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Gastro-oesophageal Reflux in Obstructive Sleep Apnoea:

Prevalence and Mechanisms

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PREFACE

The experimental work in this thesis was undertaken at the West Australian Sleep Disorders Research Institute under the joint supervision of Associate Professor Peter Eastwood and Adjunct Clinical Professor David Hillman.

The work described in this thesis is original and entirely my own, except where the contributions of others are acknowledged.

…….

Kelly Shepherd

ABSTRACT

Background. Obstructive Sleep Apnoea (OSA) is associated with an increase in *nocturnal* gastro-oesophageal reflux (*nocturnal*GOR) events and symptoms, however the mechanism for this remains undefined. Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to reduce *nocturnal*GOR in individuals with OSA however the reasons for this reduction are not clear. The combination of OSA and *nocturnal*GOR could be particularly problematic for individuals who have had a lung transplant in whom Bronchiolitis Obliterans Syndrome (BOS) limits survival. It is thought that GOR plays a role in the development of BOS in these individuals.

Methods and Results. Five interrelated studies were undertaken. The first two studies sought to determine and compare the prevalence and risk factors of *nocturnal*GOR in OSA patients with the general population. To do this, a GOR questionnaire was completed by 2,042 members of the general community as part of the Busselton Health Survey and by 1,116 patients with polysomnography-diagnosed OSA. Risk of OSA in the general population was determined using a standardised sleep questionnaire. 137 of the OSA patients completed the questionnaire before and after treatment with CPAP. The prevalence of *nocturnal*GOR symptoms reported more than once a week (frequent symptoms) was greater in OSA patients (10.1%) than the general population (5.8%) ($p<0.001$), in individuals from the general population at high (11.2%) than low risk of OSA (4.5%) ($p<0.001$) and in patients with severe (14.7%) than mild OSA (5.2%) ($p<0.001$). Treatment of OSA with CPAP decreased the prevalence of frequent *nocturnal*GOR from 9.0% to 3.8% ($p=0.04$). In the general population, high risk of OSA was independently associated with a 2.4-fold increased risk of frequent

*nocturnal*GOR symptoms than low risk. In the OSA group, disease severity was independently associated with *nocturnal*GOR symptoms, with an adjusted odds ratio of 1.7 for frequent *nocturnal*GOR symptoms.

Study three sought to determine the mechanism(s) underlying the reduction in *nocturnal*GOR observed with CPAP. As GOR is known to occur during lower oesophageal sphincter (LOS) relaxation the primary focus of this study was to determine the effect of CPAP on the LOS. To do this, 10 normal, awake, supine individuals performed 5 swallows of 5ml of water at 4 levels of CPAP (0, 5, 10 and 15cmH_20) during oesophageal manometry. CPAP increased nadir LOS barrier pressure and decreased the duration of swallow-induced LOS relaxation (4.1s with 0cmH_20 to 1.6s with 15cmH_20 CPAP, $p<0.001$). These data suggest that CPAP reduces GOR by increasing the mechanical barrier to reflux.

Study four extended the findings of study three by seeking to determine the mechanisms underlying the increased prevalence of *nocturnal*GOR in OSA and the effect of CPAP on *nocturnal*GOR during sleep by investigating the behaviour of the LOS during sleep-related upper airway obstruction and during administration of CPAP. Eight patients with OSA and *nocturnal*GOR symptoms underwent polysomnography, oesophageal manometry and oesophageal pH monitoring. The first half the night was spent without and the second half with 10cmH_20 CPAP. During the first half of the night there was an average of 2.7±1.8 *nocturnal*GOR events.hr^{-1} compared to 70±39 obstructive events.hr^{-1}. Of these *nocturnal*GOR events 57% occurred either during an apnoea/hypopnoea or within 10s of airway reopening. Upper airway obstruction did not affect the barrier pressure provided by the LOS. CPAP reduced oesophageal acid exposure (15±12% and 4±8%, $p<0.05$). CPAP tended to increase the nadir pressure

during LOS relaxation and decreased the duration of LOS relaxation, suggesting an increase in the mechanical barrier to GOR.

The final study sought to investigate the effect of *nocturnal*GOR and OSA on BOS, the major limitation to survival in lung transplant patients. Fourteen lung transplant patients underwent simultaneous polysomnography and oesophageal pH monitoring. Six of the 14 patients were in various stages of BOS. The average proportion of time spent overnight with a pH <4 was 1.7±3.1% with a pathological level of GOR evident in 8/14 patients. Notably, all patients had OSA, which had not been previously diagnosed. Despite the increased incidence of OSA and *nocturnal*GOR, there were no relationships between severity of OSA or *nocturnal*GOR and severity of BOS.

Conclusions. The results of these studies indicate that OSA is associated with specifically *nocturnal*GOR symptoms. It is unlikely that apnoeic/hypopnoeic events themselves directly precipitate these events as no consistent temporal association was observed and upper airway occlusion had no effect on the barrier to GOR provided by the LOS. CPAP appears to reduce *nocturnal*GOR events by increasing the mechanical barrier provided by the LOS. In those who have undergone lung transplantation, although both *nocturnal*GOR and OSA were common, OSA did not appear to exacerbate *nocturnal*GOR or BOS.

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LIST OF ABBREVIATIONS

AHI	apnoea hypopnoea index
AI	apnoea index
ArI	arousal index
ANOVA	analysis of variance
BMI	body mass index
BOS	bronchiolitis obliterans syndrome
cm	centimetres
cmH_20	centimetres of water
CPAP	continuous positive airway pressure
ESS	epworth sleepiness score
FEV_1	forced expiratory volume in one second
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
H_2RA	histamine receptor antagonists
HI	hypopnoea index
kg	kilograms
LOS	lower oesophageal sphincter
min	minutes
m	metres
mm	millimetres
mmHg	millimetres of mercury
n	number of subjects
*nocturnal*GOR	nocturnal gastro-oesophageal reflux
NREM	non rapid eye movement sleep
OSA	obstructive sleep apnoea
OSAS	obstructive sleep apnoea syndrome
P_b	barrier pressure (P_{LOS} referenced to P_g)
P_{di}	transdiaphragmatic pressure
P_g	gastric pressure
P_{LOS}	lower oesophageal sphincter pressure
P_{oes}	oesophageal pressure
PPI	proton pump inhibitor
P_{ph}	pharyngeal pressure

REM	rapid eye movement sleep
s	seconds
SaO_2	oxygen saturation
SD	standard deviation
SE	sleep efficiency
St 1	stage 1 sleep
St 2	stage 2 sleep
St 3	stage 3 sleep
St 4	stage 4 sleep
SWS	slow wave sleep
TLOSR	inappropriate transient lower oesophageal sphincter relaxation
TST	total sleep time
Tx	transplant
yr	year

CHAPTER ONE

Introduction

Gastro-oesophageal reflux (GOR) is defined as the movement of gastric contents from the stomach into the oesophagus. The presence of acidic gastric contents in the oesophagus results in debilitating symptoms such as heartburn and acid regurgitation. If left untreated GOR may damage the oesophageal mucosa and reduce health-related quality of life, daytime functioning and work productivity.[1-4] The prevalence of GOR symptoms is high with approximately 20% of the general community reporting reflux symptoms on a weekly basis.[5]

*Nocturnal*GOR, that is reflux which occurs during sleep, is also common with approximately 10-25% of individuals reporting symptoms.[1,6] *Nocturnal*GOR is associated with markedly prolonged oesophageal acid exposure compared with daytime GOR mainly due to a sleep-related decrease in acid clearance mechanisms.[7] For this reason, *nocturnal*GOR has been reported to cause considerably more oesophageal damage and impair quality of life to a greater extent than daytime reflux.[1,8-11] The increased acid contact time is also associated with an increase in proximal migration of acid towards or into the larynx and pharynx[7] and increased risk of pulmonary aspiration of gastric contents, potentially leading to respiratory complications such as asthma, pneumonia, chronic cough, obstructive sleep apnoea and bronchiolitis obliterans syndrome.[12-17]

*Nocturnal*GOR may be exacerbated by obstructive sleep apnoea (OSA), a condition characterised by repetitive narrowing or collapse of the upper airway during sleep. Inspiratory efforts against an occluded airway result in the development of large negative intrathoracic pressures and repetitive arousals. The pressure gradients developed during these events may predispose OSA patients to *nocturnal*GOR and its associated symptoms. Indeed, OSA is associated with an increased number and severity of *nocturnal*GOR events and increased frequency of GOR symptoms.[18-20] Approximately 60% of OSA patients experience *nocturnal*GOR symptoms,[20] suggesting an association between the two conditions. Surprisingly, the majority of studies investigating such an association have found no evidence of a relationship between GOR symptoms and the presence or severity of OSA.[19,21,22]

If OSA itself were precipitating GOR then one would assume that the association between the two disorders would be most evident when investigating the association between *nocturnal*GOR and sleep-related obstructive events. However, large studies investigating the occurrence of GOR symptoms in OSA patients have rarely separated nocturnal symptoms from overall symptoms (*i.e.* daytime and nocturnal combined). This lack of separation of daytime and nocturnal symptoms may explain the lack of reported association between OSA severity and GOR symptoms. For this reason, a focus of the studies reported in Chapters Three and Four of this thesis was to determine the prevalence of nocturnal heartburn and acid regurgitation in OSA patients compared with a well-described general population sample and to identify potential sleep-related variables which may be relate to the presence *nocturnal*GOR symptoms. The primary hypothesis was that an association between OSA severity and GOR symptoms would be evident when considering *nocturnal*GOR symptoms specifically.

The mechanism of *nocturnal*GOR in OSA remains controversial. While it is plausible that the link between the two conditions is due to similarities in their predisposing factors, such as obesity and alcohol consumption, studies matching for these factors have still shown an increase in *nocturnal*GOR symptoms and episodes in OSA patients.[18,23] It is possible that the generation of negative intrathoracic pressure during inspiration against an occluded airway results in acid being "sucked out" of the stomach. Moreover, it is also possible that the intrathoracic pressure changes during obstructive apnoeas could precipitate reflux events by reducing the barrier to GOR provided by the lower oesophageal sphincter (LOS). However, with regard to the latter possibility, there have been no previous studies investigating the effect of apnoea on LOS behaviour. Hence a study was designed to address this issue by simultaneously recording sleep, *nocturnal*GOR events and LOS pressure during sleep in a group of patients with OSA. This study is presented in Chapter Six.

