may have on obstructive sleep apnoea

Opiates/opioids reduce respiratory rate and tidal volume while decreasing UA muscle tone and the compensatory response to increased UA resistance (Santiago et al. 1985; Leino et al. 1999; Lalley 2008). This would suggest that opioids may have an adverse impact on respiratory function in people with SDB. Furthermore, opioids decrease chemoresponsiveness to hypercapnia/hypoxia, leading to concerns that ventilatory response in people with OSA who are given opioids will not be sufficient to restore normal arterial blood gas tension after an apnoea (Drummond 1983; Robinson et al. 1987). A deleterious effect of BZDs on people with OSA has been proposed as a result of their known muscle-relaxing effects leading to reduced UA muscle tone and increased UA resistance. A further concern is blunting of the respiratory response to hypoxia (Bonora et al. 1985; Leiter et al. 1985). Non-BZD GABA$_A$ receptor agonists have less effect on muscle tone, and it has been proposed that they are safer for people with SDB, including OSA (Rosenberg et al. 2007).

Objectives

1. To investigate whether administration of sedative and hypnotic drugs exacerbates the severity of OSA (as measured by AHI or 4% ODI) in people with known OSA.

Methods

Types of studies

Randomised controlled trials, double- or single-blinded, of parallel-group or cross-over design were included in this review. Studies included required a sleep study to confirm the diagnosis and severity of OSA and a subsequent sleep study on opioids/sedatives/hypnotics or placebo (or both in cross-over designs) as

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comparator. Studies reported as full text, abstract only and as unpublished data were all included.

Types of participants

Adult participants with an existing diagnosis of OSA based on a history of associated symptoms and results of sleep studies with an ODI or AHI of five or more per hour were included including participants already using continuous positive airway pressure (CPAP) or a mandibular advancement device.

Types of interventions

Trials in which participants were randomly assigned to use sedatives, hypnotics (including BZD, non-BZD $GABA_A$ receptor agonists (novel hypnotics and 'Z drugs'), gabapentin, pregabalin, sodium oxybate, melatonin or related drugs, opiates and opioids) or placebo were included. These drugs could be administered intravenously, orally or topically and no restriction was placed on study duration.

Types of outcome measures

All outcome variables were measured during the baseline sleep study and the sleep study during the study night during which participants received study medication. The sleep studies in question included nocturnal oximetry, rPG and full polysomnography.

Primary outcomes

- apnoea-hypopnoea index (AHI)
- oxygen desaturation index (ODI)

Secondary outcomes

- time spent with arterial saturation less than 90% ($TSpO_2 < 90\%$)

- minimum arterial saturation during sleep (minimum SpO_2)

- respiratory disturbance index (RDI) is reported during polysomnography and includes AHI as well as respiratory effort related arousals recorded during sleep by EEG

- arousal index- The number of arousals and awakenings registered in the study, and reported as a total number and frequency per hour of sleep

- total sleep time (TST) – "The amount of actually sleep time in a sleep episode; this time is equal to the total sleep episode less the awake time. TST is the total of all REM and NREM sleep in a sleep episode"

- apnoea index (AI)-number of apnoea events per hour sleep

- hypopnoea index (HI)- number of hypopnoea events per hour sleep

- objective measurement of daytime sleepiness including MSLT or MWT described in previous chapter

- adverse events/side effects

- ESS

Search methods for identification of studies

Electronic searches

Trials were identified from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the group. This register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, as well as by hand searching of respiratory journals and meeting abstracts. The latest search was conducted on 4 March 2015. To identify the most current literature, additional searches were conducted of the following databases: CENTRAL (searched 4 March 2015 via the Cochrane Register of Studies Online); MEDLINE (searched 5 March 2015 via Ovid) and EMBASE (searched 5

March 2015 via Ovid). A search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization trials portal (www.who.int/ictrp/en/) was also conducted. All databases from their inception with no restriction on language or type of publication were searched.

Searching other resources

Reference lists of all primary studies and review articles were checked for additional references and relevant manufacturers' websites for trial information.

Selection of studies

Two review contributors (MM and KC) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. The full-text study reports/publications were retrieved, and two review contributors (MM and KC) independently screened the full text, identified studies for inclusion and recorded reasons for exclusion of ineligible studies. Disagreements were resolved through discussion. Duplicates were identified and excluded. The selection process was recorded in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

Data extraction and management

One review author (MM) extracted the following study characteristics from included studies.

- methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals and date of study
- participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria
- Iiterventions: intervention, comparison, concomitant medications and excluded medications

- outcomes: primary and secondary outcomes specified and collected and time points reported

- notes: funding for trial and notable conflicts of interest for trial authors

MM transferred data into Review Manager (RevMan 2012).

Assessment of risk of bias in included studies

MM independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Disagreements were resolved by discussion or by consultation with the third review author (IS). The risk of bias was assessed according to the following domains.

- random sequence generation

- allocation concealment

- blinding of participants and personnel

- blinding of outcome assessment

- incomplete outcome data

- selective outcome reporting

- other bias

Each potential source of bias was graded as high, low or unclear and provided a quote from the study report together with a justification for judgement in the 'Risk of bias' table (Appendix 1).

Assessment of bias in conducting the systematic review

The review was conducted according to the published protocol.

Measures of treatment effect

Dichotomous data were analysed as odds ratios (ORs) and continuous data as mean difference (MDs) or standardised mean differences (SMDs) with 95% confidence intervals (CI's).

Meta-analyses were undertaken only when this was meaningful (i.e. if treatments, participants and the underlying clinical question were similar enough for pooling to make sense).The skewed data reported as medians and interquartile ranges were narratively described.

Unit of analysis issues

For cross-over studies, estimates of effects using generic inverse variance (GIV) data were entered. MDs between treatment groups with variance were determined by the published 95% CI when available. When 95% CIs were not available, published p values from statistical tests for paired data was used (Higgins 2011).

Assessment of heterogeneity

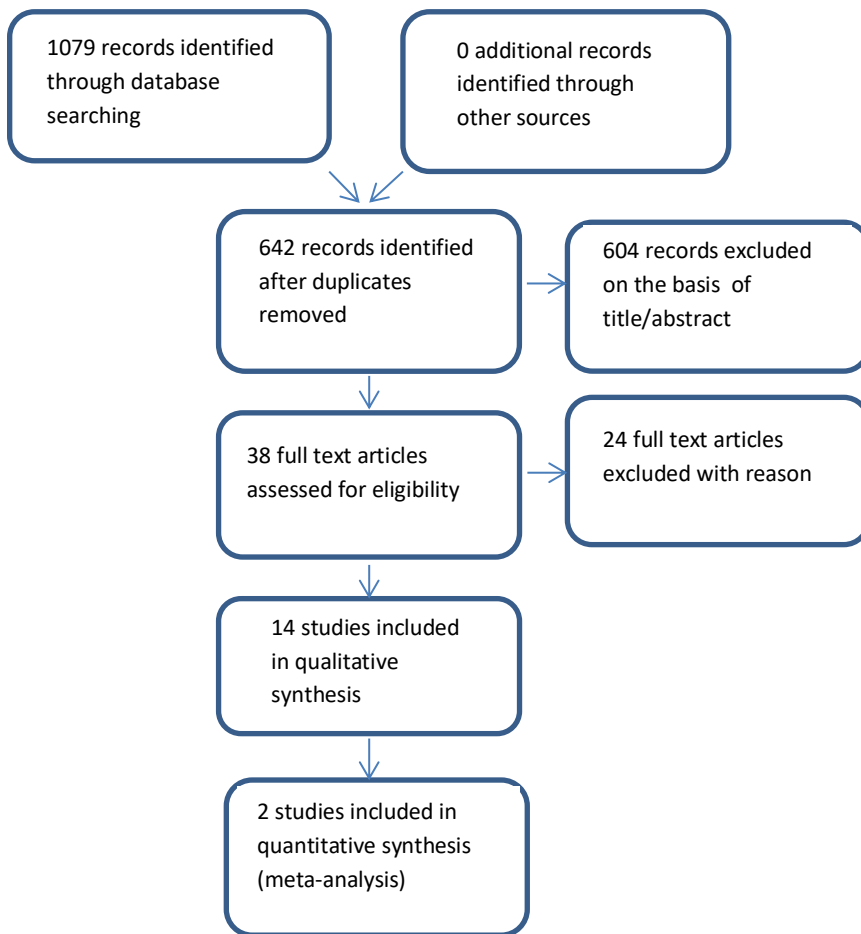The I^2 statistic to measure heterogeneity among the trials in each analysis was used.

'Summary of findings' table

The 'Summary of findings' table using the following outcomes: AHI, ODI and adverse events/side effects was created (Table 4.1).

Results of the search

Fourteen studies met the entry criteria for this review (Figure 4.1)