Continuous positive airway pressure (CPAP), the therapeutic mainstay for OSA, has been shown to reduce both daytime and *nocturnal*GOR symptoms and events.[20,24-28] However, the mechanism underlying the beneficial effect of CPAP on GOR remains unknown. Considering that *nocturnal*GOR events rarely occur during periods of stable LOS pressure, but rather during periods of relaxation of the LOS, establishing the effect of CPAP on this barrier to reflux remains a fundamental but unanswered question. Chapters Five and Six present studies that investigated the effects of CPAP on LOS relaxation during wakefulness (Chapter Five) and sleep (Chapter Six).

An association between lung disease and GOR has been recognised for some time.[29] In lung transplant patients a major limitation to long-term survival is the development of bronchiolitis obliterans syndrome (BOS).[30] Gastro-oesophageal reflux has been

implicated in the early development of BOS,[15-17,31,32] potentially via aspiration of acidic stomach contents. *Nocturnal*GOR may be particularly important in the development of BOS as longer GOR events and increased proximal migration during sleep[7] may further increase the risk of aspiration compared with daytime GOR events. The risk of nocturnal pulmonary aspiration could also be increased if OSA were present, a condition which is common in this patient group.[33] Considering that lung transplant patients have a high occurrence of *nocturnal*GOR and that OSA may further aggravate *nocturnal*GOR, the association between the two conditions may be of importance in understanding the development of aspiration-induced lung injury in this group. The potential associations between OSA, *nocturnal*GOR and chronic rejection were examined in a group of lung transplant patients, with the findings presented in Chapter Seven.

The studies undertaken in this thesis are presented as a series of five interrelated scientific papers, each with its own abstract, introduction, methods, results and discussion sections. Each study is novel, being the first to: (i) compare the prevalence of GOR symptoms in the general population to a large group of OSA patients (Chapter Three); (ii) determine risk factors for *nocturnal*GOR in both the general population and individuals with OSA (Chapter Four); (iii), investigate the effect of CPAP on the LOS to determine the mechanism underlying the effect of CPAP on *nocturnal*GOR (Chapter Five); (iv) simultaneously measure the barrier function of the LOS and oesophageal pH in OSA patients during sleep to determine the mechanism underlying the increased occurrence of *nocturnal*GOR in this population (Chapter Six); and (v) investigate the potential role of OSA in exacerbating *nocturnal*GOR in lung transplantation patients (Chapter Seven). These studies are preceded by a literature review that synthesises the most important historical and contemporary literature related to *nocturnal*GOR, OSA

and the association between the two conditions (Chapter Two). This thesis concludes with a brief general overview of the major findings (Chapter Eight).

CHAPTER TWO

Literature Review

2.1 GASTRO-OESOPHAGEAL REFLUX

2.1.1 Definition

Gastro-oesophageal reflux (GOR) describes the movement of acidic stomach contents into the oesophagus. GOR is a normal, physiological phenomenon and is experienced by all individuals occasionally in the postprandial period.[9] When experienced frequently GOR can reduce quality of life and can have severe consequences, including the development of oesophagitis and increased risk of oesophageal carcinoma.[8,34-36] GOR disease (GORD) is defined as "chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus".[37] Two distinct subgroups of GORD have been identified: (i) erosive GORD in which GOR results in oesophageal erosions such as oesophagitis; and (ii) non-erosive, or symptomatic GORD which results in no oesophageal damage but is evident by the presence of GOR symptoms.[38] Erosive GORD often develops in those with chronic GOR as a consequence of increased oesophageal acid exposure.[8] Approximately 67% of individuals with GOR symptoms sufficient to be referred for endoscopy are diagnosed as having the erosive variety.[39]

2.1.2 Oesophageal acid clearance

Oesophageal acid clearance after a GOR episode is achieved through several synergistic mechanisms. Firstly, an increase in swallowing frequency and associated primary peristaltic contractions (that is, a wave of oesophageal contraction stimulated by swallowing) along the length of the oesophagus clear the volume of acid from the oesophagus.[40-44] Secondly, an increase in bicarbonate containing saliva production neutralises the acid within the oesophagus. Both of these processes are essential for acid clearance and when combined ensure that during wakefulness acid is cleared quickly from the oesophagus.[42] The mechanisms responsible for clearance of GOR from the oesophagus may vary between events occurring in the upright and recumbent postures. Secondary peristalsis, that is oesophageal contraction unaccompanied by a swallow but stimulated by stretch receptors in the oesophagus when a bolus is not cleared by primary peristalsis, also plays a role in oesophageal acid clearance. Secondary peristalsis is more important in the clearance of acid from the oesophagus after recumbent than upright GOR events with up to 86% of recumbent GOR events followed by a secondary peristaltic wave compared to only 40% of upright episodes.[45]

2.1.3 Consequences of gastro-oesophageal reflux

The consequences of GOR will be discussed in the following section and include unpleasant symptoms, impaired quality of life, oesophageal mucosal damage and supraoesophageal complications.

2.1.3.1 Symptoms of gastro-oesophageal reflux

Heartburn (a burning sensation or discomfort behind the breastbone) and acid regurgitation (a bitter or sour tasting fluid in the back of the throat or mouth) are highly

specific and common symptoms of GOR.[46] Less common symptoms of GOR include non-cardiac chest pain, chronic cough, dysphagia (trouble swallowing solids and liquids in the absence of an obstruction)[47] and hoarseness.[29,34]

2.1.3.2 Impaired quality of life

Numerous studies have shown that GORD patients have significantly impaired quality of life compared to the general population or those without GORD.[3,4,48-50] In addition, individuals with GORD have significantly lower work productivity[48,51] and lower sleep quality than those without.[52] Presence and severity of GOR symptoms are the major contributors to this impaired quality of life.[3,4] A recent study of 10,000 individuals with GORD and 10,000 normal individuals found that quality of life and work productivity were decreased and healthcare utilization increased in those with GORD in proportion to symptom severity and frequency.[53] In a study of over 6,000 GORD patients, Kulig *et al*[4] demonstrated that the quality of life of individuals with either erosive or non-erosive GORD was similar to individuals who have suffered from acute coronary events and in some cases worse than for patients with diabetes or cancer. They and others[3] have also shown that this impairment in quality of life can be readily improved with treatment that eliminates symptoms and aids oesophageal healing, such as acid suppressive therapy.

2.1.3.3 Oesophageal mucosal damage

Oesophageal acid exposure may lead to mucosal damage in the distal oesophagus. The initial effect of acid bathing the oesophagus is the production of microscopic changes in the squamous epithelium of the oesophagus, such that the epithelial layer becomes thinner and the basal cell layer comes closer to the surface.[54] Further episodes of reflux lead to an inflammatory response within the mucosa and submucosa (oesophagitis). If

this persists it may lead to oesophageal ulceration or heamorrage.[55] Continued acid exposure leads to oesophageal strictures and Barrett's oesophagus, a premalignant condition that is a precursor for oesophageal adenocarcinoma. Prolonged inflammation may also cause oesophageal dysmotility, which further increases acid contact time and oesophageal injury.[56]

2.1.3.4 Extra-oesophageal complications

Once stomach contents have entered the oesophagus the refluxate is able to move into the proximal (upper) oesophagus or into the larynx and pharynx and be aspirated into the lungs, potentially leading to the development of both extra-pulmonary and intra-pulmonary pathologies. In a large epidemiological study, Chiocca *et al* showed that 81% of individuals with GORD reported at least one extra-oesophageal complication.[57]

Extra-pulmonary complications

Proximal and pharyngeal GOR have been implicated in the pathogenesis of laryngitis[13,58] and hoarseness.[5,12,34] In addition, GOR has also been implicated in the development of obstructive sleep apnoea[14] potentially due to upper airway inflammation resulting from pharyngeal aspiration of refluxate. It is likely that these extra-pulmonary complications result from increased laryngeal acid exposure and acid-induced tissue injury.[59,60] Laryngeal epithelium is more sensitive to acid injury than the oesophageal mucosa, therefore a relatively smaller amount of pharyngeal acid contact may result in tissue damage.[61]

Intra-pulmonary complications

Once stomach acid enters the pharynx, there is the potential for it to be aspirated into the lungs. Consequently, GOR has been associated with many respiratory conditions such as chronic cough,[12,62,63] asthma,[12,13,58,64] wheeze,[64] bronchitis[5,13] and pneumonia.[5,13]

There is also evidence that GOR may be involved in chronic graft rejection (*i.e.* development of bronchiolitis obliterans syndrome) in patients after lung transplantation.[15-17]

Despite much investigation, the precise mechanism by which GOR contributes to the pathogenesis of these respiratory complications remains controversial. Two main hypotheses exist. Firstly, aspirated stomach acid may cause lung injury, infection, or changes in airways resistance, any or all of which could contribute to the development of conditions such as asthma, pneumonia, cough or bronchitis. The finding that even small amounts of acid instilled into the airway can produce bronchospasm[65] lends support to this theory.

Secondly, GOR may contribute to these conditions via a vagally mediated reflex. Stimulation of sensory afferent pathways by acid in the distal oesophagus may trigger a neural response that results in broncospasm and changes in airways resistance. In support of this theory studies have shown that patients with asthma and cough have similar proximal acid exposure to healthy individuals, but increased distal oesophageal acid exposure.[59,63] Furthermore, oesophageal acid infusions can decrease peak expiratory flow in both healthy individuals and those with reflux or respiratory pathologies without evidence of microaspiration.[66,67] In a recent study in cats, Lang *et al*[68] found that perfusion of the oesophagus with acid caused a decrease in airway calibre, decreased mucociliary transport and increased mucus secretion, supporting the role of a reflex triggered by oesophageal acid perfusion. In addition, Rosztaczy *et al*[69] recently showed that oesophageal acid perfusion increased sensitivity to methacholine challenge in over 50% of asthmatic patients with GORD. Notably, these authors also reported that their asthmatic patients had significantly more proximal GOR than a non-

asthmatic control group, suggesting that both microaspiration and reflex responses could play a role in the development of respiratory complications in GORD.

2.1.4 Assessment techniques for gastro-oesophageal reflux

The variable nature of GORD (*i.e.* symptomatic *vs* asymptomatic, erosive *vs* non-erosive) complicates diagnosis and quantification of severity. Methods currently used in the diagnosis of GORD include symptom assessment, oesophageal pH monitoring, endoscopy and combined oesophageal impedance and pH monitoring.

2.1.4.1 Symptom assessment

The major symptoms of GOR, heartburn and acid regurgitation, have a high specificity for GORD (89% and 95%, respectively) but a low sensitivity (38% and 6%). Symptoms may be diagnostic or indicate the need for further tests, outlined later in this section. Symptom assessment combined with a trial of proton-pump inhibitor therapy has a diagnostic sensitivity for GORD of up to 92% and a specificity of up to 90%[70,71] and is considered acceptable for diagnosis in patients with typical and uncomplicated GOR symptoms. At present this represents the most commonly used method of GORD diagnosis. More complex diagnostic investigations (see below) are generally reserved for individuals with persistent symptoms on acid suppressive therapy or those with suspected erosive oesophageal damage.