Figure 4.1 Study consort diagram

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┌─────────────────────────┐     ┌─────────────────────────┐
│ 1079 records identified │     │ 0 additional records    │
│ through database        │     │ identified through      │
│ searching               │     │ other sources           │
└─────────────────────────┘     └─────────────────────────┘
              │                             │
              └──────────────┬──────────────┘
                             ▼
              ┌─────────────────────────┐      ┌─────────────────────────┐
              │ 642 records identified  │ ───▶ │ 604 records excluded     │
              │ after duplicates        │      │ on the basis  of         │
              │ removed                 │      │ title/abstract           │
              └─────────────────────────┘      └─────────────────────────┘
                             │
                             ▼
              ┌─────────────────────────┐      ┌─────────────────────────┐
              │ 38 full text articles   │ ───▶ │ 24 full text articles    │
              │ assessed for eligibility│      │ excluded with reason     │
              └─────────────────────────┘      └─────────────────────────┘
                             │
                             ▼
              ┌─────────────────────────┐
              │ 14 studies included     │
              │ in qualitative          │
              │ synthesis               │
              └─────────────────────────┘
                             │
                             ▼
              ┌─────────────────────────┐
              │ 2 studies included in   │
              │ quantitative synthesis  │
              │ (meta-analysis)         │
              └─────────────────────────┘
```

Included studies

A full description of each study, was entered into the Cochrane Database software, Review manager 5.3 "Characteristics of included studies"

Study design

Most studies had a cross-over design with the exception of four studies, which had a parallel-group design (Camacho et al. 1995; Bernards et al. 2009; Gooneratne et al. 2010; George et al. 2011). All but one study (George et al. 2010) were double-blinded. Most studies took place at a single centre, three studies had two centres participating in data collection (Rosenberg et al. 2007; George et al. 2010; George et al. 2011) one was a five-centre study (Kryger et al. 2007) and one was described as a multi-centre trial (Camacho et al. 1995).

Participants

The 14 studies recruited a total of 293 participants. Five studies recruited fewer than 15 participants (Cirignotta et al. 1988; Cirignotta et al. 1992; Höijer et al. 1994; Berry et al. 1995; Camacho et al. 1995) and two recruited more than 40 participants (George et al. 2010; George et al. 2011). The mean age of participants ranged between 44 (Wang et al. 2011) and 74 years (Gooneratne et al. 2010). Two studies enrolled only people over 60 years of age with complaints of insomnia (Camacho et al. 1995; Gooneratne et al. 2010). When data on body mass index (BMI) were recorded, trial populations were overweight or clinically obese, with mean weights ranging from 25 kg/m^2 (Gooneratne et al. 2010) to 36 kg/m^2 (Berry et al. 2006). All participants had OSA confirmed by full polysomnography. The severity of OSA as evidenced by AHI was generally mild to moderate, with mean baseline AHI ranging from 10.9 (Gooneratne et al. 2010) to 25.0 per hour (George et al. 2011). Three studies recruited participants with severe OSA (Berry et al. 1995; Berry et al. 2006; Eckert et al. 2011). In (Berry et al. 2006) and (Berry et al. 1995), no baseline AHI was described, but

participants with severe OSA compliant with CPAP for over six months and males with severe OSA were included, respectively. A total of 75 participants were using CPAP therapy before screening but not during the study night in three studies (Rosenberg et al. 2007; George et al. 2010; George et al. 2011). All participants in two studies (n = 37) were treated with CPAP, including during the study night (Berry et al. 2006; Gooneratne et al. 2010). In (Bernards et al. 2009), one of the inclusion criteria was that participants had to be off CPAP for seven nights or longer, but how many participants were treated with CPAP was not formally stated. Similarly, in six studies, participants were off CPAP during the study night, but how many could have been treated before the study is not clear (Cirignotta et al. 1988; Cirignotta et al. 1992; Höijer et al. 1994; Berry et al. 1995; Camacho et al. 1995; Wang et al. 2011). In (Eckert et al. 2011) and (Kryger et al. 2007), participants were not treated with CPAP (n = 43). It is impossible to be certain that no patients with central sleep apnoeas were recruited. However, when participants were described as suffering from OSA, and AHIs were reported as outcomes, the patient populations in each study would have met entry criteria for OSA-specific studies. Cirignotta (Cirignotta et al. 1992) excluded patients with SpO_2 levels less than 70% during apnoea. Eckert (Eckert et al. 2011) excluded patients with severe OSA (nadir overnight $SpO_2 < 70\%$ and AHI > 60 events/h) as well as those with a high arousal threshold (-25 cm H_2O to -63 cm H_2O as measured by an epiglottic pressure catheter), and (Rosenberg et al. 2007) excluded patients with severe OSA, which was defined as AHI of 40 events or more/h. Two trials recruited participants with co-existing insomnia (Camacho et al. 1995; Gooneratne et al. 2010).

Interventions

A total of 10 different study drugs were compared with placebo. No studies with gabapentin, pregabalin or melatonin fulfilling the inclusion criteria were identified.

Opiates and opioids

- Remifentanil (opioid-based analgesic) (Bernards et al. 2009).

Sedatives and hypnotics

- Eszopiclone: non-BZD GABA$_A$ receptor agonist (Rosenberg et al. 2007; Eckert et al. 2011).

- Zolpidem: non-BZD GABA$_A$ receptor agonist (Cirignotta et al. 1988; Berry et al. 2006).

- Flurazepam: benzodiazepine (Cirignotta et al. 1992).

- Brotizolam: benzodiazepine analogue, similar in effect to short-acting benzodiazepines, which are not approved for sale in the UK (Cirignotta et al. 1992).

- Temazepam: short-acting benzodiazepine with anxiolytic properties, for treatment of insomnia and used as pre-medication during the preoperative period (Camacho et al. 1995; Wang et al. 2011).

- Nitrazepam: long-acting benzodiazepine, used for short-term treatment of anxiety and insomnia (Höijer et al. 1994).

- Triazolam: benzodiazepine (Berry et al. 1995).

- Sodium oxybate: central nervous system depressant (George et al. 2010; George et al. 2011).

Melatonin and melatonin-related drugs

- Ramelteon: melatonin receptor agonist, indicated for treatment of insomnia (Kryger et al. 2007; Gooneratne et al. 2010) .

All but one drug were administered orally. Remifentanil was administered as an intravenous infusion (Bernards et al. 2009). The duration of studies varied: Seven single-night studies were conducted in laboratory settings (Cirignotta et al. 1988; Berry et al. 1995;

Berry et al. 2006; Kryger et al. 2007; George et al. 2010; Eckert et al. 2011; Wang et al. 2011), three studies were run over two to three nights (Cirignotta et al. 1992; Höijer et al. 1994; Rosenberg et al. 2007), one study was of two weeks' duration (George et al. 2011) and two were of one to two months' duration (Camacho et al. 1995; Gooneratne et al. 2010).

Outcomes

All studies reported the effects of drug therapy on at least some measurements of sleep-disordered breathing (namely, AHI; AI; HI; ODI; duration of apnoea and arousals). In addition, two studies reported outcomes of symptoms on the ESS (Gooneratne et al. 2010; George et al. 2011). Five studies reported TST [(Höijer et al. 1994; George et al. 2010; Gooneratne et al. 2010; George et al. 2011; Wang et al. 2011).

Funding

Five studies were supported by drug companies (Cirignotta et al. 1992; Kryger et al. 2007; Rosenberg et al. 2007; Gooneratne et al. 2010; George et al. 2011), four were supported by grants from research councils (Höijer et al. 1994; Camacho et al. 1995; Berry et al. 2006; Bernards et al. 2009) and one study was supported by both (Eckert et al. 2011). Four studies did not clearly state funding (Cirignotta et al. 1988; Berry et al. 1995; George et al. 2010; Wang et al. 2011).

Excluded studies

A full description of each study, has been entered directly into Cochrane Database software Review Manager 5.3 "Characteristics of excluded studies"

Risk of bias of included studies

The risk of bias was assessed using the Cochrane risk of bias tool. For a summary of the risk of bias, see Figure 4.2, Appendix 1.

Allocation (selection bias)

Only three studies reported adequate randomisation and allocation concealment procedures (Gooneratne et al. 2010; Eckert et al. 2011; Wang et al. 2011) all remaining studies were described as randomised, but no further information was provided on randomisation or concealment of allocation, making adequate judgement impossible.

Blinding (performance bias and detection bias)

Three studies described adequate blinding of participants and personnel (Gooneratne et al. 2010; Eckert et al. 2011; Wang et al. 2011). In Bernards 2009 (Bernards et al. 2009), blinding of participants and outcome assessors but not personnel was adequate. Three studies reported adequate blinding of outcome assessors (Bernards et al. 2009; Eckert et al. 2011; Wang et al. 2011). The remaining studies did not report enough details on blinding.

Incomplete outcome data (attrition bias)

All randomly assigned participants completed the intervention in two studies, and the number of dropouts in seven studies did not cause particular concern (Höijer et al. 1994; Rosenberg et al. 2007; Bernards et al. 2009; George et al. 2010; Gooneratne et al. 2010; George et al. 2011; Wang et al. 2011). In five studies, details were insufficient to allow a judgement (Cirignotta et al. 1988; Cirignotta et al. 1992; Berry et al. 1995; Camacho et al. 1995; Berry et al. 2006).

Selective reporting (reporting bias)

None of the studies appear to have issues with incomplete reporting of outcomes, although we did not have access to study protocols.

Other potential sources of bias

One cross-over study (George et al. 2010) included no washout period, leading to the potential for differential carry-over effects.

Effects of interventions

Studies reported diverse outcome measures; however AHI as the common outcome measure allowed direct comparison between studies. For an overview of the results, see Table 4.1.

Table 4.1. Summary of findings

Drug class	Study	Intervention	Control	N	Change in AHI	Change in mean SaO2	Change in minimum SaO2
Opioids/opiates	Bernards 2009	remifentanil infusion (0.075 mcg /kg/h)	placebo	19	No change	Not reported	Decrease
"Z drugs"	Rosenberg 2007	Eszopiclone 3mg	placebo	22	No change	No change	No change
	Eckert 2011	Eszopiclone 3mg	placebo	17	**Decrease**	No change	No change
	Berry 2006	Zolpidem 10mg	placebo	16	No change	Not reported	No change
	Cirignotta 1988	Zolpidem 20mg	placebo	12	No change	Decrease	Decrease
Benzodiazepines	Cirignotta 1992	Brtizolam 0.25mg	placebo	12	No change in RDI (number of O2 deasturations of >4% /hr sleep)	No change	No change
	Cirignotta 1988	Flurazepam 30mg	placebo	12	No change	Decrease	Decrease
	Cirignotta 1992	Flurazepam 30mg	placebo	12	No change in RDI (number of O2 deasturations of >4% /hr sleep)	No change	No change
	Höijer 1994	Nitrazepam 5mg or 10mg	placebo	11	No change in AI	Not reported	No change
	Camacho 1995)	Temazepam 15-30mg	placebo	15	No change RDI(number apnoeas/hypopnoeas/hr sleep)	Not reported	Not reported
	Wang 2011	Temazepam 10mg	placebo	20	No change	Not reported	No change
	Berry 1995	Triazolam 0.25	placebo	12	No change	Not reported	Decrease
SXB	George 2010	SXB 9g	placebo	42	No change	No change	Not reported
	George 2011	SXB 4.5g	placebo	48	**Decrease**	No change	No change
Melatonin and melatonin related drugs	Gooneratne 2010)	Ramelteon 8mg	placebo	21	No change	Not reported	Not reported
	Kryger 2007	Ramelteon 16mg	placebo	26	No change	No change	Not reported

AHI: apnoea-hypopnoea index; **AI:** apnoea index; **mean SpO$_2$:** mean nocturnal oxygen saturation; **minimum SpO$_2$:** minimum nocturnal oxygen saturation; **RDI:** respiratory disturbance index; **SBX:** sodium oxybate

Opiates and opioids

Remifentanil versus placebo

One parallel trial involving 19 adults with moderate OSA (Bernards et al. 2009) compared remifentanil infusion (0.075 mcg/kg/h) to placebo. Remifentanil infusion did not significantly change AHI [mean difference (MD) 10.00, 95% CI -9.83 to 29.83], however, it significantly decreased the number of obstructive apnoeas per hour (MD -9.00, 95% CI -17.40 to -0.60) and significantly increased the number of central apnoeas (MD 16.00, 95% CI -2.21 to 34.21) The increase in the average number of central apnoeas in the remifentanil group was not uniform across the group and reflected very large increases in a subset of four participants. The central apnoea index for the subset of four participants at baseline was 0.8 ± 0.9 apnoeas per hour, and during the intervention 43 ± 34 apnoeas per hour. In addition, remifentanil infusion significantly decreased minimum SpO_2 (MD -7.00, 95% CI -11.95 to -2.05) and increased the total arousal index.

No significant adverse events were reported in the remifentanil group but one participant in this group was given supplemental oxygen as the result of a drop in SpO_2 to less than 80% for longer than five minutes.
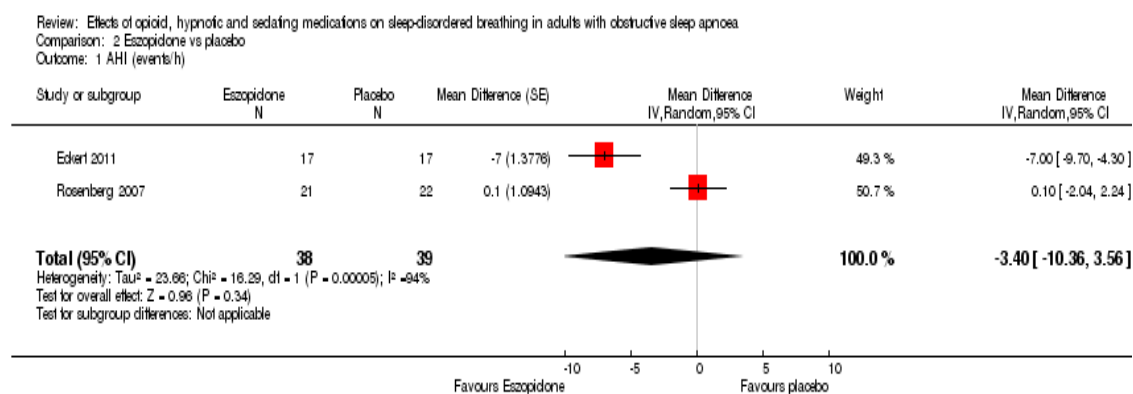
Sedatives and hypnotics

'Z drugs'

Four cross-over studies comparing "Z drugs" with placebo recruited a total of 67 participants.

Eszopiclone versus placebo

Two trials with 39 participants (Rosenberg et al. 2007; Eckert et al. 2011) compared eszopiclone 3 mg versus placebo, and pooled data show no significant change in AHI (MD -3.40, 95% CI -10.36 to 3.56; participants = 39; Figure 4.3), although in Eckert 2011, a single

administration of eszopiclone 3 mg significantly decreased AHI compared with placebo (24 ± 4 vs 31 ± 5; p value < 0.05). In addition, (Rosenberg et al. 2007) found no significant differences in AI, HI and arousal indices. No adverse events led to discontinuation of treatment. Six participants treated with eszopiclone experienced an unpleasant taste, and two developed infection, which was deemed by investigators as not related to study drug.

Figure 4.3. Eszopiclone vs placebo (outcome AHI events/h)

Review: Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea
Comparison: 2 Eszopiclone vs placebo
Outcome: 1 AHI (events/h)

Study or subgroup	Eszopiclone N	Placebo N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Eckert 2011	17	17	-7 (1.3778)		49.3 %	-7.00 [-9.70, -4.30]
Rosenberg 2007	21	22	0.1 (1.0943)		50.7 %	0.10 [-2.04, 2.24]
Total (95% CI)	**38**	**39**			**100.0 %**	**-3.40 [-10.36, 3.56]**

Heterogeneity: Tau² = 23.66; Chi² = 16.29, df = 1 (P = 0.00005); I² =94%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

-10   -5   0   5   10
Favours Eszopiclone   Favours placebo

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Zolpidem versus placebo

Two cross-over trials with 28 participants examined zolpidem versus placebo (Cirignotta et al. 1988; Berry et al. 2006). Short-term administration of zolpidem 10 mg to 16 participants with severe OSA on CPAP for at least six months (Berry et al. 2006) did not significantly change AHI (2.7 ± 0.47 vs 4.8 ±1.4) or minimum SpO_2 (91.0 ± 0.7 vs 91.4 ± 0.6). A small decrease in the arousal index was observed in the zolpidem group (16.5 ± 2 vs 19 ± 1.6; p value ≤ 0.03). Compared with placebo, a single dose of zolpidem 20 mg to 12 participants (Cirignotta 1988) increased AHI, although not significantly (30.0 vs 17.0; p value = 0.12), and significantly lowered minimum SpO_2 (76.8 vs 85.2; P value = 0.002).

No adverse events were reported in these two cross-over trials.

Benzodiazepines

Five trials comparing benzodiazepines to placebo recruited a total of 70 participants.

Brotizolam versus placebo

One cross-over trial with 12 participants reported brotizolam 0.25 mg versus placebo (Cirignotta et al. 1992). Compared with placebo, brotizolam 0.25 mg caused no significant change in RDI (15.9 ± 14.8 vs 18.5 ± 14.4), mean SpO_2 (93.9 ± 1.6 vs 93.9 ± 1.4) or minimum SpO_2 (88.5 ± 3.0 vs 88.5 ± 2.5). Investigators reported no adverse events.

Flurazepam versus placebo

Two cross-over trials with 24 participants compared flurazepam with placebo (Cirignotta et al. 1988; Cirignotta et al. 1992). In one cross-over trial with 12 participants flurazepam 30 mg in comparison with placebo led to a non-significant increase in AHI (21.5 vs 17.0; p value = 0.12) and a significant decrease in minimum SpO_2 (81.7 vs 85.2; P value = 0.002). In contrast, in Cirignotta 1992, flurazepam 30 mg compared with placebo (n = 12) did not significantly alter RDI (19.6 ± 15.9 vs 18.5 ± 14.4), mean SpO_2 (93.7 ± 1.6 vs 93.9 ± 1.4) or minimum SpO_2 (88.5 ± 2.5 vs 88.5 ± 2.5).

These trials reported no adverse events.

Nitrazepam versus placebo

One cross-over trial with 11 participants compared nitrazepam 5 mg and 10 mg to placebo (Höijer et al. 1994). Investigators found no significant change in apnoea index among participants receiving 5 mg and 10 mg, respectively (MD -0.64, 95% CI -3.98 to 2.70; MD -1.00, 95% CI -4.34 to 2.34). In addition, they reported no change in minimum SpO_2 between treatment groups receiving either 5 mg or 10 mg nitrazepam. No adverse events were reported in this trial.

Temazepam versus placebo

A parallel group study (Camacho et al. 1995) and a cross-over trial (Wang et al. 2011) with 35 participants compared temazepam to placebo. Temazepam (15 mg to 30 mg) administered to 15 participants for eight weeks (Camacho 1995) did not significantly change RDI (MD -1.60, 95% CI -5.81 to 2.61). Compared with placebo, temazepam (10 mg) did not alter AHI (MD 1.18, 95% CI -1.76 to 4.12), apnoea index, minimum SpO_2 nor arousal index (Wang 2011).

The researchers reported no adverse events in these trials.

Triazolam versus placebo

One cross-over study with 12 participants examined triazolam 0.25 mg versus placebo (Berry et al. 1995). The AHI was slightly but not significantly higher on triazolam nights (84.1 ± 6.5 vs 77.9 ± 6.6 events/h). The minimum SpO_2 was significantly lower in the triazolam group in both REM and NREM sleep (MD -14.00, 95% CI -21.84 to -6.16; MD -10.20, 95% CI -16.08 to -4.32, respectively).

This paper describes no adverse events.

Sodium oxybate versus placebo

Two trials with 90 participants compared sodium oxybate to placebo (George et al. 2010; George et al. 2011). In one cross-over trial involving 42 participants (George 2010), 9 g sodium oxybate did not significantly increase AHI compared with placebo (18.6 ± 11.1 vs 22.5 ± 10.3; p value = 0.06) nor mean SpO_2 (94.8 ± 1.4 vs 94.6 ± 2.5; p value = 0.03). However, CSA was increased in the sodium oxybate treatment group (mean 7.3 (SD 18)).A parallel-group trial (George 2011) found that compared with placebo (n = 22), administration of 4.5 g sodium oxybate (n = 26) significantly decreased AHI (MD -7.41, 95% CI -14.17 to -0.65). In addition, investigators reported no differences between treatment groups in mean

SpO_2, minimum SpO_2 or arousal index. They reported no differences between treatment and placebo groups on ESS (MD 0.10, 95% CI -4.90 to 5.10).

Adverse events, most commonly headache, were reported in nine of 26 participants and in six of 22 of those receiving sodium oxybate and placebo, respectively.
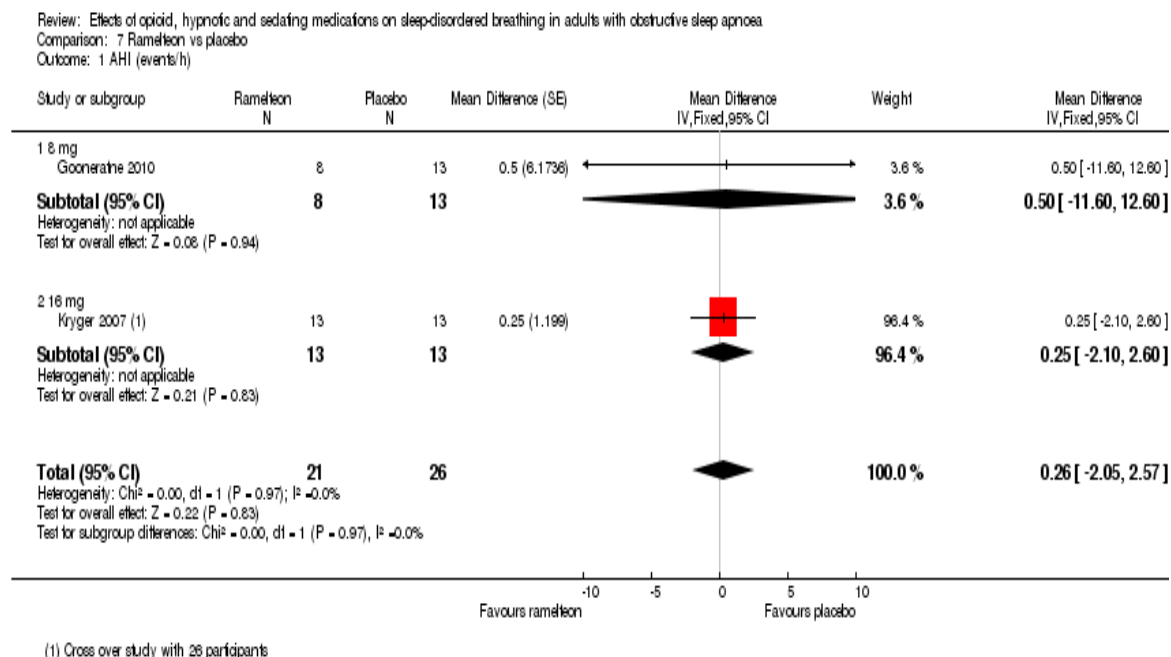
Melatonin and melatonin-related drugs

Ramelteon versus placebo

Two trials with 47 participants compared ramelteon to placebo (Kryger et al. 2007; Gooneratne et al. 2010). Pooled data showed no significant change in AHI (MD 0.26, 95% CI -2.05 to 2.57; participants = 47; Figure 4.4). In a parallel-group trial, ramelteon 8 mg (n = 8) compared with placebo (n = 13) did not significantly change AHI (MD 0.50, 95% CI -11.60 to 12.60) or ESS (MD 0.10, 95% CI -4.90 to 5.10;) in participants using CPAP. In one cross-over trial with 26 adults with mild to moderate OSA (Kryger 2007), ramelteon 16 mg compared with placebo did not significantly alter AHI (MD 0.25, 95% CI -2.10 to 2.60) or mean SpO_2 (MD 0.50, 95% CI 0.00 to 1.00) among participants not using CPAP.

In Gooneratne 2010, four adverse events were reported in the ramelteon treatment group (diarrhoea n = 1, skin ulcer n = 1, sinusitis n = 1, fracture after being hit by bicyclist n = 1) and two in the placebo group (abdominal pain n = 1, nausea n = 1). None of the adverse events were thought to be serious or related to the study drugs. In Kryger 2007, adverse events were reported by three participants in the ramelteon group (headache n = 2, urinary tract infection n = 1). No adverse events were reported with placebo.

Figure 4.4. Ramelteon vs placebo (outcome AHI events/h)

Review: Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea
Comparison: 7 Ramelteon vs placebo
Outcome: 1 AHI (events/h)

Study or subgroup	Ramelteon N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 8 mg						
Gooneratne 2010	8	13	0.5 (6.1736)		3.6 %	0.50 [-11.60, 12.60]