2.1.4.2 Oesophageal pH monitoring

Twenty-four hour ambulatory oesophageal pH monitoring utilises either catheter-based pH sensors or a wireless pH capsule (positioned in the oesophagus by endoscopy and held in place by small barbs which attach to the oesophageal mucosa) to detect the presence of acid in the oesophagus resulting from a GOR event. Oesophageal pH

monitoring has been considered the 'gold-standard' measurement for GORD diagnosis and has an advantage over other diagnostic tests such as endoscopy as it can detect GORD in the absence of endoscopically visible lesions. Although the overall sensitivity of pH monitoring is high, the specificity of pH monitoring for the diagnosis of GORD (compared to combined pH-impedance monitoring, see below) is surprising low for a 'gold standard' test, being 58% - 67% with 22% of patients being over-diagnosed.[72] In addition, oesophageal pH monitoring is unreliable in the evaluation of patients on acid suppressive therapy, as some GOR events may be non- or weakly-acidic and fail to meet the criteria for a GOR event (a pH decrease to below 4). It has been reported that oesophageal pH monitoring has a specificity of only 30% for weakly-acidic reflux.[72]

2.1.4.3 Endoscopy

The presence of reflux oesophagitis caused by gastric acid injury is considered objective evidence of GORD. Oesophago-gastro-duodenoscopy (endoscopy) has advantages over other diagnostic techniques as it allows grading of oesophagitis and biopsy to determine the presence of Barrett's oesophagus or other lesions. Despite this advantage, endoscopy is uncommonly used as a diagnostic tool for GORD as it does not identify individuals with non-erosive GORD. It is generally reserved for use in individuals who fail to respond to acid suppressive therapy.[70,73]

2.1.4.4 Combined oesophageal pH and intraluminal impedance monitoring

The most recent development in the diagnosis of GORD is the use of intraluminal impedance monitoring. Multichannel intraluminal impedance was first described by Silny *et al*[74,75] to measure gastrointestinal motility. Sifrim *et al*[76] were the first to combine impedance with pH and validate the use of this technique in adults. Intraluminal impedance monitoring utilises the difference in electrical conductivity

between the oesophageal walls and the intraluminal contents to identify the presence and characteristics of a bolus (i.e. solid, liquid or gas).[74] Multiple impedance measuring segments placed along a single catheter permit the detection of bolus movement and clearance from the oesophagus; hence retrograde movement resulting from a swallow and anterograde movement resulting from GOR can be distinguished. Combining this with oesophageal pH monitoring allows the classification of a GOR episode into acidic (pH<4.0) or weakly-acidic (pH>4.0). Combined pH-multichannel intraluminal impedance monitoring allows the evaluation of individuals on acid suppressive therapy who still experience symptoms due to non- or weakly-acidic GOR and is therefore superior to pH monitoring alone. It has been suggested that combined pH-impedance monitoring is the new 'gold standard' for diagnosing GORD and clarifying the mechanism of persistent symptoms in those on acid suppressive therapy.[77,78] However, at present, combined pH-impedance systems are extremely expensive and analysis of the required data very time consuming. Thus, its current use is limited.

2.1.5 Prevalence of gastro-oesophageal reflux

There have been numerous studies investigating the prevalence of GOR in the general population, either subjectively through symptom questionnaire and/or interview or objectively using diagnostic tools such as endoscopy.

2.1.5.1 Prevalence of gastro-oesophageal reflux symptoms

The prevalence of the 'typical' GOR symptoms, heartburn and acid regurgitation, has been reported in numerous studies from around the world. In a large, epidemiological survey in North America, Locke *et al*[5] reported that 42-45% of the population had experienced heartburn or acid regurgitation in the previous 12 months and 6-18% of the

population reported heartburn or acid regurgitation at least once a week. Overall, they found that 20% of the population had GOR symptoms at least once a week. Results from an Argentinian study using the same questionnaire reported similar results.[57] As part of a public health survey of nearly 60,000 Norwegians, Nilsson *et al*[79] found that 31% of individuals reported symptoms at some time in the previous year, with 12% reporting GOR symptoms at least once a week. Other studies have reported between 27-41% of individuals experiencing GOR symptoms within 3-12 months prior to being surveyed,[50,80-83] with between 7-21% experiencing GOR symptoms at least once a week.[49,80,81,84-90] Differences in reported prevalence rates may be due to the different countries from which the studies were conducted with the lower prevalence rates generally reported in countries such as Iran and Korea, likely due to differences in diet and body habitus. Differences in reported prevalence rates may also be due to the use of different questionnaires and interviewing techniques. Regardless, there is substantial evidence to indicate that GOR symptoms are extremely common in the general population. At present, the prevalence of GOR symptoms in the Australian community is unknown.

Up to 80% of individuals with GORD in the general population report atypical symptoms of GORD.[5,57] Such symptoms include: non-cardiac chest pain (reported in 12-23% of individuals with GORD[5,91]); dysphagia (reported in 13.5-44%[5,47,57]); dyspepsia (reported in 10%[5]); and globus sensation (reported in 7%[5]). Each of these atypical symptoms has been significantly associated with symptoms of heartburn and acid regurgitation.[5] Other atypical symptoms include hoarseness[34] and upper and lower respiratory disorders including chronic cough, wheeze, asthma, bronchitis[29] and pneumonia. Heartburn and acid regurgitation have been found to be significantly associated with asthma, wheeze and nocturnal cough.[64]

2.1.5.2 Prevalence of objectively diagnosed gastro-oesophageal reflux

Compared to symptom-based prevalence studies there has been significantly fewer studies reporting the prevalence of objectively-diagnosed GORD in the general population. To date there has been no studies using oesophageal pH monitoring to determine the prevalence of GORD in the general population. The main reason for this is likely to be due to the equipment and labour intensive nature of recording 24-hour oesophageal pH in a large sample of the general population.

Few studies have used endoscopy to determine the prevalence of erosive GORD in the general population. A study of 57 asymptomatic volunteers found that 5% of individuals had endoscopic evidence of oesophageal erosions[92] suggestive of GORD. A larger study of 350 normal volunteers found 8.5% had erosive oesophageal lesions,[93] consistent with some reports of the prevalence of weekly GOR symptoms. In 110 normal individuals, Gerson *et al*[94] diagnosed 25% of their normal group with Barrett's oesophagus, a serious consequence of GORD and a precursor to oesophageal cancer. The reason for this extremely high occurrence of Barrett's oesophagus in a seemingly normal group of individuals is unknown; however that this group were white males over 50 years of age may be a possible explanation, as this is a known high-risk group for GORD. Endoscopy is likely to underestimate the number of individuals in the population with GORD, as it does not account for individuals with non-erosive GORD.

2.1.6 Mechanisms of gastro-oesophageal reflux

GOR occurs when the barrier between the stomach and the oesophagus, the lower oesophageal sphincter (LOS) is breached (Figure 2.1). Normally, a positive pressure gradient exists across the gastro-oesophageal junction as intra-abdominal pressure

exceeds oesophageal pressure. In the absence of the LOS gastric contents would flow freely into the oesophagus. The LOS is approximately 3-4cm in length[95,96] and is distinguishable by a thickened area of oesophageal smooth muscle[96,97] with the distal 2cm lying within the stomach.[96] The segment of the LOS that is exposed to intraabdominal pressure is potentially important in maintaining the integrity of the gastro-oesophageal junction, especially during periods of abdominal straining.[96] Tone of the LOS is modulated neurogenically, by cholinergic nerves[98] and myogenically by the release of intramusular calcium.[99] In addition to the thickened area of smooth muscle the high pressure zone of the LOS also receives contribution from the crural diaphragm[100], which has a 'pinchcock' effect on the sphincter during inspiration and abdominal straining. Normal, resting LOS pressure is between 10-30mmHg (13.6-40.8cmH_20) above gastric pressure, however 5-10mmHg is sufficient to prevent GOR.[101,102] LOS pressure has been shown to fluctuate with respiration, posture and sleep.[103]

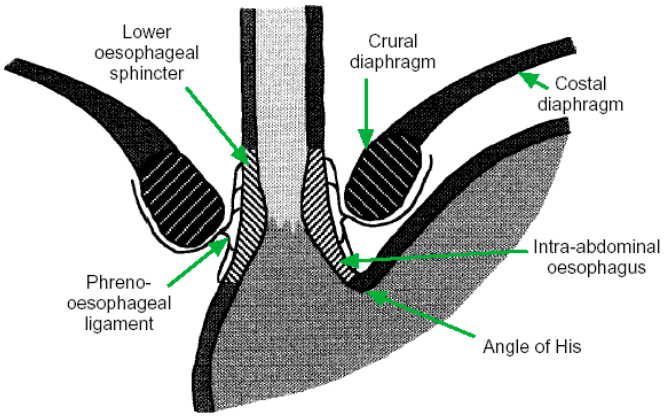

Figure 2.1. *Schematic representation of the gastro-oesophageal junction showing the major elements of the LOS, including the smooth muscle sphincter and the crural diaphragm. From Holloway et al.*[104]

Common to virtually all reflux episodes is a reduced LOS pressure, irrespective of whether the period of hypotension is transient or prolonged (Figure 2.2). There are four major mechanisms for GOR: spontaneous GOR, strain-initiated GOR, swallow-induced LOS relaxation and inappropriate, transient LOS relaxation. These are discussed in more detail in the following section.