Subtotal (95% CI)	**8**	**13**			**3.6 %**	**0.50 [-11.60, 12.60]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
2 16 mg						
Kryger 2007 (1)	13	13	0.25 (1.199)		96.4 %	0.25 [-2.10, 2.60]
Subtotal (95% CI)	**13**	**13**			**96.4 %**	**0.25 [-2.10, 2.60]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
Total (95% CI)	**21**	**26**			**100.0 %**	**0.26 [-2.05, 2.57]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² =0.0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² =0.0%						

-10   -5   0   5   10
Favours ramelteon   Favours placebo

(1) Cross over study with 26 participants

Discussion

We identified 14 studies assessing the effects of 10 drugs on sleep-disordered breathing in patients with pre-existing OSA. Most studies were of short duration, involved only a small number of participants and poorly described methodology and outcomes.

Aside from studies by (Gooneratne 2010) of 30 days' duration and (Camacho 1995) of eight to 10 weeks' duration, most trials lasted a single night only, and therefore long-term therapeutic and symptomatic benefits could not be concluded. Regarding the effects of the drugs on sleep-disordered breathing, 12 trials showed no significant change in AHI or RDI when study drug was compared with placebo. Two drugs eszopiclone (3 mg) and sodium oxybate (4.5 g) significantly decreased AHI. Compared with placebo, flurazepam (30 mg) and zolpidem (20 mg) (Cirignotta 1988) caused a significant decrease in both minimum and mean nocturnal SpO_2, and triazolam 0.25 mg in Berry 1995 and remifentanil infusion in Bernards 2009 led to a significant decrease in minimum SpO_2.

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A single trial comparing an opiate (remifentanil) versus placebo was included. Although this trial did not report an overall significant change in AHI with remifentanil infusion, a significant decrease in obstructive apnoeas was noted. One possible explanation for this finding is that remifentanil reduced the amount of time spent in REM sleep. This effect may be only temporary, as REM suppression is often followed by REM rebound (Endo et al. 1997) which could potentially worsen obstructive events. The single-night design of this trial and the controlled research environment, which does not reflect the usual clinical conditions in which patients receive opiates/opioids, make it impossible for researchers to conclude on the effects of continuous administration of opiates/opioids on sleep apnoea. Remifentanil significantly increased central apnoeas in a subset of participants, who in this trial were older and less obese. This finding may have an implication for clinical practice in that these patients may be less likely identified on preoperative screening for sleep apnoea because of normal or low body mass index (BMI). In addition, remifentanil led to a statistically and clinically significant decrease in minimum SpO_2 (MD -7.00, 95% CI -11.95 to -2.05). It must be noted that different OSA phenotypes, such as patients with more pronounced hypoxia, may respond differently to opiates/opioids. Until further studies clarify the effects of opiates/opioids on patients with OSA, the advice that caution should be exercised when prescribing opioids to patients with OSA remains valid.

Sodium oxybate is a standard treatment for patients with narcolepsy, a large proportion of whom may have concurrent OSA (Chokroverty 1986). Although results show no significant worsening in AHI and SpO_2 with sodium oxybate, given the small sample size, short duration, worsening of CSA in a cross-over trial by George 2010 and potential night-to-night variability in the severity of sleep-disordered breathing, larger studies are warranted to evaluate the long-term effect (over three months) of larger doses of sodium oxybate (6 to 9 g) on sleep-disordered breathing.

As a combination of sleep apnoea and insomnia may pose a difficult clinical management challenge, (Camacho 1995 and Gooneratne 2010) assessed temazepam and ramelteon, respectively, for treatment of insomnia, in people over 60 years of age with OSA and insomnia and found no worsening in OSA. Although the sample size was small in both studies, both ramelteon and temazepam were well tolerated and did not adversely affect respiration.

Two trials showed a beneficial effect of medication on OSA. Eckert 2011 showed that a single administration of eszopiclone (3 mg) significantly decreased AHI compared with placebo (24 ± 4 vs 31 ± 5; p value ≤ 0.05), and a parallel trial by George 2011 showed that, compared with placebo (n = 22), sodium oxybate (4.5 g) (n = 26) significantly decreased AHI (MD -7.41, 95% CI -14.17 to -0.65). In Eckert 2011, study authors postulated that the increased arousal threshold caused by eszopiclone led to a decrease in AHI, most markedly in a subgroup of participants with a low arousal threshold before the study night. These drugs may be of therapeutic benefit for a subgroup of patients with OSA.

In conclusion, this review shows that currently no evidence indicates that the compounds assessed worsen OSA as evidenced by a change in AHI, but a decrease in minimum SpO_2 was observed with remifentanil, zolpidem and triazolam. These results must be interpreted with caution, as only a single trial assessed the effects of an opioid (remifentanil), and in several studies, it was not clear how many participants were treated with CPAP in the past, and whether a residual treatment effect of CPAP could have lessened any deleterious impact of the drugs studied. Overall, the low quality of evidence with potential risk of bias due to lack of data on allocation of intervention, concealment of allocation and blinding must be borne in mind when the results of this review are interpreted. Prescribing such agents for patients with OSA, especially outside the doses and severity of the OSA cohorts studied in individual trials, merits caution.

Overall completeness and applicability of evidence

Results of this review cannot be extrapolated to patients outside the severity of the OSA cohorts in the individual studies and the corresponding doses of compounds studied. Some drugs have been studied in patients with ongoing treatment with CPAP.

Inter-participant variability is apparent in terms of the effects of the drugs administered in some studies. A subset of patients with a certain OSA phenotype may be more susceptible to potential harm and adverse effects associated with such agents. Owing to the small size and short duration of the studies included in this review, as well as the aforementioned individual variability in drug response, we cannot comment on long-term tolerability and likelihood of adverse events.

Implications for research

Larger, methodologically robust studies of longer duration including patients naive to or without additional CPAP treatment are needed to examine the effects of opioids/opiates, sedatives and hypnotics on patients with pre-existing OSA.

Currently only one RCT has examined the effects of an opiate (remifentanil) on patients with OSA. The results of this trial provide some cause for concern regarding prescribing for patients with OSA. Further studies are needed to clarify these results, including the significance of increased central apnoeas, to help with planning of optimal perioperative care for patients with known OSA requiring opioid analgesia after major surgery.

The apparently favourable effects of eszopiclone and sodium oxybate on severity of OSA may be due to chance, but further studies examining these agents as potential therapeutic options for patients with OSA could prove valuable.

Chapter 5

The effect of acute intravenous morphine administration on sleep disordered breathing in patients with moderate obstructive sleep apnoea: A paired design trial; MIMOSA trial

My personal involvement in this study includes: developing research hypothesis and writing up the protocol as well as applications for ethical approval and Medicines and Healthcare Products regulatory agency. I have been screening patients for availability to the trial as well as recruiting them to the study. I have also supervised the study night and administered the morphine to those eligible for study night. I have also collected all data. Statistical analysis was performed by Dr Jules Hernandez-Sanches and Dr Sofia Villar.

Null hypothesis

Administration of intravenous morphine sulphate to patients with moderate OSA does not worsen the severity of sleep disordered breathing as measured by change in AHI.

Introduction

The Cochrane review reported in Chapter 5 found that administration of opioids does not worsen OSA severity but there was only one RCT involving administration of an opioid (remifentanil) included in this review.

Morphine and other opiates/opioids are the treatment of choice for moderate and severe pain after surgery. A large proportion of patients with OSA remain undiagnosed and may be presenting for surgery (Young et al. 1997) and receiving postoperative opioid analgesia. It has been proposed that a sensitivity to such drugs puts patients with OSA at increased risk of respiratory depression in the post-operative period (Gross et al. 2006) and in anaesthetic guidance on the management of people with OSA, caution is recommended when using sedating drugs after the surgery (Network 2003). These anxieties are not justified on the basis of any high level published evidence and the current recommendation

from the American Society of Anaesthesiologists to limit the use of opioids in such patients, is based on expert opinion only (Gross et al. 2006).

In our hospital, as in many other units, intravenous (iv) morphine is prescribed as the 1st line drug for severe pain after cardiac surgery and remifentanil is only used for the provision of analgesia in theatres and occasionally in the critical care area in mechanically ventilated patients. To my knowledge there are no studies investigating the effect of intravenous morphine in adults with OSA.

It is necessary to establishing the risk opioids may represent to patients with OSA to allow informed decisions when prescribing such substances to patients with OSA.

Methods

The local research committee, NRES Committee East of England, Cambridgeshire and Hertfordshire, gave ethical approval for the protocol on the 30th June 2015. The first subject was recruited in May 2016 and the last patient completed the trial on 3rd November 2017. Data were collected prospectively and written consent was obtained from all participants recruited to the study. Papworth Hospital NHS Trust sponsored the trial.

The study protocol illustrating the pathway of CPAP established and CPAP naïve individuals is depicted in Figure 5.1.

Population cohort

The study was conducted at the RSSC, Papworth Hospital NHS Foundation Trust which is an accredited sleep centre with specialist expertise in the diagnosis, treatment and follow up of patients with OSA as well as respiratory and non-respiratory sleep disorders with ready access to full electroencephalogram based polysomnography. The sleep centre offers specialist diagnostic tests, treatments and follow up to patients with a great range of sleep disorders and receives referrals from across the United Kingdom. To maximise patient safety, the study night took place in the RSSC main ward, where a team of qualified nurses

supervise patients during the night. There was a supervising clinician monitoring the patients, including nocturnal oxygen saturations throughout the night and another member of staff attended to allow for an appropriate rest break. A full resuscitation team was available with immediate response.

Population

The participants were recruited from the RSSC's pool of patients with moderate OSA, established on treatment with CPAP as well as CPAP naïve patients.

Rationale for patient selection

I elected to study patients with moderate OSA, in order to maximise the chance of identifying any effect on AHI. In other studies drugs have increased and decreased AHI; an effect which might be obscured if AHI is at the physiological limits (low or high) at baseline. Patients with severe OSA may present as a high risk group and therefore a moderate OSA cohort was felt to be the most suitable population to study. To improve the recruitment process I opted to study patients with moderate OSA, already established on CPAP as there is large pool of these patients currently being cared for at the RSSC and as the recruitment process was slow we also included newly diagnosed patients naïve to CPAP . To study the effect of morphine we employed the CPAP withdrawal model. This was first described in 2011 (Kohler et al. 2011) and showed that withdrawal of CPAP is associated with return of OSA within the first night and the severity of OSA is not increased further after the first week of CPAP withdrawal. In addition, this trial showed a return of sleepiness associated with OSA after 2 weeks of CPAP withdrawal and therefore the patient's quality of life should not be compromised by a shorter period without CPAP. I asked patients to remain off CPAP for 6 nights prior to the study night. This model is useful to evaluate short term physiological effects of OSA as well as responses to various treatments (Kohler et al. 2011).

I chose to exclude participants who did not have English as their first language and would require an interpreter, as they may experience difficulties in reporting any symptoms

associated with investigational medical product (IMP) administration to the supervising clinician. As the study was conducted out of hours, an interpreter may not have been readily available. To minimise bias of any non-investigational medical product (NIMP) on OSA, ondansetron was used as the antiemetic. Ondansetron has been studied in patients with OSA and shown to have no effect on AHI (Stradling et al. 2003).

Inclusion criteria

<u>*ALL participants*</u>

1. Age ≥ 18 years

<u>*Group A*</u>

2. Patients with a diagnosis of moderate or severe OSA at diagnosis, diagnosed by nocturnal oximetry, rPG or PSG (defined as AHI or ODI of 15-50 events/hour) established on CPAP

3. and established on CPAP with confirmed moderate OSA (AHI 15-29 events/hr) 6 nights after withdrawal of CPAP (confirmed at baseline rPG)

<u>*Group B*</u>

4. Patients diagnosed with moderate OSA by rPG or PSG, naïve to CPAP treatment

Exclusion Criteria

1. Inability to give informed consent or comply with the   protocol

2. Current, clinically significant acute respiratory tract infection (at screening and/or at study visit)

3. Chronic respiratory disease (other than OSA), symptomatic ischaemic heart disease

4. Pregnancy or suspected pregnancy/breast feeding

5. Current or recent (within last week before entering the trial and for the duration of the trial) use of gabapentin, pregabalin, melatonin, mirtazapine, benzodiazepines,

barbiturates, sodium oxybate, ramelteon, Z-drugs and opiates/opioids

6. Monoamine oxidase inhibitors (MAOIs), linezolid, taken within 2 weeks of participation in the trial

7. A known allergy to the IMP or NIMP

8. Patients with an inadequate command of English requiring an interpreter overnight

9. Change in weight of > 5% since the baseline rPG (group A only)

10. Vital signs recordings (oxygen saturations, blood pressure, pulse rate) that in clinicians opinion deem the patient unsafe to participate in the trial

11. Clinician deems the patient unsafe to participate in the trial (e.g. severely sleepy patients who cannot withdraw from CPAP); group A only

12. CPAP intolerant/poor responder

13. History of drug abuse (oral or intravenous) including: alcohol, substituted amphetamines, barbiturates, benzodiazepines, cocaine, methaqualone, cannabis and opioids.

14. A drop of oxygen saturations below 85% continuously for longer than five minutes during diagnostic study (rPG/PSG).

15. Professional driver (group A only)

Intervention

All patients enrolled were given 10 mg of iv morphine sulphate in two divided 5mg doses. Morphine sulphate injection (1mg/ml) is a phenanthrene-derivative opiate agonist. It is the principal alkaloid of opium. It is presented as a clear, colourless or almost colourless, sterile solution in a syringe for injection. Peak analgesia occurs 20 minutes following IV infusion. Maximal respiratory depression occurs within 3 - 7 minutes. Analgesia may be maintained for up to 7 hours. Although the sensitivity of the respiratory centre returns to normal within 2 - 3 hours, respiratory minute volumes may remain below normal for 4 - 5 hours. Intravenous morphine sulphate is immediately bioavailable, since no absorption is

required. About 90% of the drug is excreted within 24 hours of giving the last dose. Morphine sulphate is a licensed medication manufactured by a number of licensed manufacturers within the UK. Routine clinical stocks held by the hospital pharmacy were used.

Rationale and justification for the proposed morphine sulphate dose

Opioid analgesia is commonly used to control pain after the surgery. The method of pain relief known as patient-controlled analgesia (PCA) enables patients to administer pain relief themselves – up to a preset limit – via a syringe driver attached to an intravenous drip or epidural catheter. It is widely used in hospitals and is an effective approach to limiting postoperative pain. The locally used PCA protocol for patients undergoing cardiac surgery in Papworth Hospital allows patients to administer 1mg of intravenous (iv) morphine sulphate as a bolus at five minutes intervals, totalling a maximum of 12 mg of iv morphine per hour. Yarmush et al. reported that a median number of two (0-5) 2 mg iv boluses of morphine sulphate were required for successful post-operative analgesia in surgical patients expected to experience moderate to severe pain (Yarmush et al. 1997). Similarly, Beloeil et al. found that median effective analgesic dose of morphine sulphate in sixty patients with mild to moderate pain after the minor surgery was 5mg (4-6mg) (Beloeil et al. 2004). Shaw et al investigated the effect of iv morphine (0.1mg/kg) in seven healthy volunteers, with no serious adverse effects reported (Shaw et al. 2005). Given the above evidence, 5mg a dose of 5mg of morphine sulphate was chosen as it was felt bothe effective to control pos-operative pain and safe. As respiratory minute volumes may remain below normal for 4 - 5 hours after administration of morphine, second dose was administered 4 hours after the first dose was given.

Outcomes

Respiratory polygraphy (rPG) was performed using the Embletta portable device (ResMed) during the baseline study and study night. Both assessments were performed 6 nights following CPAP withdrawal. Baseline rPG was recorded in the patient's own home in

order to confirm moderate OSA (group A) and the study rPG in the RSSC. The rPG recorded for a minimum of 6 hours and a maximum of 10 hours. The following measurements were recorded during the rPG:

1. Thorax and abdominal effort through XactTrace Respiratory Inductive Plethysmograph sensors

2. Mean and minimum oxygen saturation (SpO_2), percentage of time spent with nocturnal saturations of ≤ 90% (SpO_2≤ 90%) and pulse rate via pulse oximetry

3. Airflow via thermistor and pressure flow

4. Body position via body position sensor

Data were downloaded to an integrated system (Embla, ResMed, Bella Vista, Australia) and scored manually according to standardised criteria by a qualified sleep polysomnographer. An apnoea was defined as >90% reduction in air flow for ≥10 seconds. These were scored as central if there was an accompanying cessation of chest and abdominal movements. Hypopnea was defined as a reduction in flow of between 50% and 90% lasting ≥10 seconds accompanied by ≥3% decrease in oxyhaemoglobin saturation (SpO_2). OSA was defined as the presence of ≥5 episodes of obstructive apnoea and hypopnoea (AHI) per hour sleep. AHI cut off was used to define the severity of OSA. As such moderate OSA was defined as AHI 15-30 events /hour

Primary outcome

Change in Apnoea Hypopnoea Index (AHI) – change in mean number of apnoeas and hypopnoeas for time in bed from participant's baseline rPG to study rPG

Secondary outcomes

Change in the following parameters from participant's baseline rPG to study rPG:

1. Change in 4 % oxygen desaturation index (ODI) between baseline and study night

2.   Change in mean oxygen saturations between baseline and study night

3.   Change in minimum saturations between baseline and study night

4.   Change in % time spent with saturations <90% between baseline and study night

5.   Change in total number of obstructive apnoeas (OA) and central apnoeas (CA) between baseline and study night

6.   To assess the number and severity of any adverse events associated with IMP