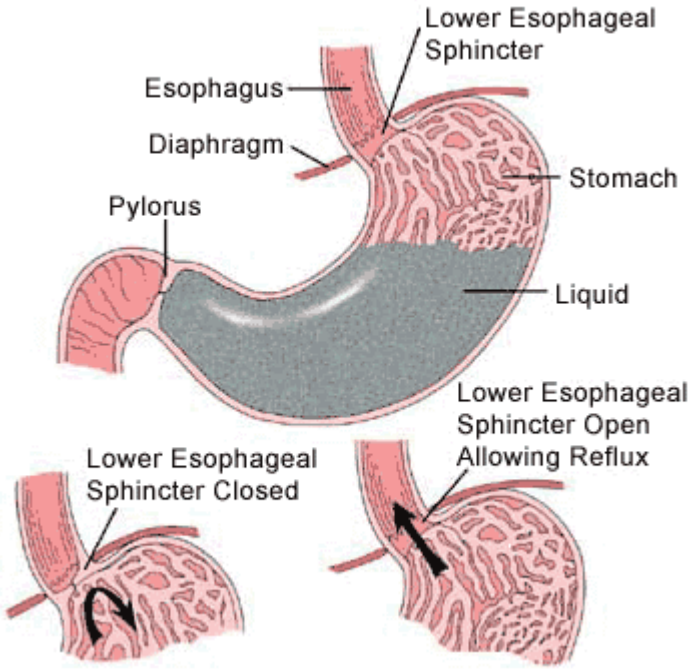

Figure 2.2. *Schematic representation of the barrier function of the LOS in preventing GOR.* [105]

2.1.6.1 Spontaneous reflux

Spontaneous reflux episodes occur when LOS pressure is near or equal to zero due to LOS hypotonia or downward drifts in LOS pressure (Figure 2.3). In the absence of LOS pressure, gastric acid is able to wash back into the oesophagus uninhibited. Although it was traditionally thought that most reflux events occurred via this mechanism, more recent studies have shown that such low basal LOS pressure accounts for a relatively small proportion of reflux episodes in both normal individuals and those with GORD.[45,102,106] In healthy individuals, spontaneous reflux is virtually non-existent,

however in reflux patients it has been found to account for 18% of reflux episodes.[102] Barham *et al* also reported that spontaneous reflux was significantly increased in patients compared to controls and increased further with increasing severity of oesophagitis.[107] Therefore, only those with severe reflux oesophagitis appear to reflux via this mechanism.[108] The low proportion of GOR episodes attributed to spontaneous reflux, even in those with GORD is likely due to the fact that most GORD patients have a resting LOS pressure within the normal range. In addition, a basal LOS pressure of only 5mmHg (relative to gastric pressure) is sufficient to prevent reflux.[101]

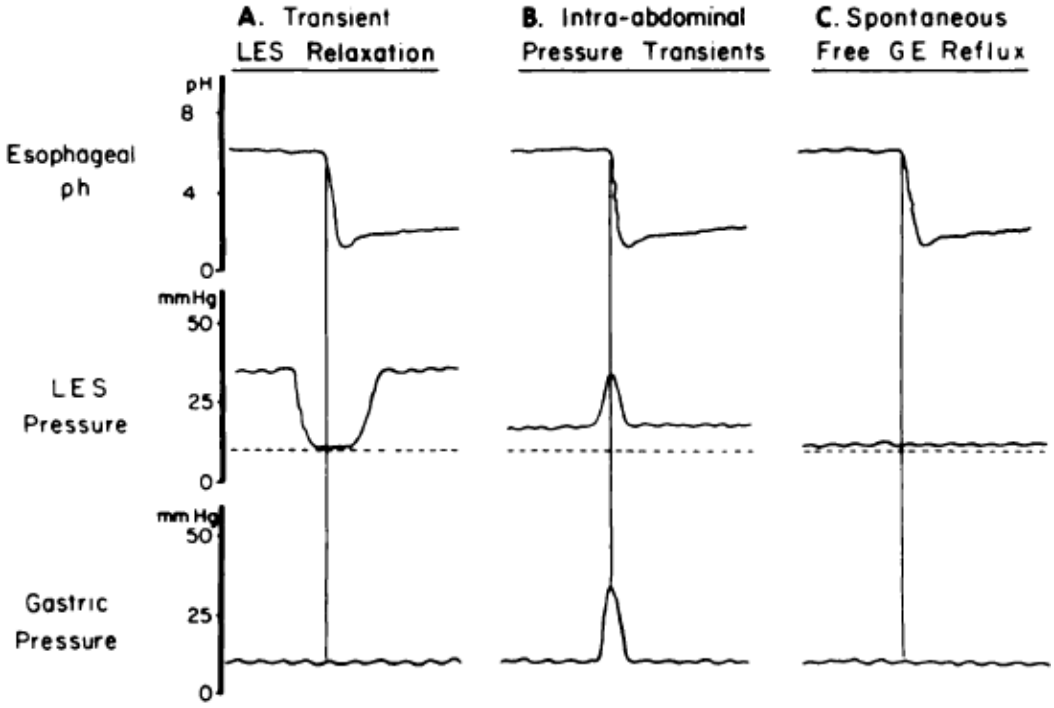

Figure 2.3. *Schematic representation of three mechanisms of* gastro-oesophageal *reflux (indicated by vertical line). Reflux may occur in association with (A) transient lower oesophageal sphincter relaxation; (B) transient increases in gastric pressure resulting from straining; or (C) extended periods of low sphincter tone. From Dodds et al.*[102]

2.1.6.2 Strain initiated reflux

Strain-initiated reflux episodes occur when intraabdominal pressure is equal to or exceeds LOS pressure, overcoming its capacity to act as a barrier (Figure 2.3). In

general, strain-initiated reflux occurs coincident with LOS relaxation. Schoeman *et al*[45] reported that 20% of reflux events were associated with straining, 90% of them occurring during LOS relaxation, with only 10% of them triggering a reflux event in the presence of a detectable LOS pressure. Other studies have also shown a close correlation between low LOS pressure and strain-initiated reflux such that the increase in abdominal pressure is able to 'blow open' an already vulnerable LOS.[42,102] In fact, straining during a LOS relaxation has been shown to almost double the risk of reflux occurring.[45] Strain-initiated reflux episodes are uncommon in normal individuals even during periods of low LOS pressure with only 4% of increases in abdominal pressure resulting in reflux. In reflux patients, strain or movement induced GOR events are much more common with up to 27% of abdominal pressure increases being associated with reflux episodes.[102] The increased occurrence of this type of reflux in erosive GORD is likely due to a decreased basal LOS pressure, which can be overcome by relatively smaller increases in intraabdominal pressure.[42]

2.1.6.3 Swallow induced lower oesophageal sphincter relaxation

Reflux associated with swallowing occurs because the LOS must relax to allow the bolus of swallowed material to enter the stomach[109,110] (Figure 2.4). Generally, the LOS does not relax fully and a residual pressure remains which is sufficient to prevent reflux occurring during a swallow.[109] Reflux episodes have been shown to rarely occur during swallow-induced LOS relaxations that are associated with a complete peristaltic sequence, accounting for only 2% of reflux events in normal individuals[106,111] and 9% of events in oesophagitis patients.[42]

Swallows associated with a complete peristaltic sequence are uncommonly accompanied by GOR because: (i) the lack of crural diaphragm relaxation maintains a

barrier against reflux; (ii) swallow-induced LOS relaxations are short, lasting less than 7s; and (iii) the oncoming peristaltic wave prevents gastric contents entering the oesophagus.[104] However, swallows associated with incomplete LOS relaxation are more commonly accompanied by GOR. Dent *et al*[106,111] found that 13-15% of reflux episodes in normal individuals and those with symptomatic GORD were associated with an incomplete peristaltic sequence. Dodds *et al*[42] reported similar findings with 9% of reflux events in normal individuals occurring during swallow-induced LOS relaxation associated with a failed peristaltic sequence and 16% of reflux events in GORD patients with oesophagitis.

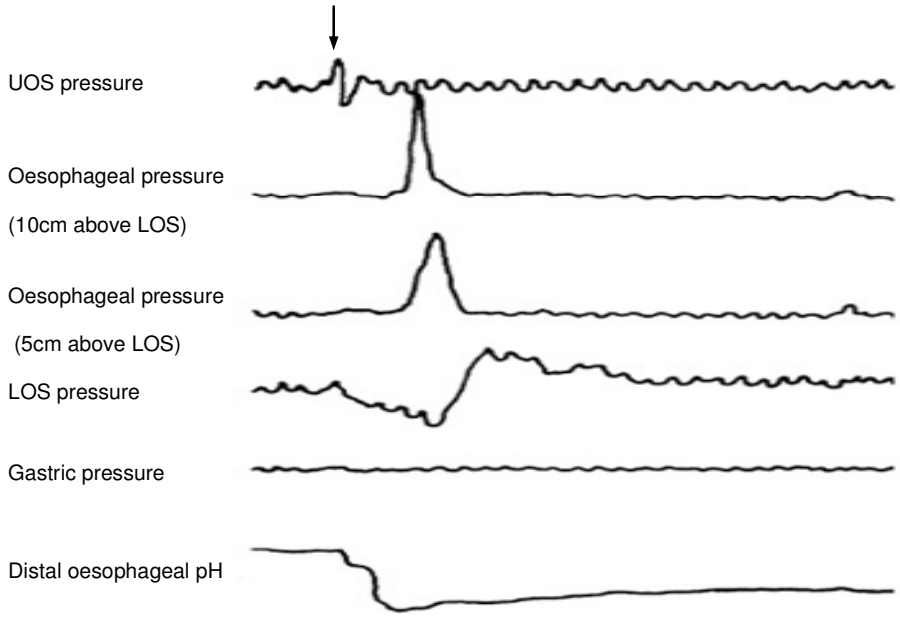

Figure 2.4. *An example of a reflux event associated with swallow-induced LOS relaxation. Adapted from Baldi et al.*[112] *UOS (upper oesophageal sphincter); LOS (lower oesophageal sphincter). Arrow indicates swallow initiation. Note: LOS pressure decreases shortly after initiation of the swallow. Distal oesophageal pH decreases shortly after that, indicating a GOR event.*

2.1.6.4 Transient lower oesophageal sphincter relaxations

Traditionally it was thought that reflux episodes occurred because of a low basal LOS pressure. More recently it has been shown that the majority of reflux episodes in both

normal individuals and those with GORD occur during transient lower oesophageal sphincter relaxation (TLOSR) (Figure 2.3). TLOSRs were first described by Dent *et al*[106] and are responsible for between 82% and 98% of GOR events in otherwise normal, healthy individuals.[45,102,106,113]

TLOSRs are non-swallow induced, vagally mediated relaxations stimulated by gastric distension. Distension of the stomach (especially the gastric cardia) is detected by mechanoreceptors in the proximal stomach which transmit signals to the brainstem via vagal afferent pathways[104] to evoke a complex sequence of events. This sequence of events includes LOS relaxation, inhibition of the crural diaphragm and oesophageal contraction. TLOSRs are defined by the fulfilment of all of the following criteria: (i) the absence of swallowing for 4s before, to 2s after the onset of LOS relaxation; (ii) a relaxation rate of $\geq$1mmHg.s^{-1}; (iii) time from onset to complete relaxation of $\leq$ 10s; and (iv) a nadir pressure of $\leq$ 2mmHg.[114]

Not all TLOSR are associated with reflux. Dent *et al*[106] noted that in the first 3 hours after a meal 93% of TLOSR were associated with reflux, whereas 3-11 hours after a meal only 69% of TLOSR were associated with reflux, suggesting that the probability of reflux is partially determined by volume of gastric contents and subject posture. Indeed, it has since been confirmed that the rate of TLOSR is dependent upon the extent of gastric distension.[115] TLOSR are thought to be important in the venting of gas from the stomach, especially after a meal.[116] In ambulant subjects it has been shown that 70% of reflux events in normal individuals are associated with both TLOSR and simultaneous belching.[107]

Recent research on TLOSR has focussed on the neurotransmitters involved in the pathway controlling TLOSR as these are potential targets for pharmacological treatment of GORD. Agents that have been shown to inhibit the increase in TLOSR which occurs with gastric distension or a meal, include glutamate receptor antagonists,[117] gamma amino butyric acid agonists[118] and nitric oxide antagonists.[119]

TLOSR have been implicated in the increased frequency of GOR episodes in those with GORD for several reasons. Firstly, there is evidence to suggest that individuals with GORD have more TLOSR than healthy individuals,[115,120] which would increase the probability of GOR occurring, however not all studies support this finding.[42,121] Secondly, a higher proportion of TLOSR are associated with reflux episodes in GORD patients than in healthy individuals.[42,115] This may be because individuals with an abnormal amount of reflux have more TLOSR associated with complete relaxations than normal individuals: GOR only occurs with TLOSR where the LOS completely relaxes.[102] Lastly, Dodds *et al* showed that 94% of GOR episodes in healthy individuals occur with TLOSR, whereas only 65% of events in GORD patients occur with TLOSR. Their GORD patients had a greater number of GOR episodes that were due to extended periods of low LOS tone and transient increases in abdominal pressure[42,102] than healthy individuals. To date our understanding of why individuals with GORD have more reflux than healthy individuals remains incomplete.

2.1.7 Treatment of gastro-oesophageal reflux

The goals of treatment for individuals with GORD are, in the short term, to eliminate reflux symptoms and heal mucosal lesions and in the long-term to maintain

symptomatic and endoscopic remission and ultimately prevent any complications.[122] The following sections provide a brief review of the treatment options for GORD.

2.1.7.1 Non-pharmacologic treatment of gastro-oesophageal reflux

Lifestyle modification

Individuals with reflux symptoms but without erosive oesophageal damage may be able to reduce or eliminate reflux symptoms with lifestyle modification. Numerous studies provide evidence that lifestyle factors such as diet (fatty food, alcohol and caffeinated drinks),[123-126] smoking[127,128] and obesity[129,130] increase acid exposure, worsen reflux symptoms and affect the LOS (see section 2.1.8). Avoidance of these triggers in susceptible individuals can be beneficial and is frequently employed as a first-line therapy for GORD or as an adjunct to medications.[37,131]

Surgical treatment

There are several surgical options for the treatment of GORD. The most common of these, fundoplication, involves wrapping the gastric fundus (the upper part of the stomach) around the inferior oesophagus to restore the function of the LOS and prevent reflux occurring (Figure 2.5). This can be done laparoscopically with relatively low complication and mortality rates (5% and 0.2% respectively). Follow-up of individuals after fundoplication shows significant reductions in medications taken, reductions in acid regurgitation episodes, heartburn scores, bloatedness, chest pain and chronic cough.[132] However, it has been reported that approximately 9 years after surgery up to 62% of fundoplication patients return to antacids and acid-suppressive therapy to control symptoms,[133] suggesting that fundoplication does not eliminate the need for medication in the long term. In contrast, Gee *et al*[134] recently reported that at 5 years follow-up 71% of patients were satisfied with the outcome and the majority of patients

undergoing fundoplication had near-normal quality of life scores. A randomised controlled trial of 550 patients comparing medical and surgical management of GORD[135] reported both treatments to be equally effective based on symptom evaluation, endoscopy and quality of life measures, with approximately 90% of individuals in remission after 3 years. Surgery was slightly more effective at controlling symptoms and improving quality of life than medical treatment. In addition, economic analysis of GORD treatment suggests that laparoscopic fundoplication is more cost-effective than lifelong medication.[136]

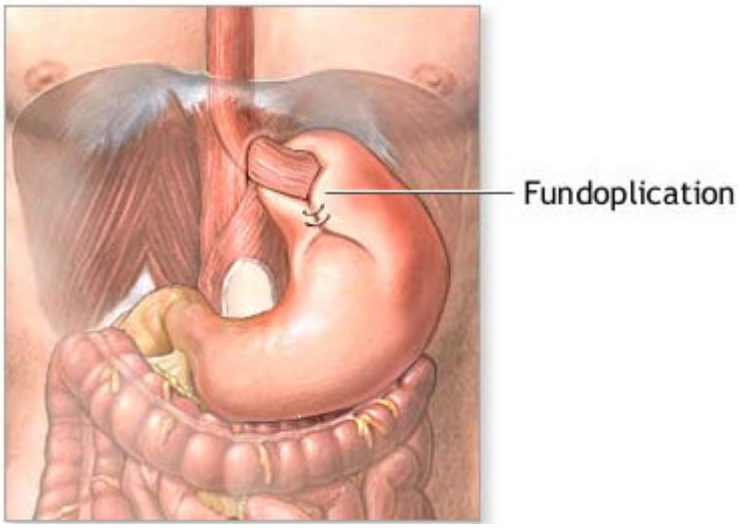

Figure 2.5. *Fundoplication surgery for the treatment of GORD. The stomach is wrapped around the distal oesophagus to form an artificial 'sphincter' to prevent GOR.*[137]

Alternative surgical treatments for GORD include endoluminal therapies, which are aimed at improving the barrier function of an incompetent LOS. The first of these involves injection of a polymer around the region of the LOS (Enteryx). Deviere *et al* were the first to describe this technique in humans[138] and showed that at 3-12 months post-procedure 87% of patients maintained an increase in LOS pressure with just 25% of patients resuming acid-suppressive therapy for persistent symptoms. In several

multicenter trials[139,140] it was found that at 6, 12 and 24 months post-procedure approximately 70% of patients were free of acid-suppressive therapy and most had significant improvements in health-related quality of life, oesophageal acid exposure and LOS tone. Despite these promising results Enteryx was withdrawn by the manufacturer after several cases of fatal complications resulting from injections of the polymer.

Another of these endoluminal therapies is radio frequency energy delivery to the gastro-oesophageal junction, distal oesophagus, LOS and gastric cardia in order to generate transmural thermocoagulation and scarring which 'tightens' the smooth muscle of the LOS (Stretta procedure). This treatment is reported to reduce postprandial TLOSR and increase basal LOS pressure[141] and results in significant reductions in heartburn scores, quality of life questionnaire scores[142] and oesophageal acid exposure at 6 and 12 months follow-up.[141,143,144] The long-term effectiveness of this procedure is unknown at present as the longest period of follow-up in any study is 12 months.

Finally, endoscopic suturing of the LOS (EndoCinch) has beneficial effects for individuals with GORD. This technique uses endoscopy to create pleats in the gastro-oesophageal junction, improving the barrier function of the LOS. Initial studies using this technique reported reductions in oesophageal acid exposure, proton pump inhibitor (PPI) use[145] and GOR symptoms.[145,146] More recently, Montgomery *et al*[147] have reported reductions in PPI use and reflux-related symptoms at 3 months post-procedure compared to a sham group. However these benefits were not evident at 6 or 12 months follow-up. They also failed to find differences (either intra- or inter-group) in endoscopic findings, oesophageal acid exposure, oesophageal manometry or quality of life. Likewise, in the only randomised, double-blind, sham-controlled study using

EndoCinch, Schwartz *et al*[148] failed to find any difference in oesophageal acid exposure between sham and treatment groups. They did, however, find improvements in reflux-related symptoms and health-related quality of life at 12 months follow-up.

2.1.7.2 Pharmacologic treatment of gastro-oesophageal reflux

Antacids

Over-the-counter products such as antacids, which neutralise gastric acid and antacid-alginates, which neutralise acid and also coat the oesophageal mucosa are helpful in providing rapid relief from symptoms of GOR.[37,149] However, as they do not block acid production their effects are short-lasting and they do not prevent erosive injury to the oesophagus.[37,150] For this reason they are most effective in mild cases of non-erosive GORD.[71] Antacids available in Australia include Gaviscon, Mylanta, Quickeze, Rennie, Gelusil, Eno, Mucaine and Tums.

Promotility agents

Promotility agents which correct oesophageal dysmotility, improve acid clearance or LOS barrier function or increase gastric emptying have shown promise with reported reductions in GORD symptoms, healing of oesophagitis and prevention of relapse of oesophagitis,[151,152] however some of these, such as Tegaserod (Zelmac) have recently been removed from the market due serious side effects including cardiac arrhythmia and others have not been approved for use due to a high side effect profile. Therefore, despite showing promising results promotility agents are uncommon in the treatment of GORD.[71] At present, there are no promotility agents marketed in Australia.

Histamine receptor antagonists

Histamine receptor antagonists (H_2RAs) are widely used as a treatment for GORD. H_2RAs act by blocking both basal gastric acid secretion and meal-stimulated acid secretion and therefore are more effective than antacids at relieving symptoms and healing erosive injury. 50-75% of patients with oesophagitis experience relief from symptoms and mucosal healing after 12 weeks of treatment with H_2RAs.[153] The effectiveness of H_2RAs in mucosal healing is related to the severity of oesophagitis.[154] In individuals with mild oesophagitis between 65-90% of individuals have oesophageal healing whereas in those with severe oesophagitis the healing rates are lower, being 40-55%. Therefore, they are generally considered for mild-moderate GORD only. In Australia, available H_2RAs include Ranitidine, Famotidine, Cimetidine and Nizatidine.

Proton pump inhibitors

Proton-pump inhibitor (PPI) therapy is the mainstay therapy for GORD.[71] PPIs act by blocking the gastric proton pump thereby preventing acid secretion. In a recent randomised, controlled trial Lundell *et al*[135] reported a remission rate of 93% in GORD patients 3 years after commencing PPI therapy. It has also recently been reported that PPI therapy, in addition to effectively treating GORD, promotes histological normalisation of the mucosa and submucosa in the distal oesophagus.[155] These results are supported by a meta-analysis on the pharmacological treatment of GORD.[153] In this analysis Chiba *et al* concluded that the overall healing proportion on PPIs was 84%. This is significantly higher than the overall healing proportion on H_2RA therapy (52%). In addition, mucosal healing occurred twice as quickly with PPI therapy.

However, gastric acid secretion may not be completely abolished in all individuals on PPI therapy. Nocturnal acid breakthrough (that is a gastric pH of less than 4 for more

than one hour during the night) occurs in up to 82% of GORD patients who are on PPI therapy.[156] If a H_2RA is added before bedtime, the occurrence of acid breakthrough is decreased to 40%. These results suggest that a combination of pharmacological therapies may be necessary to optimise acid suppression. PPIs available in Australia include Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole and Esomeprazole.