Eligible participants were sent a Patient Information Sheet (PIS) and after a few days were approached by telephone to discuss the study and enquire about their interest to participate in the study. I have telephoned and screened for eligibility those who were interested to participate, mainly to assure that they were safe to stop the CPAP treatment (screening proforma is attached in Appendix 2). Patients who met the eligibility criteria were asked to remain without CPAP for 6 nights prior to Visit 1 to employ the CPAP withdrawal model (described in Chapter 2). During this visit, patients were set up with the rPG (baseline rPG) equipment for completion at home that night and were asked to return to the RSSC the following day (Visit 2) and then restarted CPAP treatment that evening. All sleep studies were analysed by the same polysomnographer to increase reproducibility. Patients with confirmed moderate obstructive sleep apnoea were booked to attend the RSSC for an overnight inpatient rPG to complete their Visit 3 (Study visit) and asked to stop CPAP treatment 6 nights prior to this visit. During this visit demographic variables describing the participants (including age, weight, height, BMI, neck circumference) were recorded along with medical, surgical and drug history. A full clinical examination was undertaken and vital signs recorded. An intravenous cannula was placed in a forearm vein. Participants received 5mg of iv morphine sulphate with 4mg of iv ondansetron (to combat nausea, side effect of morphine sulphate) thirty minutes before lights went off and again 4 hours following the first dose. An overnight rPG was performed and patients were monitored with nocturnal oximetry

which was observed in real time by a clinician for safety resons. Patients were contacted 24 hours following discharge from Visit 3 to review adverse events.

Due to the difficulty recruiting, the trial steering committee and ethical committee agreed to include patients with moderate OSA who were newly diagnosed and not established on CPAP. These patients were given the PIS after their diagnostic study (polysomnography) and contacted a few days later to assess their interest in participating. If they agreed to participate they were screened by telephone to assess for eligibility and had the study visit booked (Visit 3), as described above.

Despite including CPAP naïve patients in the screening cohort the recruitment of patients to the study was slow and extending the proposed period for the study stretched the financial support to the limits. The Trial Steering Committee therefore took the decision to halt the study prematurely, before reaching the recruitment target.

Figure 5.1   **Study protocol**

| Screening (Patient Identification) | • Patients with moderate OSA treated with CPAP identified from the database
• PIS and trial summary sent to patients by letter. CPAP naïve patients were identified after polysomnography and given PIS.
• Patients given a few days after receiving the information to decide if they are interested in taking part in the trial
• Patients contacted by telephone to assess interest and suitability checked |

↓

| Telephone Screening Interview | • Telephone Screening Interview: telephone assessment by physician to check eligibility and ensure patient is safe to stop CPAP
• Verbal consent to stop CPAP obtained and Visit 1 organised for patients treated with CPAP
• CPAP naïve patients were booked for Visit 3 |

↓

| VISIT 1

(patient collects sleep study equipment)) | • Eligibility confirmed
• Written informed consent gained
• rPSG equipment explained and given to patient to be performed at home 6 nights after CPAP withdrawal |

↓

| VISIT 2

(patient returns sleep study equipment) | • rPSG equipment returned and analysed
• Eligibility confirmed
• Patient contacted by telephone to reconfirm interest and visit 3 booked (remind to stop wearing CPAP 6 nights prior to visit 3)
• Patients meeting inclusion criteria recruited |

↓

| VISIT 3

(study visit) | • Demographic data and physical examination recorded
• Vital signs
• IV cannula inserted |

↓

Overnight inpatient respiratory polygraphy (rPSG) →

5 mg iv morphine sulphate (**in 5mL normal saline**)

• 30 minutes before lights off plus
• 4mg iv Ondansetron

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5 mg iv morphine sulphate (**in 5mL normal saline**)

• 4 hours after the first dose plus
• 4mg iv Ondansetron

↓

Oral ondansetron 4mg following day if required

↓

Scoring of respiratory polygraphy and data collection

↓

Adverse events (including 24 hour telephone follow up)

↓

Data analysis, writing, presentation

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Statistical analysis

A prospective power analysis was conducted for a single outcome variable (AHI) to determine sample size. This analysis indicated that 26 patients were needed. The assumptions for the power analysis were that alpha =0.05, power =0.8, SD =7, desired detectable difference =4, and statistical analysis conducted on paired samples and correlation for paired data =0.8. Descriptive statistics are shown for the variables used in this study (Table 6.1). Data were analysed using Wilcoxon signed-rank non-parametric test using statistical software R, version 3.4.1. Continuous variables are reported as median (IQR) and categorical variables as percentages. Results with $p \leq 0.05$ were considered to be significant.

Results

The total of 173 patients was screened for eligibility in the study, of which 18 were eligible for participation. Of these 6 were eligible to attend visit 3 and received intravenous morphine sulphate (Figure 5.2), of whom 2 were CPAP naïve patients and 4 were established on CPAP and had to withdraw from CPAP, six nights prior to study night (Figure 5.2)

Figure 5.2 Study Consort diagram
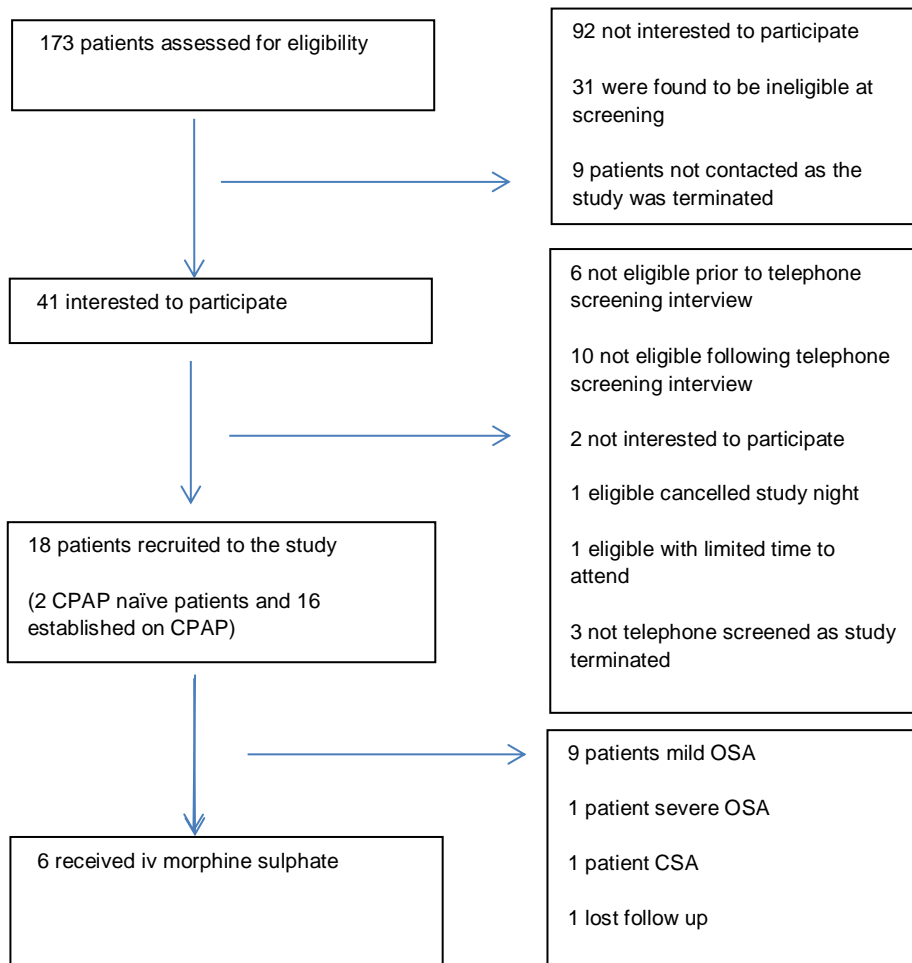
Demographics of all patients enrolled to the study and those who received intravenous morphine sulphate are populated in Table 5.1.

Table 5.1 Patient demographics at baseline

Demographics	All recruited subjects n=18	Subjects recruited to receive morphine n=6
Age yrs	50 (42-58)	55 (44-58)
Male (%)	13 (72%)	5 (83%)
Weight kg	97(91-108)	103 (99-107)
BMI kg/m2	-	33 (31-35)
AHI events/hr	13 (4-19)	19 (17-20)
Mean SpO2 %	93 (92-94)	93 (92-94)
Minimum SpO2 %	85 (81-86)	83 (81-85)
ESS	-	8 (4-17)
Neck circumference cm	-	44 (43-45)
Smoking		
Non smoker	-	2 (33%)
Ex-smoker	-	2 (33%)
Smoker	-	2 (33%)
Type 2 DM (%)	-	0 (0%)
COPD (%)	-	0 (0%)
Ischaemic Heart disease (%)	-	0 (0%)
Hypertension (%)	-	1 (17%)
Antidepressant (SSRI) (%)	-	4 (67%)
Systolic BP mmHg	-	137 (127-160)
Diastolic BP mmHg	-	86 (83-89)

Data presented as median (IQR) unless stated otherwise. BMI: Body mass index; AHI: apnoea/hypopnoea index; SpO2: peripheral oxygen saturations; ESS: Epworth Sleepiness Scale score; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; BP: blood pressure

Primary outcome

There was a non-significant fall in AHI (median difference (MD) -12.95; IQR 9.45; p=0.173) which was the primary outcome of the study using Wilcoxon signed-rank non-parametric test.

Secondary outcomes

There was significant difference in three of the secondary outcomes (Table 5.2) namely the total number of obstructive apnoeas MD -24, IQR 43.5, p=0.039 (Figure 5.3), total number of central apnoeas MD -3 IQR 2.75, p=0.027(Figure 5.4) and mean nocturnal SpO2 MD -0.9, IQR 0.83; p=0.05. To ensure that the difference in total number of OA and CA was not attributed to the rPG recording time, post hoc analysis of obstructive/central apnoea indexes was carried out. This showed that the obstructive apnoea index (MD -2.7, IQR 7.37, p=0.03) and central apnoea index (MD – 0.35, IQR 0.83, p=0.04) were both significantly reduced.

Figure 5.3. Obstructive Apnoea Index pre and post administration of iv morphine sulphate
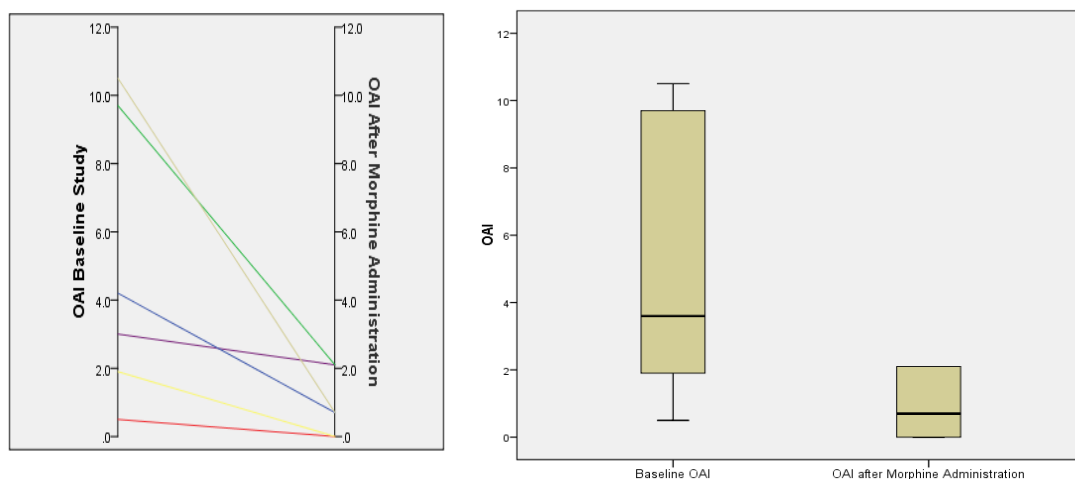
Figure 5.4. Central Apnoea Index pre and post administration of iv morphine sulphate
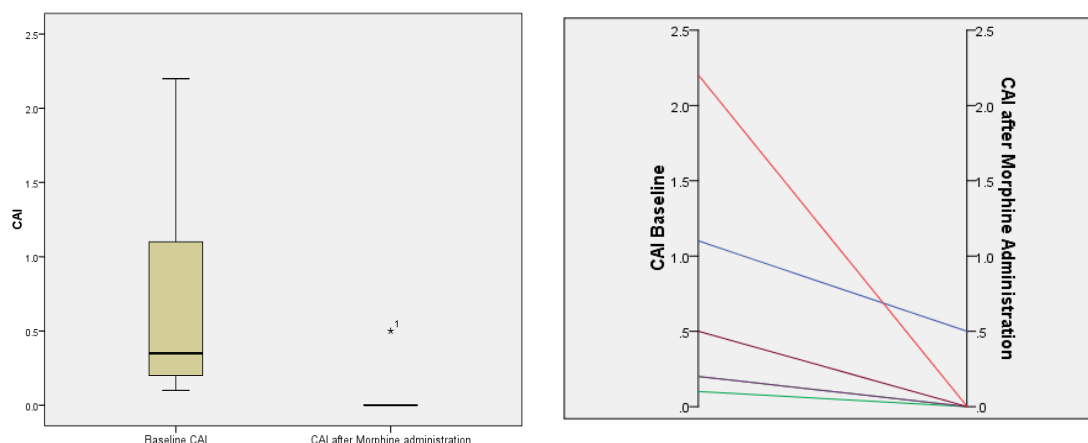
Table 5.2 Secondary outcomes variables

Variable	MD	IQR	p
ODI	-7.4	5.95	0.35
Mean SpO$_2$	-0.9	0.83	0.05
Minimum SpO$_2$	0	6.5	0.67
% time spent with SpO2<90%	-23.85	97.7	0.12
Total number of OA	-24.0	43.5	0.04
Total number of CA	-3.0	2.75	0.03

MD: median difference; IQR: interquartile range; SpO$_2$: peripheral arterial saturations

Adverse events

Two patients receiving iv morphine sulphate reported adverse events. One in terms of bradycardia that may not have been related to the IMP or NIMP and could represent physiological nocturnal bradycardia. For the safety reasons he did not received the second dose of the IMP. The second patient experienced headache which was possibly related to IMP but resolved promptly with administration of paracetamol.

Discussion

In this small cohort of patients with moderate OSA administration of 10mg of iv morphine during the night has not significantly worsened the severity of OSA in terms of an increase in AHI but has led to significant reduction of OAI and CAI as well as small decrease in mean nocturnal saturations. Given the small number of patients recruited to this study no robust conclusion can be drawn but these results raise the interesting hypothesis that opiates, in some OSA patient phenotypes, contrary to current beliefs, can stabilise respiration during the night and lead to a reduction of OSA severity.

A similar outcome was reported from the RCT by Bernards et al. Remifentanil infusion did not significantly change AHI (MD 10.00, 95% CI -9.83 to 29.83) but led to a significant reduction in OAI (MD -9.00, 95% CI -17.40 to -0.60). Contrary to the improvement in CSI in our patients, remifentanil infusion led to a significant increase in the number of central apnoeas (MD 16.00, 95% CI -2.21 to 34.21) in patients with moderate OSA. This was not uniform across the group but reflected very large increases in a subset of four participants. These participants with significant increase in CSI were older (age, 56 ± 11 *vs.* 46 ± 11 y) and less obese (BMI, 28 ± 7 *vs.* 33 ± 8), compared to patients in the remifentanil group in whom no significant increase in CSI was seen. It is possible that I have not observed a significant increase in CSI as my patient cohort was too small and participants were more obese and younger compared to those in the remifentanil trial.

Opioids may reduce respiratory rate and tidal volume, decrease chemoresponsiveness to hypercapnia/hypoxia as well as decrease upper airway muscle tone which might impair respiratory function in patients with SDB (Koo 2011). Despite this fact, in several previous studies, excluded from the Cochrane review reported in Chapter 5 due to not meeting inclusion criteria, the administration of a moderate opioid dose to opioid naive individuals without SDB did not lead to development of SDB . Bernards et al. and the current trial have shown an improvement in OAI in patients with diagnosed moderate OSA.

Bearing in mind the limitations of both studies, in particular the small size, these results nonetheless raise an interesting hypothesis that in certain people with OSA, administration of opioids may not be deleterious to the respiration but may lead to fewer obstructive events during the sleep. These trials were not designed to answer the pathophysiological mechanism of this finding but do provide pilot data and hypotheses for further trials. Recently, Rowsell et al. examined the effect of 40 mg, orally administered morphine to 60 male patients with various OSA severity, in a single night, RCT trial and reported that this dose did not worsened nocturnal hypoxia or AHI but reduced minimal SpO_2 by 1.3%. In ptients with severe OSA a lower baseline CO2 ventilatory response threshold correlated with worsening hypoxia, AHI and ODI. This may suggest that opiod response in patients with OSA realtes to baseline CO2 response threshold and that patients with more severe OSA may be more at risk when given opiods (Rowsell et al. 2019).

The effect of iv morphine on sleep architecture has been studied. Morphine reduces the amount of REM sleep during the night in healthy volunteers. (Shaw et al. 2005) but also in patients with moderate OSA (Bernards et al. 2009). Reduction in pharyngeal tone in REM sleep leading to an increase in UA resistance and worsening severity of OSA in REM sleep has been described (Horner et al. 1991; Horner 2007). It is possible that opioid induced REM sleep reduction may be responsible for the improvement in OAI with both remifentanil and in the current study. It has been shown that short term suppression of REM sleep leads to REM sleep rebound and as such short term suppression of REM sleep due to opioid administration in the postoperative period may lead to REM sleep rebound and worsen the severity of OSA once the opioids are withdrawn a few days post- operation. The exact effect of opioid related REM suppression together with previously reported postoperative REM suppression is unknown and will require further evaluation.

The current study has significant limitations, mainly the small sample size. I have tried hard to maximise recruitment through various amendments in inclusion criteria of the studied population but despite all the efforts the recruitment remained below the target. The

current study aimed to provide pilot data for future a RCT evaluating the effect of opioids on patients with OSA and it became clear that a multicentre approach with dedicated research staff concentrating on patient recruitment will be needed. Another limitation of the current study is comparing the results of respiratory polygraphy undertaken in different environments (home and hospital) which may lead to different sleep quality potentially affecting the severity of SDB. Performing the baseline study at home was chosen to reduce the need for hospital visits to help with recruitment. I have only studied patients with moderate OSA without significant nocturnal hypoxia and it is possible that patient with more severe OSA with more pronounced desaturations during the night and out of the currently studied age group may respond differently to the administration of iv morphine.

Future directions

Due to the small sample size of currently available studies examining the effect of opioids on the patients with OSA, no recommendation or definite conclusions can be drawn. Given the difficulty in recruiting patients into the current trial the study is underpowered to provide meaningful results but it is the first trial examining the effect of iv morphine sulphate on patients with diagnosed OSA. The results of this pilot study provide a basis for further research examining the effect of opiods on patients with OSA. From anecdotal experience we know that only a small number of patients experience significant morbidity and mortality when treated with opioids in the postoperative setting and it is likely that specific OSA phenotypes are particularly at risk of opioid related morbidity and the aim of future research should be to identify these at risk patients and examine the mechanisms by which opioids affect respiratory physiology in them.

Chapter 6

Conclusion

OSA is common and its prevalence is expected to rise with increasing obesity and aging of the population leading to the possibility of increasing numbers of patients with

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unknown and untreated OSA presenting for surgical procedures. There is moderate evidence for an increased risks of postoperative complications in patients with OSA undergoing general and upper airway surgery. To date only a few studies have investigated the prevalence and postoperative outcomes in patients with OSA undergoing major cardiac surgery. These studies show conflicting results in terms of risk of post-operative complications with an increased risk of AF, prolonged mechanical ventilation, ICU and hospital LoS, post-operative infection and encephalopathy, all being reported. The main issue with these studies is that the majority has been either retrospective or used questionnaires to diagnose OSA and there are significant differences in reported outcomes and the definition of OSA which has changed over the years.

Preoperative assessment is aimed at reducing the perioperative complications and identifying patients with significant respiratory or cardiac comorbidities. Standardised screening for OSA prior to surgery has not yet been established despite emerging evidence of an association of OSA and postoperative complications, although some centres in UK have started using screening questionnaire to screen for OSA before surgery. Perhaps the main reason for the lack of standardised screening is the lack of evidence that treating OSA pre or post-surgery significantly improves outcomes in these patients.

Both surgeons and anaesthetists fail to identify a significant proportion of patients with symptomatic undiagnosed OSA during assessment in preoperative clinics (Singh et al. 2013) and despite efforts to develop accurate and simple screening tools to identify patients with OSA most lack high enough sensitivity and specificity to be recommended for routine clinical practice. Their cost effectiveness has not been established. Patients with OSA are at increased risk during the perioperative period due to difficult intubation and a small proportion of OSA patients may be vulnerable to anaesthetic medication and opioid analgesia. These agents may worsen OSA by reducing UA dilator muscle tone and increasing UA resistance but may also impair ventilation which may be particularly important for patients with obesity related hypoventilation. However to date there is only one RCT

examining the effects of the opioid, remifentanil, on patients with OSA which shows that this drug does not worsen OSA. There are a few case reports describing deleterious effects of morphine on patients with OSA receiving opioid analgesia during surgery. This is important as the early postoperative period may represent a risky time for patients with OSA due to REM rebound and sleep fragmentation which have been shown to worsen nocturnal hypoxia and decrease pharyngeal muscle tone. However, the exact mechanisms for deleterious effects of OSA on postoperative outcomes remain unknown.

This thesis aimed to investigate the prevalence of sleep apnoea and its association with postoperative complications in a very specific cohort of patients undergoing major cardiac surgery. It also explored the effect of intravenous opioid analgesia on postoperative outcomes in this patient cohort. As a separate study, I explored the effect of intravenous opiate, morphine sulphate, on the severity of OSA in patients with moderate OSA. Secondary research was undertaken to examine extant evidence of the effect of opioids and sedatives on patients with OSA. All the new findings are summarised in this chapter.

The results of the SACS study reported in Chapter 2 show a high prevalence of OSA (47%) in cardiac patients requiring revascularisation surgery which may not be surprising given that coronary artery disease and OSA share common risk factors including obesity, age and male sex. The prevalence of sleep apnoea reported in this thesis is lower compared to the prevalence reported in other prospective studies in this surgical cohort which used polysomnography. This is likely due to the fact that polysomnography represents a more sensitive diagnostic tool compared to oximetry as used in my study. Diagnosis of sleep apnoea in this thesis was based on significant, intermittent oxygen desaturations reflected in 4% ODI. Since oximetry cannot distinguish between central and obstructive sleep apnoea the reported prevalence is that of sleep apnoea as it is likely that some patients suffered with central sleep apnoea.

Regardless of the nature of sleep apnoea (central vs. obstructive) it was found that the probability of developing postoperative complications rose with severity of sleep apnoea, defined as oxygen desaturations during the night (OR1.1 for each unit increase in ODI, p=0.014)) suggesting that the intermittent nocturnal desaturations may be implicated in the pathophysiology of the effect of sleep apnoea on postoperative outcomes. This was the first prospective study in cardiac population showing a severity response effect and that even patients with mild sleep apnoea had a higher probability of developing postoperative complications than people with no desaturations at night. The mechanism of this effect is unknown and was not the focus of this thesis. The effect of central sleep apnoea on postoperative outcomes has not been studied but it is possible that some patents in my cohort had CSA and it is important that future studies use diagnostic methods able to distinguish obstructive and central breathing events and separately examine their association with postoperative outcomes.

The association of OSA with health care utilisation including LoS on ICU, reintubation rate and in hospital LoS were examined as part of SACS. I did not find that an increased probability of developing complications in patients with sleep apnoea led to increased health care utilisation in this population. One possible explanation for this finding was small sample size but it is also possible that LoS depends on many non-biological factors including: local ICU discharge policies, bed availability on the hospital ward and therefore LoS on ICU may not represent a robust primary outcome. For future studies complications may be a more appropriate primary outcome.

Other independent risk factors for increased probability of developing postoperative complications in the SACS study were administration of IOA (OR 3.1, p=0.010) and EuroSCORE (OR 1.34, p<0.001). On further analysis it was found that patients with sleep apnoea but also those without had a higher probability of developing postoperative complications, when given intravenous opioid analgesia. When I examined for associations between the dose of morphine and postoperative complications, no significant association

was found but this could have been due to the loss of power for assessing this outcome. It is possible that there may be a dose association for worse postoperative outcomes in patients with OSA but larger trials are needed to clarify the effect.

It is difficult to be dogmatic about the clinical implications of the association between morphine use and complications. Opioid analgesia remains widely used in the postoperative setting with no obvious viable alternative. Further research is needed to further explain this result. It is possible that patients who received iv morphine simply represented a more unwell group of patients with causation the other way around, namely complications required the use of morphine. For the moment intravenous opioids should still only be used with caution in this cohort of patients.

Given the association between sleep apnoea and ICU complications it is possible that these complications are more likely to arise if responsible clinicians are unaware of the diagnosis of sleep apnoea in patients presenting for surgery. Identifying high risk patients, prior to surgery would allow for cautious monitoring and taking preventative measures in perioperative settings. A simple and cost effective screening tool could help with identifying such patients prior to surgery. The results of this thesis show that the STOP-Bang questionnaire, validated against nocturnal oximetry, at the conventional cut-off value, performed poorly to accurately identify patients at high risk for mild and moderate/severe SA but scores of 0-2 would with high confidence exclude those without the diagnosis. The best performance was found for moderate SA at cut-off value of ≥6 with moderately high sensitivity and specificity of 75%. Given the high specificity at this cut off in this cardiac, surgical cohort, all patients with the STOP-Bang ≥6 could be screened with nocturnal oximetry prior to surgery. I found that ODI is independently associated with increased risk of developing postoperative ICU complications and thus this simple screening method could identify patients who may be at higher risk and would allow for appropriate monitoring to mitigate the risks. At present, however, there is no evidence that this approach reduces the risks, and moreover no evidence that treating OSA with CPAP improves postoperative

outcomes. Future research should therefore concentrate on establishing the clinical and cost effectiveness of CPAP in the treatment of OSA in patients presenting for cardiac as well as general surgery.

Following the results of SACS study and in particular, the effect of morphine on postoperative complications, the existing literature was examined via a Systematic Cochrane review for evidence of the effect of opiates/opioids, sedatives and hypnotics on patients with pre-existing OSA. This review examining evidence from RCT's comparing these compounds with placebo, showed that there is currently no robust evidence to guide clinicians when prescribing these drugs to patients with OSA. The available evidence consists of short trials with small numbers of people randomly assigned to these treatments, with most trials unblinded and with unclear risk of selection bias. There was only one trial in this review examining the effect of an opioid, remifentanil, on patients with OSA. The result of the review showed that there is currently no available evidence supporting deleterious effects of the compounds, studied in the review, on worsening the severity of OSA as evidenced by change in AHI. There is nonetheless, a need for larger and methodologically robust trials to assess the true effect.

Based on the conclusion from the Cochrane Systematic review and the aforementioned results from the prospective observational cohort trial, I studied the effect of intravenous morphine on patients with pre-existing moderate OSA, (MIMOSA). Unfortunately, despite the various measures to improve recruitment to this study I struggled with recruitment and the trial was stopped before reaching the target sample. Given the small sample size no definite no conclusion can be reached. Analysis of the data showed that morphine sulphate did not worsen the severity of OSA in terms of change in AHI but rather found that there was an improvement in OAI and CAI in my patient cohort, a finding similar to that shown with remifentanil infusion (Bernards et al. 2009). Both of these trials

included only a small number of participants but raise a hypothesis that morphine given to certain phenotype of OSA patients may have a protective effect.

In conclusion, this thesis showed that sleep apnoea is prevalent in the cardiac surgical population as previously reported. More importantly, the hallmark of sleep apnoea, intermittent oxygen desaturations during the night were found to be an independent predictor for an increased risk of ICU complications in patients with undiagnosed sleep apnoea undergoing cardiac surgery. Even patients with mild sleep apnoea were found to have a higher probability of developing such complications and the probability rose with the severity of sleep apnoea. Patients presenting for cardiac surgery can be screened by the STOP-Bang questionnaire, where a score 0-2 would , with high confidence exclude sleep apnoea but those scoring ≥ 6 could be tested with nocturnal oximetry prior to surgery to identify patients at risk. The administration of intravenous opioids was associated with worse postoperative outcomes among cardiac surgical patients. The effect of opiates and opioids on patients with OSA remains unknown as the current Cochrane review concluded that there is not enough evidence to advise regarding the safety of morphine on patients with OSA although there is currently no evidence for a deleterious effect. The MIMOSA trial, reported in this thesis, failed to clarify this clinical question as the trial had to be stopped prematurely due to difficulty recruiting eligible subjects. In the small numbers of participants studied all improved on measures of sleep apnoea rather than deteriorated. Further research in this area is needed.

Reflection of the trial methodology

The selected trial methodology was governed by a number of constraints including available financial resources, ethical considerations, population available for recruitment and technology available to measure study outcomes. On reflection of the methodology used in this thesis, changes in trial's methodology may have improved the value of the research.

In the prospective observational cohort study, using nocturnal oximetry to diagnose sleep apnoea did not allow differentiation of central, obstructive of mixed sleep apnoea. If rPSG was used instead such distinction would be possible and would allow better understanding of association of type of sleep disordered breathing with postoperative complications and could possibly identify more patients in the severe spectrum of OSA. Using sleep diagnostics in the patient's own home instead of in hospital, the night before surgery, could allow better sleep quality and possibly more accurate outcomes. The in hospital assessment was favoured to reduce patient's travelling time for home studies.

In the MIMOSA trial, a double blinded, RCT would provide the highest level of evidence on the effect of morphine on patients with OSA but in view of the high number of subjects needed to show a difference when the power calculation was employed it was decided that a paired design trial was more pragmatic. More accurate assessment of the effect of morphine on patients with moderate OSA would be available if patients were studied in hospital on both, the baseline and morphine night visits as different quality of sleep may be observed in hospital and at home introducing the possibility of assessment bias. It was felt that to minimise the hospital admissions for patients it was more pragmatic to perform baseline study at home.

Areas for future study

The results of this thesis show an association between sleep apnoea and an increased risk of postoperative complications. The next important question is to assess the effect of CPAP treatment on postoperative outcomes in patients with OSA presenting for surgery. To confirm the effect of morphine on patients with OSA and to identify phenotypes at risk the effect of opioids require a larger RCT. The results of the Cochrane review will require an update in due course to gather and report up to date evidence

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Appendix 1

Systematic Cochrane Review (Chapter 4). Figure 4.2. A summary of the risk of bias of included studies

Appendix 2

MIMOSA study, Chapter 5.

Screening questionnaire employed to check for eligibility to participate in the study and for safety to stop the CPAP treatment.

Patient Addressograph Label
Name:
Date of Birth:
Hospital No:
NHS No:

MIMOSA

Morphine In Moderate Obstructive Sleep Apnoea

Telephone Screening Proforma to check

ensure suitability to withdraw from CPAP

Date of telephone call: _____   **Time of telephone call:** _____

Is the patient interested in participating in the MIMOSA study and happy to proceed with the telephone screening call?   Yes ☐   No ▨

SECTION 1:

Check Inclusion Criteria	Yes	No
1. Age ≥ 18 years	☐	▨
2. Currently using CPAP for a previous diagnosis of moderate OSA diagnosed by nocturnal oximetry, respiratory PSG or PSG (defined as AHI or ODI of 15-29 events/hour) *(diagnosis to be confirmed by baseline respiratory polygraphy after CPAP withdrawal for 6 nights)*	☐	▨

If answered yes to all inclusion criteria, please complete exclusion criteria below

Check Exclusion Criteria	Yes	No
16. Inability to give informed consent or comply with the protocol	▨	☐
17. Current, clinically significant acute respiratory tract infection (at screening and at study visit)	▨	☐
18. Chronic respiratory disease (other than OSA), symptomatic ischemic heart disease	▨	☐
19. Pregnancy or suspected pregnancy/breast feeding	▨	☐
20. Current or recent (within last week of entering the trial and for the duration of the trial) use of gabapentin, pregabalin, melatonin, mirtazapine, benzodiazepines, barbiturates, sodium oxybate,	▨	☐

ramelteon, Z-drugs and opiates/opioids		
21. Monoamine oxidase inhibitors (MAOIs) linezolid, taken within 2 weeks of participation in the trial	☒	☐
22. A known allergy to the IMP or NIMP(s)		
23. Patients with an inadequate command of English and requiring an interpreter overnight	☒	☐
24. CPAP intolerant/poor responder	☒	☐
25. History of drug abuse including alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methaqualone, cannabis and opioids	☒	☐
26. Professional Driver	☒	☐

Page 1 completed by:

Signature: _____

Print name: _____

Date: _____ Designation: _____

Patient Addressograph Label
Name:
Date of Birth:
Hospital No:
NHS No:

If answered no to all exclusion criteria, please complete section 2 below

SECTION 2: Further questions to the patient:	**Yes**	**No**
1. Are you too sleepy to withdraw from CPAP for six consecutive nights?	▨	☐
2. Prior to starting CPAP, have you ever fallen asleep whilst driving?	▨	☐
3. Prior to starting CPAP, have you ever had a road traffic accident due to falling asleep?	▨	☐

The patient will be deemed unsafe to participate in the trial if <u>they answer yes to any one of the above questions</u> in Section 2.

Decision:	**Eligible**	☐	**Not Eligible**	☐

I have confirmed with the patient that they are eligible to participate in the MIMOSA study. I am happy for the patient to stop using CPAP for 6 nights prior to undergoing a baseline respiratory polygraphy study at home. I have emphasized to the patient that if they feel concerned, unsafe or wish to start using their CPAP machine again during these 6 nights they can do so and should let research team know as soon as it is convenient.

_____ _____ _____

Print Name   *Signature*   *Delegation*

_____

Date

Baseline rPSG visit

Date: __ __ / __ __ / __ __ __ __   Time: __ __ : __ __

Last night of CPAP: __ __ / __ __ / __ __ __ __

Page 2 completed by:
Signature: _____
Print name: _____
Date: _____ Designation: _____

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Appendix 3

NRES Committee East Midlands - Northampton
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839435
Facsimile: 0115 8839294

21 December 2012

Dr Ian Smith
Respiratory and Sleep physician
Papworth Hospital NHS Trust
Respiratory Support & Sleep Centre
Papworth Hospital
Papworth Everard
CB23 3RE

Dear Dr Smith

Study title:	**Impact of sleep disordered breathing on immediate post operative outcomes in patients undergoing elective surgical coronary revascularisation with or without heart valve surgery**
REC reference:	**12/EM/0485**
IRAS project ID:	**115532**

The Proportionate Review Sub-committee of the NRES Committee East Midlands - Northampton reviewed the above application on 20 December 2012.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Miss Georgia Copeland , NRESCommittee.EastMidlands-Northampton@nhs.net.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved were:

Document	Version	Date
Covering Letter		10 December 2012
GP/Consultant Information Sheets	A 1.0	04 December 2012
GP/Consultant Information Sheets	B 1.0	04 December 2012
Investigator CV		12 June 2012
Other: CV - Dr Mason		04 December 2012
Other: DVLA Leaflet		
Other: Letter		13 December 2012
Participant Consent Form	1.0	04 December 2012
Participant Information Sheet	1.0	04 December 2012
Protocol	1.0	04 December 2012

Questionnaire: STOP-BANG		
Questionnaire: Epworth Sleepiness Scale		
REC application	115532/3916 62/1/105	06 December 2012

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
information is available at National Research Ethics Service website > After Review

12/EM/0485	Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp.

Mr John Aldridge
Chair

Email: NRESCommittee.EastMidlands-Northampton@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

                      "After ethical review – guidance for researchers"

Copy to: *Dr Victoria Stoneman*

NRES Committee East Midlands - Northampton

Attendance at PRS Sub-Committee of the REC meeting on 20 December 2012

Committee Members:

Name	Profession	Present	Notes
Mr John Aldridge	Senior Lecturer in Nursing	Yes	
Ms Elaine Blackshaw	Clinical Trial Manager	Yes	
Mr Alan Caswell	Lay Member	Yes	
Ms Elizabeth Gibbons	Senior Research Officer	Yes	

Also in attendance:

Name	Position (or reason for attending)
Miss Georgia Copeland	Assistant Committee Co-ordinator
Miss Jessica Parfrement	Co-ordinator

NHS

Health Research Authority

NRES Committee East of England - Cambridgeshire and Hertfordshire

Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 883 9435

30 June 2015

Dr Martina Mason
Papworth Hospital NHS Trust
Papworth Everard
CB23 3RE

Dear Dr Mason

Study title:	The effect of acute intravenous (iv) morphine administration on Sleep Disordered Breathing (SDB) in patients with moderate Obstructive Sleep Apnoea (OSA): A paired design trial
REC reference:	15/EE/0194
Protocol number:	P01911
EudraCT number:	2014-001950-41
IRAS project ID:	148632

Thank you for your letter of 18 June 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and one other member.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Miss Georgia Copeland, nrescommittee.eastofengland-cambsandherts@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

<u>Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.</u>

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

<u>Registration of Clinical Trials</u>

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

<u>Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).</u>

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study.   The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
GP/consultant information sheets or letters [MIMOSA GP Example Letter v1.0 dated 09.04.2015]	Version 2.0	18 June 2015
Investigator's brochure / IMP Dossier [File Note IMPD and nIMPD]	1.0	13 April 2015
IRAS Checklist XML [Checklist_19062015]		19 June 2015
Letters of invitation to participant [MIMOSA Invitation letter v1.0 dated 16.03.2015]	1.0	16 March 2015
Other [Summary of Product Characteristics (SmPC) for Ondansetron 4mg film coated tablets]		
Other [Telephone Screening Proforma]	Verson 2.0	18 June 2015
Other [Peer Review - Dr Justin Pepperell]		29 January 2014
Other [Peer Review - Dr SueWilson]		04 February 2014
Other [Patient Group Review (SATA)]		06 February 2014
Other [Cover Letter Response to Research Ethics Committee]		18 June 2015
Other [Response to Reseasrch Ethics Committee]		18 June 2015
Participant consent form [MIMOSA Consent Form v1.0 dated 09.04.2015]	1.0	09 April 2015
Participant information sheet (PIS) [MIMOSA Patient Information Sheet v1.0 dated 09.04.15]	Version 2.0	18 June 2015
REC Application Form [REC_Form_23042015]		23 April 2015
Research protocol or project proposal [MIMOSA Protocol v0.13 dated 09.04.2015]	Verson 2.0	18 June 2015
Summary CV for Chief Investigator (CI) [IE Smith CV 23.04.15 scanned signed]	1.0	23 April 2015
Summary of product characteristics (SmPC) [Summary of Product Characteristics (SmPC) for Morphine Sulphate 10mgml injection]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

<u>Reporting requirements</u>

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

Wallace

PP

Professor Barry Hunt
Chair

Email:nrescommittee.eastofengland-cambsandherts@nhs.net

Enclosures: "After ethical review – guidance for
                          researchers"

Copy to: *Victoria Stoneman, Papworth Hospital NHS Foundation Trust*

NHS
Health Research Authority

East of England - Cambridgeshire and Hertfordshire Research Ethics Committee

Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 883 9435

03 November 2015

Dr Martina Mason
Papworth Hospital NHS Trust
Papworth Everard
CB23 3RE

Dear Dr Mason

Study title:	**The effect of acute intravenous (iv) morphine administration on Sleep Disordered Breathing (SDB) in patients with moderate Obstructive Sleep Apnoea (OSA): A paired design trial**
REC reference:	**15/EE/0194**
Protocol number:	**P01911**
EudraCT number:	**2014-001950-41**
Amendment number:	**1**
Amendment date:	**04 October 2015**
IRAS project ID:	**148632**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Discussion

The Sub-Committee noted the changes to the exclusion criteria, and asked if consideration had been given to adding Pregabalin, noting that this is similar to Gabapentin.

The applicant submitted an updated Protocol and Telephone Screening Interview Proforma, listing Pregabalin within the exclusion criteria.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering letter on headed paper		22 September 2015
Notice of Substantial Amendment (CTIMP)	1	04 October 2015
Other [Telephone screening proforma]	2.1	22 September 2015
Research protocol or project proposal	2.1	22 September 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/EE/0194:	Please quote this number on all correspondence

Yours sincerely

Wallace

PP

Mr David Grayson
Chair

E-mail: nrescommittee.eastofengland-cambsandherts@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Victoria Stoneman*

NHS

Health Research Authority

East of England - Cambridgeshire and Hertfordshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 26 October 2015

Committee Members:

Name	Profession	Present	Notes
Mr David Grayson (Chair)	Retired Local Government Administrator	Yes	
Dr Wassim Matta	General Practitioner	Yes	

Also in attendance:

Name	Position (or reason for attending)
Miss Lindsey Wallace	REC Assistant

Project Reference No: PO1911
REC Reference No: 15/EE/0194
CSP No: n/a

Papworth Hospital **NHS**
NHS Foundation Trust

Papworth Hospital
Papworth Everard
Cambridge
CB23 3RE

16/02/2016

Dr Martina Mason
Respiratory Support and Sleep Centre
Papworth Hospital NHS Foundation Trust
Papworth Everard
Cambridge
CB23 3RE

Tel: 01480 830541
Fax: 01480 831315
www.papworthhospital.nhs.uk

Dear Dr Mason,

Study: Effect of acute intravenous morphine administration on Sleep Disordered Breathing (SDB) and sleep architecture in patients with moderate Obstructive Sleep Apnoea (OSA): A randomised controlled trial

I am writing to confirm that the following amendment to the above project has been reviewed by the R&D Unit and permission for the project to continue at Papworth Hospital NHS Foundation Trust has been granted.
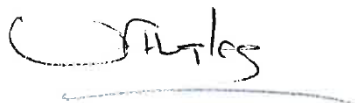
Non Substantial Amendment
Amendment Date: 25/01/16
Amendment Summary:

- Information added to ensure that participants make appropriate eating arrangements prior to attending for their visit
- Consent form changed to reflect updated PIS

You are reminded that the agreed protocol must be followed and any further amendments must be submitted to the R&D Unit.

If you require any further information please do not hesitate to contact the R&D Unit.

Yours sincerely,

Dr Vikki Hughes
Senior R&D Manager

Electronic copy: Dr Martina Mason, Victoria Stoneman and Stephanie Clutterbuck
Attached: Version control document

Papworth Hospital NHS Trust: Version Control of Trust Approved Documents

R&D number: P01911, **REC Reference No:** , CSP number: n/a, PI: Dr Martina Mason