2.1.8 Modifying factors for gastro-oesophageal reflux

Numerous factors have been shown to increase the risk for GOR symptoms and complications including body weight, cigarette smoking, alcohol consumption, fatty food consumption, coffee consumption, the presence of hiatus hernia and body position. Each of these risk factors and the mechanism underlying their effect on GOR will be discussed in the following section.

2.1.8.1 Body weight

The association between body weight and presence of GOR, severity of GOR and complications arising from GOR have been extensively studied. Cross-sectional studies of the general population and studies in patients with GORD symptoms agree that excess weight and obesity are significant risk factors for GOR symptoms,[83,90,123,124,129,130,157-167] increased oesophageal acid exposure and number of reflux episodes,[129,130,168] oesophagitis,[166,169-171] Barrett's oesophagus[172] and oesophageal adenocarcinoma.[173] The relationship between GOR symptoms and body mass index (BMI) is dose dependent[123,168,174,175] with weight gain associated with the worsening of GOR symptoms,[160,175] and weight loss associated with symptom improvement.[171,175]

The mechanism for the increased risk of reflux and its complications in obesity remains a point of discussion with several mechanisms being suggested. Firstly, overweight and obese individuals have higher intragastric pressure[176-178] than normal weight individuals, and therefore an increased gastro-oesophageal pressure gradient,[179,180] both of which have been shown to increase risk of GOR.[181] Abdominal obesity may be particularly important as several studies have reported associations between measures of abdominal obesity such as waist circumference or abdominal diameter and GORD[130,158,165,176,182] with some suggesting that at least part of the BMI-GORD association is mediated through increased abdominal obesity.[158,177] Secondly, obese patients have up to 3 times more TLOSRs in the postprandial period than normal individuals.[179] Taking into account that the majority of reflux events occur during such events, this would significantly increase the chance of GOR occurring. Thirdly, there may be an effect of sex hormones on GOR in obese individuals as several studies have shown a stronger association between BMI and GOR in women than men[162,167,169,170,175] and hormone replacement therapy has been significantly correlated with increased risk of GOR.[170,175] Obese women also have more circulating oestrogens[183] which are known to increase nitric oxide synthesis[184] and may lead to a reduction in LOS tone. Finally, obesity is a risk factor for hiatus hernia[83,185] which is associated with an increase in GOR[92,186] (see section 2.1.8.6).

2.1.8.2 Smoking

The effect of cigarette smoking on GOR and related complications is controversial with some studies reporting no effect of smoking on GOR symptoms, reflux oesophagitis or risk of Barrett's oesophagus[84,87,91,92,187] and others reporting a detrimental effect of both current- and ever-cigarette smoking on GOR.[90,123,124,127,128,162,188-191] In addition to increasing GOR symptoms and events, there is also evidence suggesting smoking

increases the risk of complications such as erosive oesophagitis[192], Barrett's oesophagus[172] and oesophageal adenocarcinoma.[173]

The mechanism underlying an effect of smoking on GOR is uncertain, however there are several likely candidates. Smoking has been shown to alter LOS pressure.[189] Initially it was thought that smoking caused an acute decrease in LOS pressure up to 8 minutes after smoking cessation.[193] However, Kahrilas *et al*[189] showed that smokers have significantly lower resting LOS pressures than non-smokers, although acute smoking did not decrease resting sphincter pressure further. Smoking did, however, significantly increase the number of TLOSR during the smoking period. In the same study Kahrilas also showed that during the smoking period there was a significant increase in GOR relative to before or after the smoking period. Despite the greater number of TLOSRs during the smoking period the majority of reflux events were precipitated by stress events such as coughing or deep inspiration. A combination of chronically low LOS pressure, increase in TLOSRs and the frequent occurrence of stress events during smoking,[193] such as coughing, are likely to be responsible for the reported increased risk of GOR and its complications in smokers.

2.1.8.3 Alcohol consumption

The effect of alcohol consumption on GOR is also controversial. Studies have shown that alcohol consumption is associated with an increase in GOR symptoms,[90,123,124,194] oesophageal acid contact time[195-198] and a 2-3 fold increased risk of oesophagitis and Barrett's oesophagus.[164,173] Despite the large amount of evidence for an effect of alcohol on GOR there is also evidence against it with many studies not finding an association between the two.[50,87,91,94,127,187,190,191,199,200]

The most likely mechanism for any potential effect of alcohol on GOR is its effects on oesophageal motility and LOS pressure. Several studies have shown that alcohol consumption reduces both primary and secondary peristalsis in the distal third of the oesophagus, these being replaced with non-propulsive, simultaneous oesophageal contractions,[197,198,201] which would prolong oesophageal clearance of any refluxed material, increasing the risk of oesophageal damage. The number of swallows required to clear acid from the oesophagus is increased after alcohol consumption,[197] which would also increase oesophageal acid exposure. In addition, decreases in LOS pressure have been noted after alcohol consumption,[201] which would weaken the anti-reflux barrier.

2.1.8.4 Fatty Foods

Fatty foods are one of the most frequently reported precipitating agents for GOR[85] and those with GORD are counselled to avoid them, however there are conflicting results regarding the effect of fatty food on GOR. While some studies have shown a high fat meal in normal individuals increases oesophageal acid exposure compared to a low fat meal[125,202] others have failed to show a difference in GOR after meals of different fat content.[203,204 ,205]

There are several possible mechanisms for the potential effect of high fat meals on GOR. Firstly, fat has been shown to have an effect on the LOS. In two separate studies Nebel and Castell[206,207] reported significant decreases in LOS pressure with ingestion of a fat meal, which may explain the increase in GOR after a high fat meal reported in some studies. Secondly, Fox *et al*[208] reported that their subjects experienced significantly more reflux symptoms after a high fat than low fat meal, suggesting that dietary fat, although having no effect on actual reflux events, may increase visceral

sensitivity to acid. This is supported by a recent study by Shapiro *et al*[209] who investigated the effect of dietary components on GOR symptoms and reported that individuals who had a diet high in cholesterol, saturated fats or one with a high proportion of calories from fat were more likely to report symptoms associated with a GOR event. Finally, caloric density may play a role[204,208] as a high calorie meal may delay gastric emptying, leaving the stomach distended for longer, increasing the time during which reflux is most likely to occur.

2.1.8.5 Coffee

Coffee has also been implicated in GOR with 70% of individuals with daily heartburn reporting it as a precipitating factor.[85] Despite laboratory-based studies showing an effect of coffee consumption on oesophageal acid exposure and GOR symptoms,[126,210] the findings of population-based studies are conflicting. Zheng *et al*[162] reported a dose dependent effect of coffee on GOR symptom risk in women, however coffee consumption was associated with a decreased risk of symptoms in men. Nilsson *et al*[191] also showed a protective effect of coffee consumption on risk of GOR symptoms. Several other studies have found no effect of coffee on GOR.[84,87,123,124,190]

Laboratory-based studies have shown that the effects of coffee consumption on GOR are significantly reduced after decaffeination.[126,211] However it appears that the caffeine content of coffee alone is not responsible for precipitating GOR as caffeine added to tap water does not have any effect on either oesophageal acid exposure[126] or the occurrence of GOR symptoms.[212] Moreover, both caffeinated and decaffeinated coffee have been shown to reduce LOS pressure.[213,214] These findings are not universal as others have reported either no effect of coffee on LOS pressure[215] or an increase in LOS pressure.[212,216] The reasons for these discrepancies may lie in methodological

differences between studies such as: the type of coffee used, as the caffeine content of brewed coffee is greater than instant; or in the method of administration, such as drinking versus instilling directly into the stomach.

Another potential mechanism underlying the increase in GOR events and symptoms with coffee consumption is the increase in gastric acid secretion observed with both caffeinated and decaffeinated coffee consumption.[212,216] Recent studies suggest that the method of processing of coffee beans may also be important in the response of the LOS and acid secretion to coffee.[217-220]

2.1.8.6 Hiatus hernia

Hiatus hernia occurs when the proximal part of the stomach is displaced through the diaphragmatic hiatus[186] (Figure 2.6), likely due to loss of elasticity of the phrenoesophageal ligament or oesophageal shortening which occurs with frequent acid perfusion.[186,221] The prevalence of hiatus hernia amongst healthy individuals is approximately 20%.[83,92] This prevalence increases to 50% in GORD patients.[222] Hiatus hernia has been associated with increased occurrence and severity of GOR on 24-hour pH monitoring and increased GOR symptoms[83,92,95,223-226] as well as erosive oesophagitis,[83,223,225-228] suggesting that hiatus hernia is not only an important precipitator of reflux but may also play a role in the development of oesophageal damage. This contention is supported by several studies which have found individuals with hiatus hernia to have reduced oesophageal clearance relative to those without.[223,229]

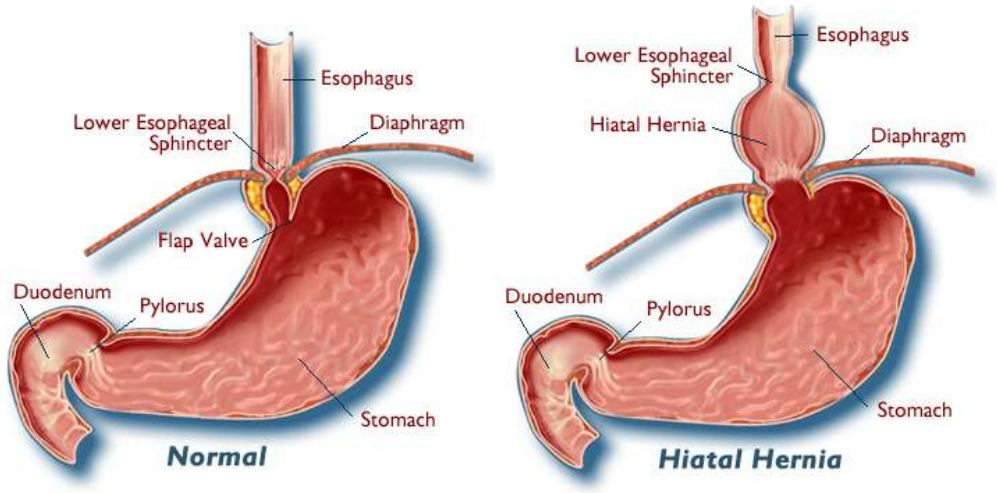

Figure 2.6. *The lower oesophageal sphincter in (a) the normal anatomical position and (b) in the presence of hiatus hernia. Note the crural diaphragm and smooth muscle sphincter act on different sites in the herniated patient, decreasing the barrier function of the LOS. The herniated pouch fills with stomach acid, which is then refluxed into the oesophagus.*[230]

Hiatus hernia almost certainly predisposes to reflux due to the disruption of the barrier provided by the LOS. Separation of the smooth muscle from the crural diaphragm results in LOS pressure being significantly lower in individuals with hiatus hernia than those without.[92,95,225,231] There is a significant correlation between both LOS pressure and severity of GORD and the size of the herniation.[95,223] Compared to those without hiatus hernia, hernia patients have a significantly increased number of GOR episodes during swallow-induced LOS relaxation, strain or deep inspiration, suggesting that the lower LOS pressure may leave the LOS vulnerable to GOR during these or similar stressors.[95] It has also been shown that stomach distension in hiatus hernia patients causes the LOS to open to a larger cross-sectional area than in normal or non-hernia GORD patients,[231] enhancing the flow of fluid and air across the junction.