Study: Effect of acute intravenous morphine administration on Sleep Disordered Breathing (SDB) and sleep architecture in patients with moderate Obstructive Sleep Apnoea (OSA): A randomised controlled trial

Study documents reviewed for Trust Approval:

REC Approval Date: 30/06/15

Trust approval incorporates the following amendments: SA1, 03/11/15

Trust Approval Date: 14/01/16

Documents	Version number	Version date
GP/Consultant information sheets or letters	2.0	18/06/15
Letters of invitation to participant	1.0	16/03/15
Telephone screening proforma	2.1	22/09/15
Participant consent form	1.0	09/04/15
Participant information sheet	2.0	18/06/15
Research protocol or project proposals	2.1	22/09/15

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Papworth Hospital NHS Trust: Version Control of Trust Approved Documents

R&D number: P01911, **REC Reference No:** , CSP number: n/a, PI: Dr Martina Mason

Study: Effect of acute intravenous morphine administration on Sleep Disordered Breathing (SDB) and sleep architecture in patients with moderate Obstructive Sleep Apnoea (OSA): A randomised controlled trial

Amendments submitted to R&D with revised or new documentation.

REC Amendment Approval / Acknowledgement Date: 25/01/16

Amendment Identification: (n)SA

Trust Amendment Approval Date: 16/02/16

Documents	Version number	Version date
Participant consent form	1.1	14/01/16
Participant information sheet (PIS)	2.1	14/01/16

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NHS
Health Research Authority

East of England - Cambridgeshire and Hertfordshire Research Ethics Committee

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

04 January 2017

Dr Ian Smith
Consultant Respiratory and Sleep Physician
Papworth Hospital NHS Trust
Respiratory Support & Sleep Centre
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Papworth Everard, Cambridge
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Dear Dr Smith

Study title:	The effect of acute intravenous (iv) morphine administration on Sleep Disordered Breathing (SDB) in patients with moderate Obstructive Sleep Apnoea (OSA): A paired design trial
REC reference:	15/EE/0194
Protocol number:	P01911
EudraCT number:	2014-001950-41
Amendment number:	2
Amendment date:	23 November 2016
IRAS project ID:	148632

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Discussion

The Sub-Committee requested that the Participant Information Sheet be amended to quantify the risks associated with the use of morphine in the study, in terms that are suitable for a lay reader.

The applicant submitted a revised Participant Information Sheet which was reviewed by the Sub-Committee.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering letter on headed paper		02 December 2016
Notice of Substantial Amendment (CTIMP)	2	23 November 2016
Participant information sheet (PIS)	4	03 January 2017
Research protocol or project proposal	3	14 November 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/EE/0194:	Please quote this number on all correspondence

Yours sincerely

wallace
PP

Mr David Grayson
Chair

E-mail: nrescommittee.eastofengland-cambsandherts@nhs.net

Enclosures: *List of names and professions of members who took part in the*

review

Copy to: *Dr Victoria Stoneman*
                    Hannah Munday

NHS
Health Research Authority

East of England - Cambridgeshire and Hertfordshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 20 December 2016

Committee Members:

Name	Profession	Present	Notes
Mr David Grayson (Chair)	Retired Local Government Administrator	Yes	
Diana Kornbrot	Statistician	Yes	

Also in attendance:

Name	Position (or reason for attending)
Miss Lindsey Wallace	REC Assistant

Appendix 4

ELSEVIER

Original Article

Association between severity of untreated sleep apnoea and postoperative complications following major cardiac surgery: a prospective observational cohort study

CrossMark

Martina Mason[*], Jules Hernández Sánchez, Alain Vuylsteke, Ian Smith

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ABSTRACT

Objective: To examine whether untreated sleep apnoea is associated with prolonged Intensive Care Unit (ICU) stay and increased frequency of postoperative ICU complications, in patients undergoing major cardiac surgery.
Patients/methods: Adult patients, undergoing elective coronary artery bypass grafting with or without cardiac valve surgery, between March 2013 and July 2014, were considered. We excluded patients participating in other interventional studies, those who had a tracheostomy before surgery, required emergency surgery or were due to be admitted on the day of surgery. Patients underwent inpatient overnight oximetry on the night prior to their surgery to assess for the presence of sleep apnoea. Since oximetry alone cannot differentiate obstructive from central apnoea, the results are reported as sleep apnoea which was diagnosed in patients with an arterial oxygen desaturation index (ODI) $\geq$ 5/h.
Results: The primary outcome measure was length of stay (LoS) in ICU in days. The secondary outcome was a composite measure of postoperative complications in ICU. Multivariate models were developed to assess associations between ODI and the primary and secondary outcome measures, adjusting for preselected predictor variables, relative to primary and secondary outcomes. There was no significant association between ODI and ICU LoS, HR 1.0, 95% CI 0.99—1.02; p = 0.12. However we did find a significant association between ODI and postoperative complications in the ICU, OR = 1.1; 95% CI 1.02—1.17; p = 0.014. The probability of developing complications rose with higher ODI, reflecting sleep apnoea severity.
Conclusions: Acknowledging the limitations of this prospective study, untreated sleep apnoea did not predict an increased length of stay in ICU but we do report an association with postoperative complications in patients undergoing major cardiac surgery.

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1. Introduction

Obstructive sleep apnoea (OSA) is partial or complete upper airway occlusion during sleep. Increasing respiratory muscle effort against the obstructed upper airway, in an attempt to maintain air flow, causes arousal from sleep and sleep fragmentation which can be associated with symptoms of un-refreshing sleep and adverse health outcomes [1]. The prevalence of OSA in the adult population has been increasing [2]. Severe OSA has been associated with increased risk of fatal and non-fatal cardiovascular events [3]. OSA shares some risk factors with coronary artery disease [4] and so while the exact prevalence of OSA among people undergoing coronary artery bypass surgery is unknown we might expect it to be higher than in the general adult population.

Association between OSA and postoperative complications in patients undergoing cardiac surgery has previously been reported in retrospective reviews and studies using screening questionnaires to diagnose OSA [5—11]. Two prospective studies reported an association between OSA and postoperative atrial fibrillation and

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lelirium in patients undergoing cardiac surgery, using respiratory polygraphy to diagnose sleep apnoea [12,13]. Two more recent prospective observational studies using recognised sleep diagnostics showed no association between OSA and adverse short term postoperative complications [14,15].

Central sleep apnoea is characterised by pauses in breathing with no apparent occlusion of the airway. There are no published data on its impact on surgical outcomes though it has been implicated in adverse outcomes for patients with cardiac disease [16].

There is currently limited evidence specifically linking OSA or central sleep apnoea, to postoperative complications. Moreover, here are currently no data showing that the application of perioperative continuous positive airway pressure therapy to patients with sleep apnoea reduces the risk of perioperative complications [17]. Despite this lack of robust evidence screening preoperatively for OSA is now the norm in some parts of the United Kingdom, eading to additional National Health Service cost and a potential delay in surgery. We designed a prospective observational study to examine whether untreated sleep apnoea is associated with prolonged ICU stay and increased frequency of postoperative ICU complications, in patients undergoing major cardiac surgery.

2. Materials and methods

2.1. Design

This prospective observational cohort study recruited patients who were undergoing elective coronary artery bypass grafting (CABG) with or without cardiac valve surgery at Papworth Hospital, a specialist cardiothoracic centre. Patients were screened for sleep apnoea the night before their surgery. The primary aim of the study was to assess whether sleep apnoea was associated with a prolonged stay in ICU.

Ethical approval was granted by The National Research Ethics Service East Midlands Northampton Proportionate Review Subcommittee on 20 December 2012 (12/WM/0433). All participants who agreed to enter the study gave signed, informed consent.

2.2. Recruitment

We recruited patients over 18 years of age undergoing elective cardiac surgery and excluded patients who were participating in other interventional studies, those not able to give informed consent or comply with the protocol and patients with a tracheostomy before surgery. Moreover, patients requiring emergency CABG/valve surgery and those admitted on the day of surgery (thereby not allowing in hospital overnight oximetry the night before surgery) were excluded. Some patients were subsequently excluded as intraoperative events or findings led them to have a different operation which did not meet our entry criteria (Fig. 1).

2.3. Data collection

Patients underwent inpatient overnight oximetry (Konica-Minolta PULSOX-300i) while self-ventilating in room air on the night prior to their surgery. The oximetry results were automatically analysed (Visidownload, Stowood Ltd, Oxford UK) and reviewed by a sleep physician, blinded to all clinical data. The anesthetic and surgical teams had no access to the results of preoperative nocturnal oximetry. Since oximetry alone cannot differentiate obstructive from central apnoea, the results are reported as sleep apnoea, which was diagnosed in patients with an arterial oxygen desaturation index (ODI) $\geq$ 5. The ODI was defined as the number of dips in oxygen saturations of greater than 4% relative to the moving average, per hour of sleep. The oximeter was programmed to average measurements over 1 s. As per our usual clinical practice, oximetry records without at least 4 h of adequate data were excluded. Demographic variables, co-morbidities and the Epworth Sleepiness Scale (ESS) score [18] were recorded on the night of admission for surgery. The EuroSCORE, a mortality risk score developed for patients undergoing cardiac surgery, was calculated for all patients [19]. Data regarding postoperative complications were collected from the digital Clinical Information System in the ICU.

2.4. Outcomes

The primary outcome was length of stay (LoS) in ICU (days) a key performance indicator for assessing impact on resources. The secondary outcome was a composite measure of postoperative complications in ICU that included: use of continuous positive airway pressure/bi-level positive pressure ventilation via a mask after extubation, re-intubation, occurrence of new arrhythmias necessitating drug treatment or intervention, need for additional organ support (intra-aortic balloon pump/haemofiltration), major organ complication (defined as those requiring treatment or intervention for cardiovascular, respiratory, renal, neurological, hepatic, coagulation issues), readmission to ICU and 30 days mortality.

2.5. Predictor variables

The primary predictor in all models was ODI analysed as a continuous variable. In view of its clinical relevance, sleep apnoea was divided into categories according to the ODI: mild if ODI $\geq$ 5 but <15, moderate if ODI was $\geq$15 but <30 and severe when ODI $\geq$30. Additional predictor variables thought to be risk factors relevant to the outcomes included EuroSCORE, age, body mass index, surgery type, administration of intravenous opioid analgesia (either intravenous morphine sulphate or fentanyl) during the ICU stay, comorbidities and mean nocturnal oxygen saturations. Although the euroSCORE has been reported to be the best predictive score of mortality for patients undergoing cardiac surgery, certain risk factors within the euroSCORE may have different statistical weight for predicting morbidity and thus individual components of the euroSCORE were used as additional predictor variables [20]. Administration of opioids was selected as a predictor due to previously reported effects including suppression of ventilatory drive and reduction of upper airway dilator muscle activity, potentially exposing patients with sleep apnoea to additional risk [21].

2.6. Sample size

Through discussion with the Critical Care Team we determined a watershed LoS in ICU at 36 h. Unpublished historical clinical data showed LoS <36 h for approximately 75% of patients. The null hypothesis was that patients with sleep apnoea (ODI $\geq$5) did not remain on ICU for >36 h more frequently than patients without sleep apnoea. Fifty seven patients with sleep apnoea, and the same number without, were required to achieve 80% power at 5% significance with a two-sided test for proportions, assuming the proportion of individuals staying longer than 36 h at ICU was 40% in the presence of sleep apnoea compared to 15% in its absence (based on unpublished internal preliminary data).

2.7. Statistical analyses

A parametric accelerated failure time model (Weibull regression) was used to analyse LoS as a continuous response to preselected predictor variables.
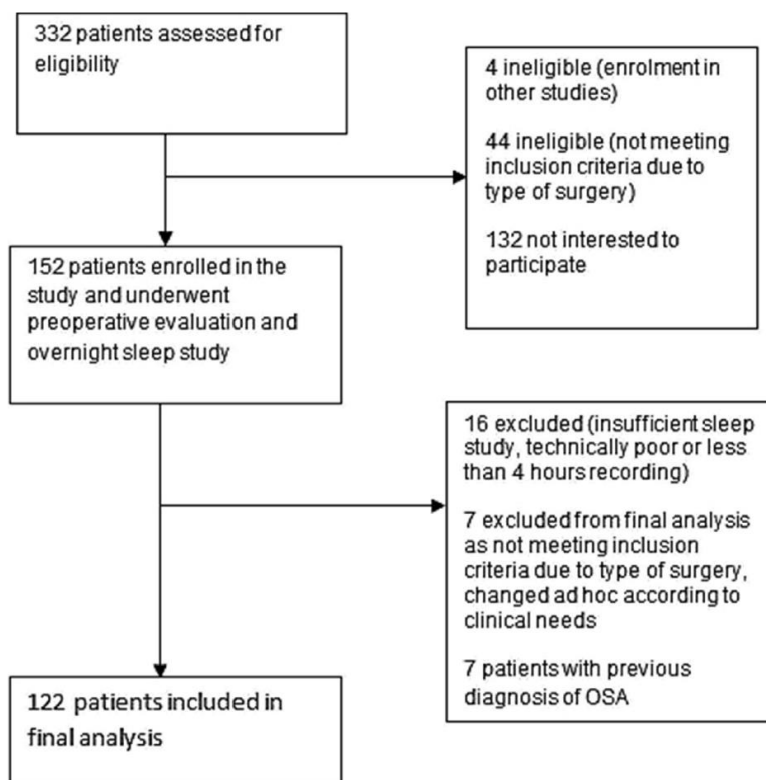
Fig. 1. Flow diagram of the study.

Postoperative complications were dichotomised (yes/no) and analysed with a binary logistic regression. The same predictors used to analyse LoS (except complications) were used.

For all regressions, parsimonious models were developed using a combination of, removing predictors, step-wise and manually, and interactions that did not reach 5% significance level.

3. Results

All patients older than 18 years, between March 2013 and July 2014, were screened and contacted by letter prior to surgery. A total of 152 patients consented to participate in the study, of whom 30 were subsequently excluded (Fig. 1). Of the 122 patients remaining, 57 (47%) had a new diagnosis of sleep apnoea. Table 1 shows characteristics of study participants.

3.1. Primary outcome analysis

The ICU LoS varied from 0.6 to 27 days with 88 patients (72%) remaining on ICU for 36 h or less. The median LoS in ICU was 0.95 days (95% CI 0.91–1 days). There was no significant association between ODI and ICU LoS (HR 1.0, 95% CI 0.99–1.02; p = 0.12). The most significant association with ICU LoS was the presence of postoperative complications in ICU (HR 3.7, 95% CI 2.8–4.8; p < 0.001). Multivariate analysis showed that the effect of complications on LoS was the same across both surgical interventions (CABG and CABG/valve surgery).

In our cohort all patients stayed in the ICU for one night of observation, irrespective of the time of day they were admitted after surgery. Patients operated on earlier in the day were more likely to stay in the ICU over 24 h than those admitted to ICU at the end of the day but no association between finishing time of surgery and LoS in ICU was found among patients who stayed in ICU 36 h or less, using a simple linear regression of LoS in ICU onto finishing time of surgery ($R^2 = 46\%$, p = 2.41).

We examined association between opioid use and LoS in ICU. There was no significant association between intravenous opioid analgesia and LoS on ICU. The hazard ratio for intravenous opioid analgesia (yes/no) on ICU LoS is 0.866 with CI = (0.693–1.083), p = 0.205. The hazard ratio for the interaction between intravenous opioid analgesia and type of surgery on ICU LoS is 1.23 with CI = (1.126–1.343), p < 0.001. Therefore, overall intravenous opioid analgesia does not lengthen LoS but that when looked at within surgery type (CABG vs CABG + valve) it lengthens LoS in the CABG + valve type.

3.2. Secondary outcome analysis

Thirty six patients (30%) met our criteria for postoperative complications. Of these, 21 (58%) had sleep apnoea. The frequency

Table 1
Baseline characteristics of study subjects.

Demographics	All n = 122	No sleep apnoea (ODI <5/h) n = 65 (53%)	Sleep apnoea (ODI ≥5/h) n = 57 (47%)	p
Age yrs	70.3 (0.80)	70.6 (1.08)	69.9 (1.19)	0.69[a]
BMI kg/m^2	29.0 (0.42)	28.0 (0.52)	30.1 (0.64)	0.01[a]
ODI	6.2 (0.49)	3.0 (0.16)	11.3 (0.94)	<0.001[a]
Mean SpO$_2$	94.4 (0.29)	94.4 (0.43)	93.5 (0.39)	0.12[a]
ESS	6.5 (0.32)	6.2 (0.43)	6.7 (0.49)	0.47[a]
EuroSCORE	4.7 (0.27)	4.5 (0.36)	4.9 (0.41)	0.52[a]
LVEF	55.7 (1.31)	58.0 (1.37)	52.7 (2.3)	0.05[a]
Male	107 (88%)	57 (47%)	50 (41%)	1[b]
Smoking				0.88[b]
Non smoker	44 (36%)	24 (20%)	20 (16%)	
Ex-smoker	69 (57%)	37 (30%)	32 (26%)	
Smoker	9 (7%)	4 (3%)	5 (4%)	
Habitual snorers				0.78[b]
Never	20 (16%)	12 (10%)	8 (7%)	
Sometimes	75 (61%)	40 (33%)	35 (29%)	
Most nights	23 (19%)	11 (9%)	12 (10%)	
Diabetes mellitus II	38 (31%)	17 (14%)	21 (17%)	0.24[b]
COPD	12 (10%)	6 (5%)	6 (5%)	1[b]
IOA	70 (57%)	39 (32%)	31 (25%)	0.58[b]
CABG	84 (69%)	43 (35%)	41 (34%)	0.56[b]

Continuous variables: mean (standard error); Categorical variables: total (% out of 122 patients); IOA: Intravenous Opiate Analgesia (administration of morphine sulphate in terms of patient controlled analgesia (n = 66) or intravenous fentanyl (n = 4)); CABG: Coronary artery bypass grafting without valve replacement/repair (the other interventions included CABG and valve); BMI: body mass index; ODI: 4% oxygen desaturation index; ESS: Epworth Sleepiness Scale score; LVEF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease.
[a] *t*-test.
[b] Fisher's exact test.

and type of encountered complications are described in Table 2. Patients with sleep apnoea were found to have significantly higher frequency of cardiovascular (p = 0.05) and renal (0.02) complications, compared to patients without sleep apnoea. All but one patient who encountered renal complications suffered acute kidney injury (AKI).

We found a significant association between ODI and post-operative complications in the ICU (OR = 1.1 for each increase in unit of ODI; 95% CI 1.02–1.17; p = 0.014), that is the probability of developing complications rose with increasing ODI (Fig. 2). The other independent predictors of postoperative complications were administration of intravenous opioid analgesia, in particular morphine sulphate and fentanyl (OR = 3.6; 95% CI 1.41–10.06; p = 0.010) and euroSCORE (OR = 1.3; 95% CI 1.15–1.61; p < 0.001). In our population, intravenous opioid analgesia was found to have the strongest effect on postoperative complications. Patients with sleep apnoea, but also those without who received intravenous opioids during their stay in ICU, had a higher probability of suffering postoperative complications with little difference in the

Table 2
Frequency and type of complications in patients with and without Sleep Apnoea.

Complication	Sleep apnoea ODI <5/h (n = 65)	No sleep apnoea ODI ≥5/h (n = 57)	p
Cardiovascular	3 (3%)	9 (7%)	0.05
Respiratory	7 (6%)	12 (10%)	0.14
Neurological	2 (2%)	2 (2%)	1
Renal	2 (2%)	9 (7%)	0.02
Coagulation	2 (2%)	2 (2%)	1
Arrhythmia	12 (10%)	8 (7%)	0.63
Infection	4 (3%)	2 (2%)	0.68
Reintubation	3 (3%)	2 (2%)	1
CPAP/bi-level PAP	8 (7%)	9 (7%)	0.61
30 days mortality	3 (3%)	2 (2%)	1
ICU readmissions	3 (3%)	1 (0%)	0.62

absolute risk increase (Table 3). In the same table, the relative risk appears higher for patients without sleep apnoea reflecting low baseline risk of suffering complications in patients without sleep apnoea. No significant association was found between dose of intravenous opioids and the risk of postoperative complications (OR = 1; 95% CI = 0.98, 1.04; p = 0.62). This could be due to the loss of statistical power as only 70 out of 122 patients received intravenous opioids. Compared to patients without sleep apnoea those with it received on average more intravenous opioid, 17.5 mg vs 21 mg, but this difference was not statistically significant (p = 0.51).

4. Discussion

We report that untreated sleep apnoea in our population of patients undergoing major cardiac surgery at Papworth Hospital is associated with an increased risk of postoperative complications, even though we identified no significant association with LoS in ICU. The LoS in ICU was chosen as the primary outcome for the study, due to its tangible impact on healthcare cost and resources. In contrast to our study, a very large retrospective analysis extracted data on 530,089 patients undergoing orthopaedic surgery and found significant association between sleep apnoea and utilization of critical care resources [22]. In that study sleep apnoea had been previously diagnosed, which may indicate a different degrees of physiological impact compared to the largely asymptomatic patients found on screening in our study. In addition, asymptomatic sleep apnoea was not excluded in the comparator group. Both of these points are relevant in any discussion of the value of screening surgical patients for sleep apnoea. It is possible that the negative finding in our study may be due to smaller cohort size.

ICU discharge is a complex process and depends on local policies and the availability of beds on the receiving ward over and above the clinical condition of the patient. It has previously been reported that institutional polices regarding ICU discharge affect ICU LoS [23]. We did not find significant correlation between finishing time of surgery and LoS in ICU among patients who stayed in ICU 36 h or less. For future studies the incidence of complications may represent a more appropriate study primary outcome.

Previous retrospective analyses reported a relationship between OSA and postoperative complications in patients undergoing cardiac surgery. Three studies demonstrated an increased risk of atrial fibrillation following CABG surgery [6,9,12]. Furthermore, two studies reported prolonged mechanical ventilation [7,8], three prolonged ICU and hospital length of stay [5,8,9] and one, postoperative infection and encephalopathy [5]. In contrast, three studies found no association between OSA and postoperative complications in patients undergoing CABG [14,15,24]. A more recent prospective study by Roggenbach et al. reports that OSA may be a risk factor for postoperative delirium [13]. Studies reporting association between sleep apnoea and atrial fibrillation by Mungan [6] and Van Oosten [9] used sleep questionnaires to diagnose sleep apnoea. A trial by Mooe et al. recorded prospective preoperative sleep studies [12], and reported a relationship between ODI and postoperative atrial fibrillation. We did not find a significant difference in frequency of postoperative arrhythmia in patients with sleep apnoea, compared to those without such a diagnosis. The reason for this disagreement is not obvious and may require a further, larger study to settle the question. We found an association of sleep apnoea with postoperative complications, in particular cardiovascular, and renal (Table 3), predominantly AKI. An association between sleep apnoea and postoperative AKI was reported in a more recent retrospective analysis of prospectively collected data in multi-ethnic Asian population. In this study sleep apnoea was defined as Apnoea Hypopnea Index (AHI)≥15, diagnosed using a
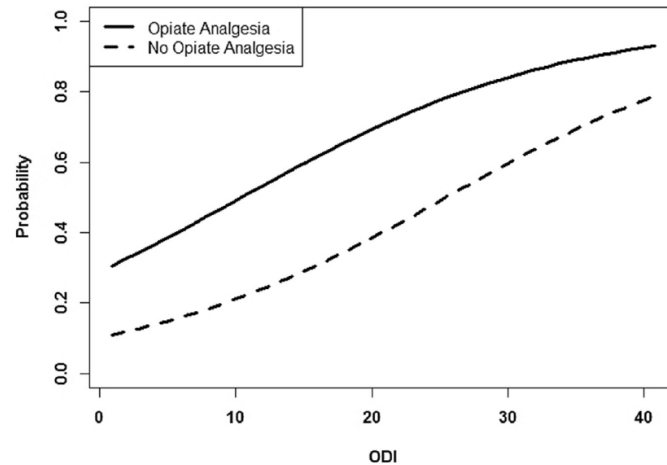
Fig. 2. Predicted probabilities of suffering a complication at Intensive Care Unit in patients with euroSCORE 5 according to sleep apnoea severity and administration of Intravenous Opioid Analgesia.

Table 3
Predicted percentage of postoperative complications according to Sleep Apnoea severity and administration of additional Intravenous Opioid Analgesia (IOA), in patients with euroSCORE 5.

	No SA (ODI 3/h)	Mild SA (ODI 8/h)	Moderate/severe SA (ODI 22/h)
No IOA/IOA	13%/35%	19%/45%	44%/74%
ARI/RRI	0.22/2.7	0.26/2.4	0.30/1.7

Predicted proportions are representative of patients with euroSCORE of 5 and ODI of 3/h, 8/h and 22/h. These values were the observed mean euroSCORE and mean ODI in each SA severity class in our study population. ARI: absolute risk increase; RRI: relative risk increase.

monitor of peripheral arterial tone, and as in our study no distinction between obstructive and central sleep apnoea was made [10]. Although different mechanisms of OSA may predominate in Asian and Caucasian populations, our study, in a Caucasian population complements previous evidence. We have extended this evidence showing that even patients with mild sleep apnoea in our series presenting for CABG or CABG and valve surgery had a higher risk of postoperative complications. The risk increased with the severity of sleep apnoea. Up until now, only one previous retrospective study reported an association between severity of sleep apnoea and postoperative outcomes in patients undergoing various general surgical procedures [25]. In view of the observational nature of our study it must be noted that it is not possible to confirm the causal relationship between sleep apnoea and the risk of postoperative complications.

Patients with OSA and concomitant heart failure and peripheral vascular disease have previously been found to have asymptomatic OSA [26,27]. Similarly, our cohort of patients, with significant ischaemic heart disease, presents in the main with asymptomatic sleep apnoea. We found no significant difference in mean ESS between patients with sleep apnoea and those without: 6.2 (0.43) vs 6.7(0.49). Compared to patients without sleep apnoea, patients with sleep apnoea in our cohort were obese with significantly higher BMI, as previously demonstrated in people with OSA [28]. It is not possible to distinguish between central and obstructive sleep apnoea with nocturnal oximetry alone. In the UK, around two thirds

of respiratory sleep studies do employ just oximetry [29]. A high resolution oximeter represents an economical and practical screening tool prior surgery and an ODI >10 was previously found to have a sensitivity of 93% and specificity of 75% against respiratory polygraphy to detect moderate and severe OSA in patients undergoing general surgery [30]. For the current study we were not able to perform respiratory polygraphy for practical reasons. Regardless, ODI has shown positive associations in our analyses.

The predictor which associated most strongly with postoperative complications in our patients was the administration of intravenous opioids on ICU. It is proposed that opiates/opioids could worsen the severity of OSA in perioperative settings due to their effect on ventilatory drive and upper airway dilator muscles [21]. In our population, not only patients with sleep apnoea, but also those without were found to be at higher risk of postoperative complications when given postoperative opioids. We found that the absolute risk increase did not differ significantly between patients with and without sleep apnoea. When examined the effect of opioids on primary outcome, LoS on ICU, we did not find that intravenous opioids lengthen overall LoS but it lengthens LoS in the CABG + valve type surgery. Although speculative, it is possible, that patients requiring intravenous opioids were a generally more vulnerable sub-population.

5. Conclusion

Despite its limitations, this study is the first prospective study using recognised sleep diagnostic that reports an association of increasing severity of sleep apnoea with postoperative complications in patients undergoing CABG and CABG/valve surgery. Notably, even patients with ODI 5–15/h, often regarded as clinically insignificant, had a higher probability of developing postoperative complications than patients with no desaturations overnight preoperatively. There was no association between sleep apnoea and ICU LoS. This negative finding may be due a relatively small sample size in the current study or local discharge policy in ICU and larger future studies may clarify this finding. We also found that intravenous opioids administered after surgery were independently associated with postoperative complications both in patients with and without sleep apnoea.

6. Future directions

Acknowledging the study's limitations, our results raise an interesting question worth further research. Examining the literature, the effect of opiates and opioids on postoperative outcomes in patients with sleep apnoea has to date been described in case reports and one retrospective review only [31,32]. The results of our study complement existing literature on the importance of sleep apnoea as a predictor of postoperative morbidity. There are currently no randomised controlled trials reporting any effects of perioperative continuous positive airway pressure on postoperative complications in patients with OSA. Our results strengthen the case for further research to assess the clinical and economic impact of perioperative treatment with CPAP.

Acknowledgement

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.06.010.

Funding

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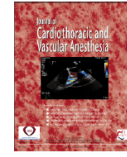
Original Article

Usefulness of the STOP-Bang Questionnaire in a Cardiac Surgical Population

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Objective: The aim of this study was to assess the predictive accuracy of the STOP-Bang questionnaire in relation to obstructive sleep apnea (OSA) detected by nocturnal oximetry, as well as postoperative outcomes, in a population undergoing cardiac surgery.

Design: A prospective observational cohort study.

Setting: The specialist cardiothoracic center at the Royal Papworth Hospital, Cambridge University Health Partners, United Kingdom.

Participants: All adult patients, undergoing elective coronary artery bypass grafting with or without cardiac valve surgery between March 2013 and July 2014 were included. The authors excluded patients participating in other interventional studies, those who had a tracheostomy before surgery, and those who required emergency surgery or were due to be admitted on the day of surgery.

Interventions: None.

Measurements and Results: Cardiac surgical patients were screened for the risk of OSA with the use of STOP-Bang questionnaire. The presence of OSA prior to surgery was assessed with overnight oximetry. The predictive performance of the STOP-Bang questionnaire was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC)–receiver operating characteristic curve (ROC). Multiple-logistic regression models were used to assess for associations between the STOP-Bang scores and postoperative outcomes. The STOP-Bang questionnaire discriminated poorly between mild OSA (AUC-ROC 0.57 [95% confidence interval (CI) 0.47–0.67]) and moderate/severe OSA (AUC-ROC 0.82 (95% CI 0.69–0.95)]. Accuracy was increased by modifying the cut-off value to 6 or greater, with sensitivity and specificity of 75% and 77%, respectively. A STOP-Bang score indicating the possibility of OSA was not significantly associated with prolonged intensive care unit lengths of stay (hazard ratio [HR] 1.1; 95% CI 0.99–1.19; p = 0.08) or postoperative complications (odds ratio [OR] 1.0; 95% CI 0.59–1.72; p = 0.98).

Conclusions: In the study population, a STOP-Bang questionnaire score of 3 or greater had limited predictive value for identifying cardiac surgical patients at high risk of OSA. STOP-Bang scores were not significantly associated with worse postoperative outcomes. A STOP-Bang score of 6 or greater could help identify patients in need of a sleep study to confirm the presence of OSA as such patients may be at increased risk of postoperative complications.

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Key Words: screening; questionnaires; sleep apnea; cardiac surgery; STOP-Bang questionnaire

Introduction

The term *obstructive sleep apnea* (OSA) refers to partial or complete upper airway occlusion during sleep. Increasing respiratory muscle effort against the obstructed upper airway, in an attempt to maintain air flow, causes arousal from sleep and sleep fragmentation, which can be associated with symptoms of unrefreshing sleep and adverse health outcomes.[1]

OSA is common[2] in patients undergoing various surgical procedures, with a reported prevalence of 7.2%.[3] Prevalence ranging from 13.2% to 78% has been reported in patients undergoing cardiac surgical procedures.[4] A high proportion of patients present for surgery with unknown OSA[5,6] and may be at risk of worse postoperative outcomes in terms of increased incidence of major cardiac and cerebrovascular events; there are reports of postoperative atrial fibrillation in patients undergoing cardiac surgery[4] and of postoperative cardiac events, acute respiratory failure, and intensive care unit (ICU) transfers in patients undergoing general surgery.[7,8] Central sleep apnea (CSA) is characterized by pauses in breathing with no apparent occlusion of the airway. There are no published data on the impact of CSA on surgical outcomes, although it has been implicated in adverse outcomes for patients with cardiac disease.[9]

Although polysomnography is the most accurate diagnostic tool for OSA, it is costly with regard to time and resources and could cause a delay to surgery. To address this concern, various screening tools, including nocturnal oximetry and questionnaires, have been developed and validated in different surgical cohorts to identify patients at high risk of OSA prior to surgery.

The STOP-Bang questionnaire was developed and validated in a general surgical population[10] and has been adopted as a screening tool in surgical preassessment clinics for its easy use. In systematic reviews of screening questionnaires for OSA, the STOP-Bang questionnaire had the highest methodologic validity, moderately high sensitivity, and best negative predictive value for assessing the risk of moderate/severe OSA.[11,12] It was found that the higher the STOP-Bang score, the greater was the probability of OSA,[13] and that a high STOP-Bang score might predict higher risk of postoperative pulmonary and cardiac complications in patients undergoing various surgical procedures.[14] In validation studies of the STOP-Bang questionnaire, selection bias and high prevalence of OSA in the studied population may have influenced the results, and therefore validation in specific target population is recommended.[15] To the authors' knowledge, the STOP-Bang questionnaire has not presumably been validated in cohorts undergoing cardiac bypass and valve surgery.

In this study of patients undergoing elective coronary artery bypass grafting (CABG) with or without cardiac valve surgery, the authors examined the diagnostic performance of the STOP-Bang questionnaire against the arterial oxygen desaturation index (ODI; number of dips of $\geq 4\%$ per hour of sleep) obtained from nocturnal oximetry. The authors also explored the associations between STOP-Bang scores and postoperative outcomes.

Methods

Ethical approval for this prospective observational cohort study was granted by the National Research Ethics Service East Midlands Northampton Proportionate Review Sub-committee (12/WM/0433). All participants who agreed to enter the study gave signed, informed consent.

Population Cohort

Patients older than 18 years, without previous diagnosis of OSA, undergoing elective CABG with or without cardiac valve surgery at a specialist cardiothoracic hospital between March 2013 and July 2014 were screened and contacted via letters prior to surgery. The authors excluded patients participating in other interventional studies and those who were not able to give informed consent, were unlikely to comply with the protocol, had a tracheostomy before surgery, required emergency surgery, or were due to be admitted on the day of surgery. Some patients were subsequently excluded as intraoperative events or findings had resulted in their having a different operation, thus not meeting the study entry criteria (Fig 1).

Sleep Apnea Assessment and Data Collection

All participants included in this prospective observational cohort study completed the STOP-Bang questionnaire (see Fig 2),[10] which consists of 8 questions scored as yes/no responses. The total score can range from 0 to 8 according to the number of positive answers. From previous data, patients scoring 3 or greater on the STOP-Bang questionnaire are perceived to be at high risk of OSA.[10]

In addition, all participants underwent nocturnal oximetry (Konica-Minolta PULSOX-300i) on the night before surgery while self-ventilating on room air. The oximetry results were automatically analyzed (Visidownload, Stowood Ltd., Oxford, UK) and reviewed by a sleep physician, who was blinded to all clinical data. The anesthetic and surgical teams had no access to the results of preoperative nocturnal oximetry. Sleep apnea was diagnosed in patients with an ODI greater than 5. The oximeter was programmed to average measurements over 1 second. Nocturnal monitoring without at least 4 hours of adequate data was excluded per the usual accepted practice at the authors'
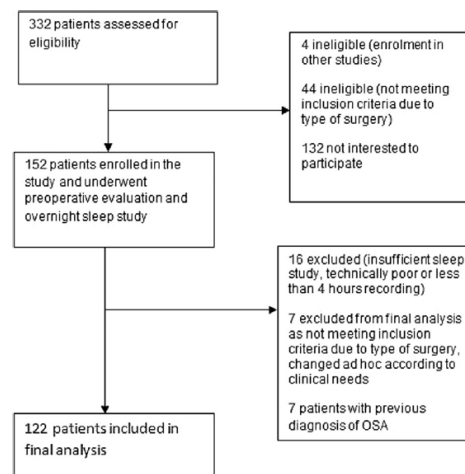

Fig 1. Flow diagram of the study.

STOP-Bang Questionnaire

1. **S**noring: Do you snore loudly (loud enough to be heard through closed doors)?
   Yes   No

2. **T**ired: Do you often feel tired, fatigued, or sleepy during daytime?
   Yes   No

3. **O**bserved: Has anyone observed you stop breathing during your sleep?
   Yes   No

4. Blood **P**ressure: Do you have or are you being treated for high blood pressure?
   Yes   No

5. **B**MI: BMI more than 35 kg/m²?
   Yes   No

6. **A**ge: Age over 50 years old?
   Yes   No

7. **N**eck circumference: Neck circumference greater than 40 cm?
   Yes   No

8. **G**ender: Male?
   Yes   No

High risk of OSA: Yes to 3 or more questions

Low risk of OSA: Yes to less than 3 questions

Chung F et al. *Anesthesiology* 2008;108:812-21.

Fig 2. STOP-Bang questionnaire.

institution. The results are reported as "sleep apnea" because nocturnal oximetry cannot distinguish between OSA and CSA. Demographic information, comorbidities, Epworth Sleepiness Scale (ESS) score,[16] and the EuroSCORE were recorded prospectively on the night of admission. The EuroSCORE, which is a mortality risk score developed for patients undergoing cardiac surgery, was calculated for all patients.[17] Data regarding postoperative complications were collected from the digital Clinical Information System in the ICU.

Outcomes

The primary outcome was to assess the diagnostic performance of the STOP-Bang questionnaire against the ODI from nocturnal oximetry by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve–receiver operating characteristic curve (AUC-ROC).

The secondary outcome was length of stay (LoS) in the ICU (days) and a composite measure of postoperative complications in the ICU, which included use of continuous positive airway pressure/bilevel positive pressure ventilation via a mask after extubation, reintubation, occurrence of new arrhythmias necessitating drug treatment or intervention, need for additional organ support (intra-aortic balloon pump/hemofiltration), major organ complication (defined as need for treatment or intervention for cardiovascular, respiratory, renal, neurologic, hepatic, coagulation problems), readmission to the ICU, and 30-day mortality.

Predictor Variables

The primary predictor variable was the STOP-Bang score analyzed as a continuous variable. Additional predictor variables

Table 1
Baseline Characteristics of Participants

Demographics	All n = 122	No Sleep Apnoea (ODI < 5/hr) n = 65 (53%)	Sleep Apnoea (ODI ≥ 5/hr) n = 57 (47%)	p
Age (years)	70.3 (0.80)	70.6 (1.08)	69.9 (1.19)	0.69*
BMI kg/m²	29.0 (0.42)	28.0 (0.52)	30.1 (0.64)	0.01*
ODI	6.2 (0.49)	3.0 (0.16)	11.3 (0.94)	< 0.001*
Mean SpO₂	94.4 (0.29)	94.4 (0.43)	93.5 (0.39)	0.12*
ESS	6.5 (0.32)	6.2 (0.43)	6.7 (0.49)	0.47*
EuroSCORE	4.7 (0.27)	4.5 (0.36)	4.9 (0.41)	0.52*
LVEF	55.7 (1.31)	58.0 (1.37)	52.7 (2.3)	0.05*
Male	107 (88%)	57 (47%)	50 (41%)	1†
Smoking				0.88†
Nonsmoker	44 (36%)	24 (20%)	20 (16%)	
Ex-smoker	69 (57%)	37 (30%)	32 (26%)	
Smoker	9 (7%)	4 (3%)	5 (4%)	
Habitual snorers				0.78†
Never	20 (16%)	12 (10%)	8 (7%)	
Sometimes	75 (61%)	40 (33%)	35 (29%)	
Most nights	23 (19%)	11 (9%)	12 (10%)	
Diabetes mellitus type 2	38 (31%)	17 (14%)	21 (17%)	0.24†
COPD	12 (10%)	6 (5%)	6 (5%)	1†
IOA	70 (57%)	39 (32%)	31 (25%)	0.58†
CABG	84 (69%)	43 (35%)	41 (34%)	0.56†

Continuous variables: mean (standard error); Categorical variables: total (% out of 122 patients). BMI, body mass index; CABG, coronary artery bypass grafting without valve replacement/repair (the other interventions included CABG and valve); COPD, chronic obstructive pulmonary disease; ESS, Epworth Sleepiness Scale score; IOA, intravenous opiate analgesia (administration of morphine sulphate in terms of patient controlled analgesia [n = 66] or intravenous fentanyl [n = 4]); LVEF, left ventricular ejection fraction; ODI, 4% oxygen desaturation index; SpO₂, blood oxygen saturation.
*t test,
†Fisher's exact test

thought to be risk factors relevant to the outcomes included the EuroSCORE, patient age and body mass index, surgery type, administration of intravenous opioid analgesia (either intravenous morphine sulphate or fentanyl) during the ICU stay, comorbidities, and mean nocturnal oxygen saturation.

Statistical Analysis

Descriptive statistics are shown for all variables used in this study (Table 1). Continuous variables are reported as mean (SE), categorical variables as percentages. The severity of sleep apnea according to the ODI was defined as follows: no sleep apnea = ODI less than 5; mild sleep apnea = ODI 5 or greater and less than 15; moderate = ODI 15 or greater and less than 30; and severe = ODI 30 or greater. The prevalence of sleep apnea according to severity was calculated.

The AUC-ROC was calculated to assess the discriminating ability of different STOP-Bang scores for sleep apnea. ROC curves were used to identify the best STOP-Bang discriminating score in terms of sensitivity and specificity for predicting sleep apnea. The STOP-Bang diagnostic performance for

mild and moderate/severe sleep apnea, at both the conventional cut-off value of 3 or greater and at the best discriminating value, was assessed by using multiple 2 × 2 contingency tables and expressed as sensitivity, specificity, PPV, and NPV.