2.1.8.7 Body position

Occurrence of reflux is also altered by body position, with GOR occurring less frequently in the supine than upright position. The supine position is associated with: (i) an increase in basal LOS pressure,[232-234] the reason for which is not known; and (ii) a reduction in TLOSRs. The difference in the number of TLOSR in the supine compared with the upright position maybe due to less distension of the proximal stomach when supine, which has previously been shown to be the most potent area for stimulation of TLOSRs.[115] This decrease in distension likely occurs due to dispersion of stomach gases throughout the stomach in the supine posture, whereas in the upright position stomach gases congregate around the proximal stomach, stimulating TLOSR. In normal individuals and the majority of individuals with non-erosive GORD the occurrence of supine reflux is rare.[235,236]

Although less common than upright GOR, supine GOR is more strongly associated with oesophageal damage. Studies show that individuals with erosive oesophageal damage have significantly more supine GOR than those without oesophageal damage[235,236] due to significantly delayed acid clearance during sleep.[7] Therefore the distinction between those who reflux during the day and those who reflux at night (*nocturnal*GOR) is important with regard to risk of oesophageal damage. The consequences and mechanisms of nocturnal reflux are discussed in detail in the following section.

2.1.9 Nocturnal reflux

2.1.9.1 Definition of nocturnal reflux

*Nocturnal*GOR refers to GOR that occurs in the recumbent position during sleep. The pattern of reflux overnight is significantly different to the pattern of reflux during the

day, where most episodes occur in the postprandial period and, although frequent, are cleared quickly. Overnight, reflux episodes are infrequent but are less readily cleared.

2.1.9.2 Prevalence of nocturnal gastro-oesophageal reflux

There is limited data available on the prevalence of *nocturnal*GOR symptoms in the general population. Results from a survey of 15,000 individuals from the general population in North America reported that 25% of individuals experience nocturnal heartburn[6] whereas a telephone survey of the 9,000 individuals from the general population in North America[1] reported that 10% of individuals reported frequent nocturnal symptoms of GORD. Amongst those with symptomatic GORD approximately 30-80% of individuals report symptoms during the night.[1,5,12,48,57] Differences in the reported prevalence of *nocturnal*GOR symptoms are likely due to the use of different definitions of symptomatic GORD and different frequencies of nocturnal symptoms used to categorise patients.

Reflux events overnight are rare in normal individuals[113] and those with mild GORD but tend to occur more commonly in those with erosive GORD or Barrett's oesophagus.[8,10,113,237] This observation supports the notion that delayed acid clearance during sleep is important in the development of reflux-related complications.

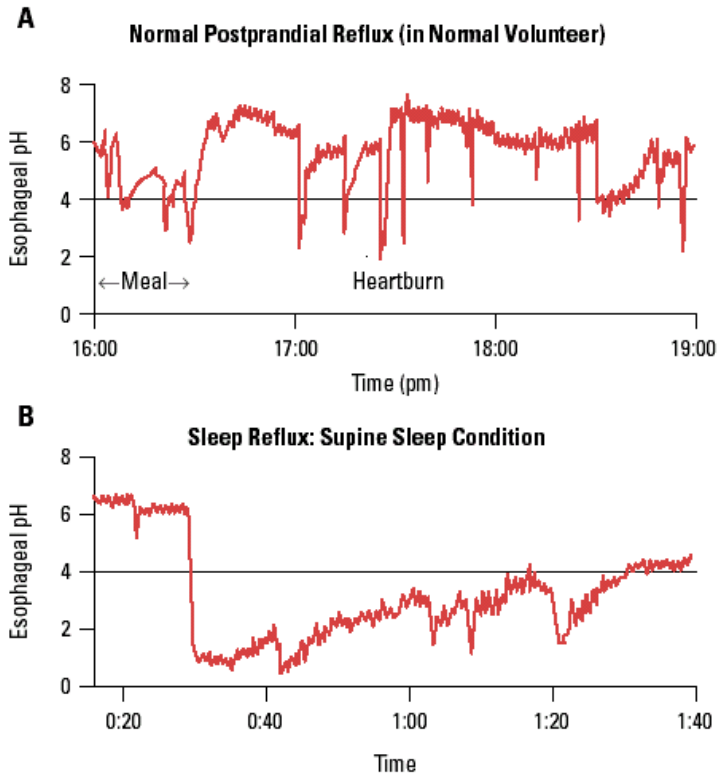

Figure 2.7. *(A) Postprandial reflux in a normal, awake subject. Normal pattern of daytime reflux is that of several short postprandial reflux events (B) Night-time reflux in symptomatic GORD patients. Shown is the pattern of sleep-related oesophageal acid exposure in a patient with erosive oesophagitis. Compared to the pattern of daytime reflux oesophageal acid exposure is considerably prolonged. From Orr et al.*[238]

2.1.9.3 Consequences of nocturnal gastro-oesophageal reflux

In addition to the consequences of GOR discussed previously (unpleasant symptoms, impaired quality of life, oesophageal mucosal damage and supraoesophageal complications), *nocturnal*GOR has some additional consequences including increased oesophageal acid contact time, increased risk of proximal migration and impaired sleep and quality of life.

Increased oesophageal contact time and oesophageal damage

Sleep is associated with a decrease in acid clearance mechanisms, specifically swallowing, primary peristalsis and saliva production. Swallowing, like GOR, rarely

occurs during stable sleep but occurs during brief arousal from sleep or during more extended periods of wakefulness.[239] If reflux occurs during one of these arousals and an individual falls asleep again before the acid is cleared from the oesophagus, the acid will remain until the next time the individuals arouses from sleep and swallows. Thus, the pattern of nocturnal reflux tends to be one of infrequent reflux episodes that are poorly cleared, resulting in extended periods of oesophageal acid exposure, compared to the daytime pattern where the majority of events are postprandial and cleared quickly (Figures 2.7 and 2.8). Acid has been shown to remain in the oesophagus for up to 45 minutes, compared with 6 minutes in the supine position during wakefulness.[7] Also affecting oesophageal acid clearance is the acidity of the refluxate with more acidic refluxate taking longer to be cleared (Fig 2.8)[240]: gastric acid secretion is at its peak and gastric pH at its lowest during the nocturnal period which could act to prolong acid clearance. Due to the markedly increased acid contact time during sleep, *nocturnal*GOR has been associated with increased risk of mucosal injury such as oesophagitis and increased severity of oesophagitis than daytime GOR episodes.[8-11]

Increased proximal acid migration

Another consequence of *nocturnal*GOR is the increase in proximal acid migration during sleep. Orr *et al*[7] reported that during sleep 73% of acid infusions into the distal oesophagus reached the proximal oesophagus, compared to 23% of infusions during wakefulness. This increased proximal migration may increase the risk of aspiration of refluxate, with aspiration during sleep common, even in healthy individuals.[241] These observations suggest individuals with *nocturnal*GOR have an increased risk of developing atypical GOR symptoms. This contention is supported by a study which found that individuals with frequent *nocturnal*GOR symptoms had a greater occurrence

of globus sensation, choking, dry cough, sore throat and daytime hoarseness than individuals without frequent nocturnal symptoms.[48]

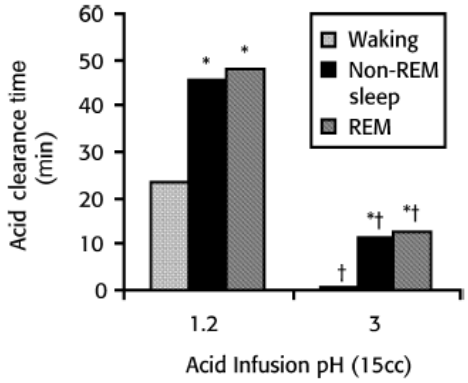

Figure 2.8. *During sleep acid clearance time is considerably greater than during waking. Data shown are the mean minutes between the time oesophageal pH dropped below 4.0 after an acid infusion into the oesophagus to the time it returned to above 4.0. pH of the infused acid is shown along the x-axis. Note that during both REM and non-REM sleep acid clearance is prolonged for both infusions. From Orr et al.*[242]

Impaired sleep quality, work productivity and quality of life

*Nocturnal*GOR impairs health by disturbing sleep either by interfering with falling asleep or causing awakenings overnight.[243] Patients with *nocturnal*GOR have lower subjective sleep quality,[244,245] more difficulty falling asleep after an awakening, more daytime drowsiness and less hours of sleep per night compared to normal volunteers and those without *nocturnal*GOR.[12,48,51,245] Consequently, *nocturnal*GOR is also associated with reduced work productivity,[48,51] impaired daytime functioning[12] and impaired quality of life compared to individuals with no nocturnal symptoms. Specifically, discomfort with nocturnal symptoms, frustration with sleep loss and concern about symptoms have been strongly associated with decreased quality of life scores.[1]

2.1.9.4 Mechanisms of nocturnal gastro-oesophageal reflux

In normal individuals TLOSR account for between 94% and 100% of *nocturnal*GOR episodes,[102,106,113] with strain associated reflux and spontaneous reflux accounting for the remaining episodes.[102,113] It is notable that in normal individuals, GOR events overnight are extremely rare as TLOSR are considerably reduced[45] and basal LOS pressure increased[232,233] in the supine position. *Nocturnal*GOR episodes and TLOSR appear to occur only during periods of arousal from sleep, not during stable sleep itself.[106,113,246-248]

In individuals with erosive GORD nocturnal reflux episodes occur more frequently than in non-erosive GORD (although less frequently than daytime episodes). TLOSRs are the primary mechanism of *nocturnal*GOR in these individuals however, they account for only 40%-65% of episodes, with a much greater proportion of episodes attributable to other mechanisms. Approximately 20% of episodes are due to strain or an increase in intraabdominal pressure and another 20% occur as spontaneous reflux.[102,113] The increased heterogeneity of reflux mechanisms in erosive GORD patients may be due to an ineffective LOS or a low basal LOS pressure.[10,102]

2.1.9.5 Modifying factors for nocturnal gastro-oesophageal reflux

In addition to the factors that modify GOR discussed in Section 2.1.8 (body weight, smoking, alcohol consumption, fatty foods, coffee, hiatus hernia and body position), there are several other factors that uniquely modify *nocturnal*GOR including sleeping posture, time since last meal, sleep stage and sleeping disorders.