A parametric accelerated failure time model (Weibull regression) was used to analyze LoS as a continuous response to preselected predictor variables. Postoperative complications were dichotomized (yes/no) and analyzed with a binary logistic regression model by using the same predictors used to analyze LoS. For all regressions, parsimonious models were obtained with a combination of step-wise and manually removed predictors and interactions that did not reach the 5% significance level.

Results

The authors assessed 322 patients for eligibility, of whom 152 underwent preoperative evaluation with the STOP-Bang questionnaire and nocturnal oximetry. Of these, 30 patients were excluded (Fig 2). A total of 122 patients were included in the final analysis. Of those, 6 patients (5%) scored as low risk for OSA with use of the STOP-Bang score, whereas 116 (95%) scored as high risk (STOP-Bang score ≥ 3). Sleep apnea was diagnosed by using nocturnal oximetry in 57 patients (47%). Table 1 shows the demographic details of the individuals included.

Diagnostic Performance of the Stop-Bang Score Against the ODI From Nocturnal Oximetry

The authors found that the STOP-Bang score poorly predicted mild sleep apnea (AUC-ROC 0.57; 95% confidence interval [CI] 0.47–0.67]) but was better for moderate sleep apnea (AUC-ROC 0.82; 95% CI 0.69–0.95]). Setting the STOP-Bang score at 6 or greater improved the accuracy in terms of sensitivity (75%) and specificity (77%) in detecting moderate/severe sleep apnea (Fig 3).

At the conventional cut-off value of 3 or greater, the STOP-Bang score demonstrated high sensitivity for mild (95%) and moderate/severe sleep apnea (100%), but the specificity was very low (5% and 6%, respectively). In view of 100% sensitivity and 100% NPV for moderate/severe sleep apnea, STOP-Bang scores of 0 to 2 could confidently exclude patients with at least moderate sleep apnea, in the cardiac preoperative settings. However, in the study population, only six (5%) of 122 participants scored as low risk for sleep apnea.

Assessing predictive values for severe sleep apnea was not possible because of the lack of severe sleep apnea cases. The sensitivity, specificity, NPV, and PPV for the STOP-Bang scores at cut-off values 3 or greater and 6 or greater are summarized in Table 2.

Secondary Outcome Analysis

The median LoS in the ICU was 0.95 days (95% CI 0.91–1.00 days). In the multiple logistic regression models, the study authors found that there was no significant association
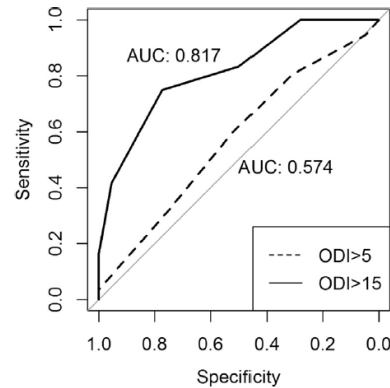

Fig 3. Receiver operating curves (ROCs) for STOP-Bang scores to predict mild sleep apnea (oxygen desaturation index [ODI] ≥ 5) and moderate/severe sleep apnea (ODI ≥ 15). The area under ROC curve was 0.57 (95% confidence interval [CI] 0.47–0.67) for mild sleep apnea and 0.82 (95% CI 0.69–0.95) for moderate/severe sleep apnea.

between STOP-Bang scores and LoS in the ICU (HR 1.1; 95% CI 0.99–1.19; p = 0.08) and no significant association between STOP-Bang scores and postoperative ICU complications (OR 1.0; 95% CI 0.59–1.72; p = 0.98).

Discussion

In the study population predominantly composed of men with cardiac disease, the STOP-Bang questionnaire had poor diagnostic accuracy in detecting sleep apnea. Many patients had false-positive results when the generally accepted cut-off value of 3 or greater was used, leading to inappropriate utilization of sleep diagnostics and potential delays in surgery. However, STOP-bang scores less than 2 allowed for confident exclusion of moderate/severe sleep apnea in patients; however, because only 5% of patients scored at that level, only a small proportion of patients not suffering from OSA could be excluded.

Table 2
Sensitivity, Specificity, PPV, and NPV of STOP-Bang Questionnaire for Predicting Mild (ODI ≥ 5) and Moderate/Severe Sleep Apnea (ODI ≥ 15)

STOP-Bang ≥ 3	Mild Sleep Apnea (ODI ≥ 5–14 /hr)	Moderate/Severe Sleep Apnea (ODI ≥ 15/hr)
Sensitivity (%)	95	100
Specificity (%)	5	6
PPV (%)	47	10
NPV (%)	50	100
STOP-Bang score ≥ 6	Mild sleep apnea (ODI ≥ 5–14 /hr)	Moderate/Severe sleep apnea (ODI ≥ 15/hr)
Sensitivity (%)	32	75
Specificity (%)	75	77
PPV (%)	53	27
NPV (%)	56	97

NPV, negative predictive value; ODI, 4% oxygen desaturation index; PPV, positive predictive value.

The poor performance of the STOP-Bang score in the patient cohort in this study is explained by the inherent characteristics of the cardiac surgical population (male sex, older age, hypertension in the majority) that are common to the trait detected by the STOP-Bang questionnaire.

The STOP-Bang questionnaire was introduced as a scoring model in the general surgical population to exclude patients with undiagnosed moderate/severe OSA prior to surgery. In the general surgical population, at a cut-off level of 3 or greater, for moderate OSA, the questionnaire showed sensitivity and specificity of 93% and 43%, respectively, and for severe OSA 100% and 37%, respectively.[10] The NPVs for moderate and severe OSA were 90% and 100%, respectively, and therefore scores of 0 to 2 would, with high confidence, exclude patients with moderate to severe disease in patients presenting for general surgery. In view of its low specificity for moderate and severe OSA in the general surgical cohort, the predictive probability was examined at the higher scores, and it was found that scores greater than 5 identified patients with high probability of moderate/severe OSA.[18] Because of its concise nature and easy application, it has been adopted in the preoperative settings.

In contrast to previous studies, where patients undergoing general surgery scoring high on STOP-Bang questionnaire were reported to have higher odds of developing postoperative complications,[14] this study did not show a significant association between STOP-Bang scores and ICU LoS or risk of developing postoperative complications, and this may be attributed to the low specificity of the questionnaire at the conventional cut-off value of 3 or greater, falsely identifying patients with the disease.

In the study patients, the authors found that the best discriminating score for moderate/severe sleep apnea was at 6 or greater. This score would decrease the false-positive rates for predicting sleep apnea, but at the expense of lower sensitivity, and up to 25% of patients with moderate/severe sleep apnea would still have either a false-positive or a false-negative result. The authors have previously reported a significant association between sleep apnea, defined as a continuous measure of the ODI, with postoperative complications,[19] and this adds to the evidence of a positive association between untreated sleep apnea and postoperative complications in patients undergoing cardiac surgery.[4] The authors suggest that a STOP-Bang score of 6 or greater in the cardiac surgical population may help identify those in need for further screening for sleep apnea with use of nocturnal oximetry for planning of perioperative care because these patients may be at higher risk of perioperative complications. Data from randomized controlled trials are still needed to define the clinical effectiveness and cost implications of screening and treatment of OSA prior to surgery,[20] but identifying patients with untreated sleep apnea before cardiac surgery may aid in establishing perioperative precautions and airway management.

The limitations of the current study include the lack of patients with severe sleep apnea, and therefore, the utility of the STOP-Bang questionnaire in such patients remains unknown. The STOP-Bang questionnaire was not compared with formal polysomnography, but in the United Kingdom, in approximately two-thirds of respiratory sleep studies, oximetry alone is used.[21] The authors have opted to use nocturnal oximetry rather than respiratory polysomnography because it was felt to be less disruptive to patients' quality of sleep on the night prior to major cardiac surgery. It is possible that some of the patients with a raised ODI had CSA, but as previously reported by the study authors, there is a positive association between oxygen desaturations from nocturnal oximetry (ODI) and worse postoperative outcomes in cardiac surgical cohort;[19] thus, identifying patients at risk of sleep apnea with the help of the STOP-Bang questionnaire may help recognize patients in need of nocturnal oximetry and subsequently those who may be at risk of postoperative complications. Patient selection bias may be responsible for the high prevalence of OSA found in this study. OSA and cardiovascular disease share common risk factors, and therefore, it is likely that a high prevalence of OSA will be found in highly selected cardiovascular cohorts, such as that in this study, where the authors report that 47% of patients undergoing major cardiac surgery suffered from sleep apnea. In view of the emerging evidence for an association between OSA and worse postoperative outcomes, screening of surgical cohorts with a high prevalence of OSA will identify those with sleep apnea prior to surgery. This may allow for instituting perioperative precautions and interventions to mitigate patients' risks, but further research is needed to confirm this hypothesis.

Conclusions

The STOP-Bang questionnaire had limited diagnostic value in identifying patients at high risk of sleep apnea prior to major cardiac surgery at the conventional cut-off score of 3 or greater, but scores of 2 or less would be highly predictive of the absence of sleep apnea. A STOP-Bang score of 6 or greater would be more accurate but would still give false-positive or false-negative results in up to 25% of patients. Because of its high specificity, a STOP-Bang score of 6 or greater in the cardiac surgical population could help identify those in need for further screening for sleep apnea with use of nocturnal oximetry. STOP-Bang scores were not significantly associated with worse postoperative outcomes in this cohort, contrary to previous reports in patients undergoing general surgical procedures.

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Obstructive sleep apnoea in patients undergoing cardiac surgery: Screening, postoperative outcomes and perioperative care

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ABSTRACT

Obstructive sleep apnoea (OSA) is common and high prevalence has been described amongst patients undergoing cardiac revascularisation surgery. An excess of postoperative complications has been reported in patients with untreated Obstructive Sleep Apnoea (OSA) following surgical procedures, including those undergoing cardiac surgery. This has led some clinicians towards pre-operative screening for OSA though the best screening methodology has not yet been established. Moreover, the effect of screening and of treatment for OSA on surgical outcomes remains unknown. Does current evidence justify screening and treating patients before they present for surgery? Is this leading to potential delay in surgery whilst awaiting sleep diagnostics and commencing the treatment? This review article will examine the available evidence base and endeavour to answer these questions and identify implications for future research.

OSA and cardiovascular disease

Sleep Disordered Breathing is a term used to cover a range of breathing events encountered during sleep and includes obstructive sleep apnoea (OSA), central sleep apnoea, Cheyne–Stokes respiration and respiratory effort related arousals. OSA is the most common form of sleep disordered breathing. OSA is common[1] and the reported prevalence has increased in the last two decades[1] with the new data reported mainly in European population of adults 40-85 years old showing that at least mild OSA (apnoea-hypopnoea index ≥5) was present in 84% of men and 61% of women and at least moderate disease (apnoea-hypopnoea index ≥15) was present in 50% of men and 23 % of women[2]. OSA and cardiac disease share some common risk factors and in patients undergoing coronary artery bypass graft (CABG) procedures reported prevalence is high, ranging between 41 and 87%[3-5].High proportions of patients may present for surgery without a previous diagnosis of OSA[6,7] and may be at risk of worse postoperative outcomes[8]. In patients with moderate to severe OSA syndrome Continuous Positive Airway Pressure (CPAP) is the conventional treatment with established clinical and cost effectiveness[9] but its effect on cardiovascular outcomes has not been confirmed. A recent, large, randomised controlled trial of adults with moderate to severe OSA and pre-existing cardiovascular disease showed that the use of CPAP had no significant effect on the prevention of recurrent serious cardiovascular events[10]. It is possible that patients with compliance exceeding 4h/night may

benefit in terms of cardiac outcomes but further research is needed to clarify this benefit[11,12].

Postoperative outcomes in patients with OSA undergoing cardiac surgery

There is evidence that patients with untreated OSA, compared to those without this diagnosis, undergoing general surgical procedures, have worse postoperative outcomes including increased risks of post-operative cardiac events, acute respiratory failure and ICU transfers reported in two meta-analyses[13,14]. Data in patients undergoing cardiac surgery are inconsistent with some results suggesting an association between OSA and postoperative complications and others not supporting this association[15,16]. A study of 67 prospectively recruited participants, assessed for OSA by polysomnography (PSG) showed no association between OSA and short term complications but reported that the OSA was independently associated with a higher rate of long-term cardiovascular events after CABG[15]. Another study by Foldvary-Schaefer et al. recruited prospectively 107 patients and shown that OSA was not significantly associated with worse postoperative outcomes but authors commented that a small study sample could have influenced results[16].

A recent meta-analysis of 11 studies showed higher odds of adverse cardiac and cerebrovascular events with an odds ratio (OR) of 2.4; 95% CI 1.38-4.2; p=0.002 as well as newly documented postoperative atrial fibrillation (POAF), OR = 1.94; CI 1.13-3.33; p=0.02 in patients with OSA compared to non OSA patients[8]. It included 11 studies and showed higher odds of adverse cardiac and cerebrovascular events with an odds ratio (OR) of 2.4; 95% CI 1.38-4.2; p=0.002 as well as newly documented postoperative atrial fibrillation (POAF), OR = 1.94; CI 1.13-3.33; p=0.02 in patients with OSA compared to non OSA patients[8]. The majority of patients in this meta-analysis were newly diagnosed, untreated patients with OSA. The studies included were of mixed quality. Only five out of 11 of the studies were prospective and used recognised sleep diagnostic (PSG or watch-PAT) to diagnose OSA[15-19] whilst the rest were either retrospective cohort assessments or used questionnaires to examine for high risk of OSA. Out of the five higher quality studies, two report no association between OSA and postoperative outcomes[15,16], two report an association between OSA and POAF[17,19] and one with prolonged ventilation, tracheostomy, Intensive Care Unit and hospital stay[18]. The fact that the definitions of hypopnea have changed several times over the years, and that many of the studies included in the meta-analyses do not give specifics about their diagnostic procedures, may be a reason why studies reach different conclusions.

We have recently reported outcomes on 122 prospectively recruited patients undergoing CABG and CABG and valve

surgery in a Tertiary cardiothoracic centre. Patients underwent inpatient overnight oximetry on the night prior to their surgery to assess for the presence of sleep apnoea which was diagnosed in patients with an arterial oxygen desaturation index (ODI) ≥ 5/hr. The primary outcome measure was length of stay (LoS) in ICU in days and the secondary outcome a composite measure of post-operative complications in ICU. We found a high prevalence of newly diagnosed sleep apnoea (47%) in our cohort as well as an association of increasing severity of sleep apnoea with postoperative complications, in particular cardiovascular and renal, including acute kidney injury, heart failure and hypotension. This adds to the evidence for a positive association between sleep apnoea and adverse postoperative outcomes in this surgical cohort. Our study was the first to report an association between severity of sleep apnoea and adverse postoperative outcomes in a cardiac surgical cohort, where interestingly, even patients with ODI 5-15/hr , often regarded as clinically insignificant, had a higher probability of developing post-operative complications than patients with no desaturations overnight preoperatively[4]. An association between sleep apnoea and postoperative acute kidney injury was also reported in a recent study in multi-ethnic Asian population. OSA with the repetitive nocturnal arousals causes sympathetic nervous system activation which persists during the day[20, 21] and along with fluid imbalances during and after surgery could contribute to hypoperfusion of the renal arteries and development of kidney injury.

In our study we could not distinguish between OSA and central sleep apnoea as our diagnostic was nocturnal oximetry. It is possible that central sleep apnoea, common in patients with heart failure and ischaemic heart disease[22,23] contributed to significant respiratory events identified on overnight sleep monitoring. Central sleep apnoea is characterised by pauses in breathing with no apparent occlusion of the airway and there are no published data on its impact on surgical outcomes though it has been implicated in adverse outcomes for patients with cardiac disease[24]. Further research is needed to assess its impact on postoperative outcomes in patients undergoing surgical procedures.

In keeping with the outcome from one recent meta-analysis[8], we did not find a significant association between OSA and Intensive Care Unit length of stay. It is possible that the lack of such an association is due to the small sample size of individual studies and complexity of the process of Intensive Care Unit discharge, which can depend on local policies and the availability of beds on the receiving ward over and above the clinical condition of the patient.

Effect of Continuous Positive Airway Pressure on postoperative outcomes

It is apparent, from the presented evidence, that OSA

is common in cardiac surgical population and that it is associated with worse postoperative complications[4,8,25]. Although Continuous Positive Airway Pressure (CPAP) is the conventional treatment for patients with OSA syndrome with established clinical and cost effectiveness[9] its effect on patients with OSA in perioperative settings has yet to be demonstrated. A reduction in pulmonary complications, in patients without a diagnosis of OSA, undergoing thoraco-abdominal and cardiac surgery has been reported[26,27] but the evidence supporting the application of perioperative CPAP to patients with OSA is currently lacking. A recent meta-analysis of 6 studies including 904 patients showed no significant difference in post-operative adverse events between CPAP and non-CPAP treatment groups in patients undergoing general surgery[28]. There is some evidence for improvement in cardiovascular morbidity in a retrospective cohort of 26,842 patients with OSA undergoing vascular surgery where those not treated with positive airway pressure preoperatively were at increased risks for cardiopulmonary complications including unplanned reintubations (OR 2.5) and myocardial infarction (OR 2.6) compared with treated OSA patients[29]. The effect of CPAP on patients with OSA undergoing cardiac surgery has not been examined in randomized controlled trials.

Implications for practice and future direction

Current evidence from observational studies suggests increased risks of adverse cardiac, cerebrovascular events as well as POAF in patients with untreated OSA undergoing cardiac surgical procedures. In addition two prospective observational studies also report association between sleep apnoea and adverse renal outcomes. The effect of central sleep apnoea on postoperative outcomes in cardiac surgical cohort remains unknown and further research is needed in this area. There is no evidence at present that confirms that early awareness and treatment of OSA with CPAP improves perioperative outcomes and further research is necessary to clarify the costs and benefits of preoperative diagnosis and treatment of OSA. Until then a pragmatic approach in the pre-assessment setting should be adopted focusing mainly on a detailed clinical history. In addition, various screening tools, including questionnaires, have been developed and validated in different surgical cohorts to identify patients at high risk of OSA prior to surgery. In systematic reviews of screening questionnaires for OSA, the STOP-Bang questionnaire had the highest methodological validity, moderately high sensitivity and best negative predictive value for assessing the risk of moderate/severe OSA and could be used to help clinician to identify patients at high risk for OSA in pre-assessment clinics[30,31], with prompt onward referral of those with suspected OSA syndrome to avoid unnecessary delays in surgery.

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