Posture

Recumbent body posture has a profound effect on supine GOR. Many studies have shown that the right lateral decubitus position is associated with a greater amount of reflux than the left lateral decubitus[249-252] in both healthy, asymptomatic subjects and patients with GORD. The right lateral decubitus posture is also associated with significantly longer acid clearance times compared to the left side.[250,251] Basal LOS pressure is not different between the two positions, however in the right lateral decubitus posture there is a significantly greater number of TLOSR than the left and also a greater proportion of TLOSR associated with GOR,[251] potentially explaining the increase in reflux in the right lateral decubitus posture. In a recent study using oesophageal impedance to detect GOR episodes Shay and Lopez[252] whilst finding longer acid exposure time in the right lateral decubitus posture, reported a trend for a higher number of total GOR episodes in the left lateral decubitus posture. In several studies[236,252] they found that the composition of refluxate was different between recumbent postures. Specifically, refluxate in the right posture was comprised mostly of liquid or a liquid and gas mixture and therefore acidic, whereas in the left lateral and upright postures the majority of reflux events were gas and non-acidic. These studies also showed that in the right lateral decubitus posture the oesophago-gastric junction was completely submerged or directly adjacent to the liquid/air interface, whereas in the left lateral decubitus and upright postures the oesophago-gastric junction was sitting in air, thereby potentially explaining the differences in refluxate composition between these positions and perhaps also the increase in acid reflux in the right compared to the left lateral decubitus postures.

Another aspect of recumbent posture is the effect of elevation of the head or upper body. Individuals with GORD are often advised to sleep with the head of the bed

elevated, however there are only a few studies which have investigated this. Elevation of the bed head by 6-10 inches (15-25cm) has been shown to have beneficial effects on oesophageal acid exposure[253] and clearance[254], suggesting that elevating the head of the bed might change the pattern of reflux from the typical supine pattern of infrequent episodes that are poorly cleared to one of more frequent reflux episodes which are cleared quickly, the latter pattern less likely to lead to mucosal damage.[9] Elevation of the bed head also improves the treatment outcome of those on H_2RA therapy with individuals who elevated the bed head three times more likely to show an improvement in symptoms that those who slept with the bed flat.[255]

Time since last meal

The length of time between the evening meal and bedtime may have an effect on the amount of nocturnal reflux an individual may experience. GORD patients and asymptomatic controls with a short dinner-to-bed time have been shown to have significantly more supine reflux than individuals with a longer dinner-to-bed time.[256,257] In contrast, however, Orr *et al*[258] found in a group of symptomatic subjects that supine reflux was not different when subjects had an early evening meal compared to a late evening meal, suggesting no effect of dinner-to-bed time. Any effect of mealtime on GOR may be due to the volume of stomach contents remaining at bedtime, causing stomach distension and potentially triggering TLOSRs, and therefore *nocturnal*GOR events.

Sleep Stage

It is unknown if sleep stage influences the occurrence of *nocturnal*GOR episodes, however it is possible that this may occur as muscle and neural activity differ between non-rapid eye movement sleep (Stages 1-4) and rapid eye movement sleep (Stage 5). Studies reporting the stage of sleep in which reflux episodes occur tend to agree that

most nocturnal reflux episodes occur during stage 2 sleep.[113,246,259] While this suggests an effect of sleep stage such a finding may also simply reflect that the majority of sleep (50% or more) is spent in stage 2 sleep.[260]

Sleep Disorders – Obstructive Sleep Apnoea

Obstructive sleep apnoea (see Section 2.2) is a condition characterised by repetitive narrowing or collapse of the upper airway. It is well documented that individuals suffering from obstructive sleep apnoea have an increase in both reflux episodes and symptoms. The relationship between obstructive sleep apnoea and GOR will be explored in detail in the following sections.

2.2 OBSTRUCTIVE SLEEP APNOEA

2.2.1 Definition of obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is characterised by repeated narrowing or collapse of the upper airway (Figure 2.9) with associated oxygen desaturation and arousal from sleep.[261] Individuals with OSA frequently have excessive daytime sleepiness (somnolence) due to sleep fragmentation from these repetitive arousals.

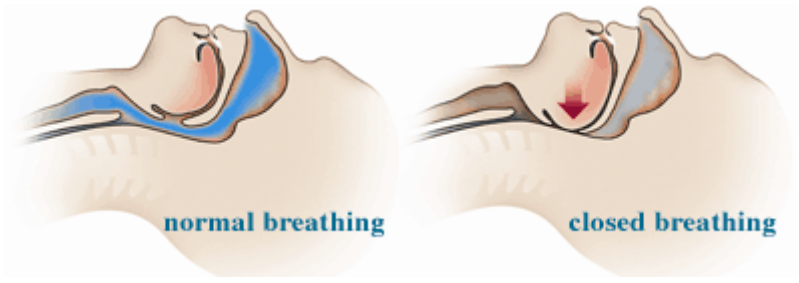

Figure 2.9. *Representation of a normal airway (left) and upper airway obstruction (right) as occurs in OSA.*[262]

OSA is diagnosed using polysomnography (Figure 2.10), which provides objective measures of respiration during sleep and sleep quality and is performed as part of routine evaluation in patients with suspected sleep disorders. Polysomnography incorporates measurements of electroencephalogram, left and right electrooculograms, submental electromyogram, tibial electromyogram, electrocardiogram, abdominal and thoracic effort, nasal and oral airflow, nasal pressure, oxygen saturation, body position and sound intensity. Time spent in each sleep stage is defined, as well as the pattern of progression between stages to provide information on sleep architecture. Awakenings and arousal index (number of arousals per hour of sleep) are used to quantify sleep fragmentation. Oximetry, nasal airflow (nasal pressure), oral airflow and abdominal and thoracic effort are used to identify any overnight respiratory dysfunction.

Periods of apnoea (airway collapse) and hypopnoea (airway narrowing) are determined based on reduction in airflow measurements (Figure 2.10). An apnoea is defined as a cessation in airflow lasting for more than 10s; a hypopnoea defined as a reduction in airflow of >50% or a reduction in airflow of <50% but accompanied by a 3% oxygen desaturation or arousal, also lasting more than 10s.[261] Severity of OSA is determined by the Apnoea-Hypopnoea Index (AHI), which is defined as the number of apnoeas or hypopnoeas per hour of sleep. OSA is defined as 'mild' if the AHI is >5-15; 'moderate' if the AHI is <15-30; and 'severe' if the AHI is >30 events per hour. A clinical diagnosis of OSA syndrome (OSAS) is made if an individual has an AHI > 5 and they suffer from excessive daytime somnolence. There are many individuals who may have apnoeas and/or hypopnoeas during sleep but without daytime somnolence, these individuals do not meet the criteria for OSAS.[263]

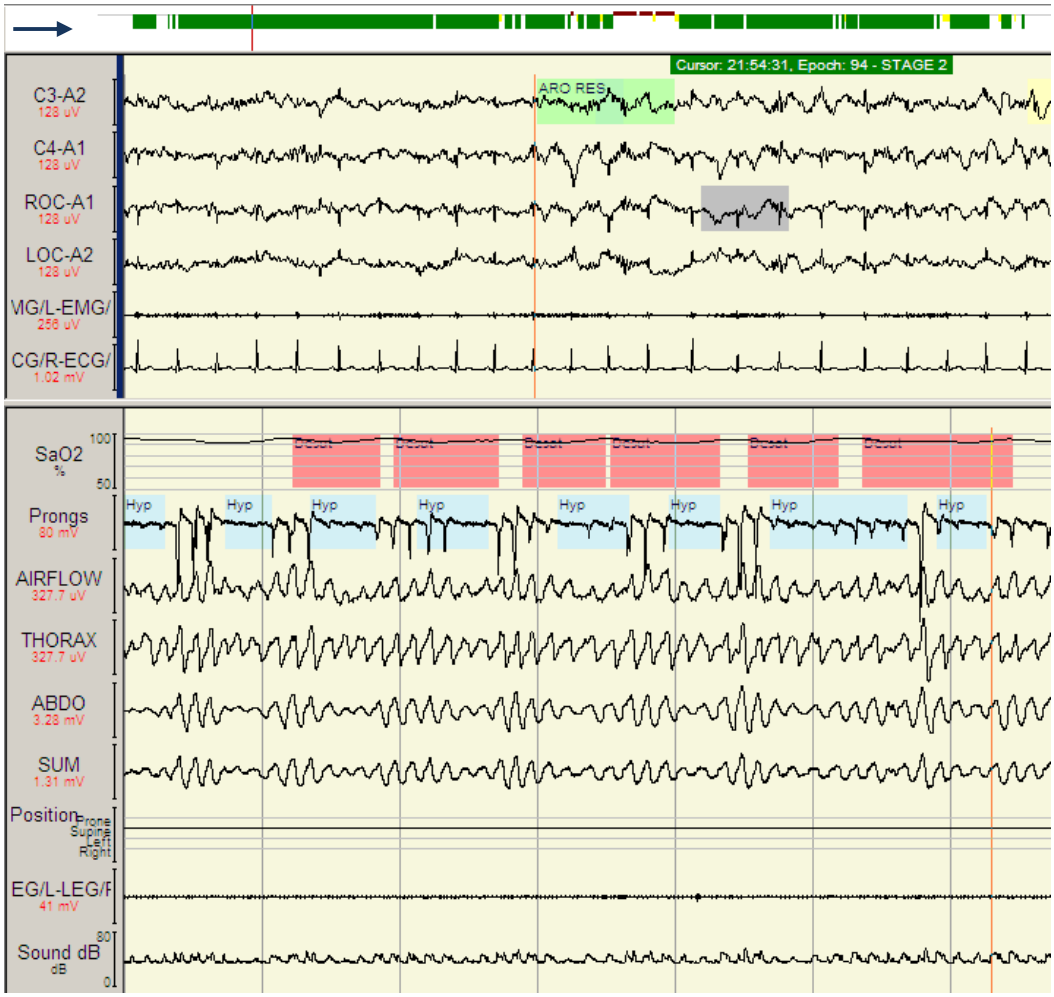

Figure 2.10. *A section of recording taken during a polysomnographic study on an OSA patient. Note the nasal pressure ("prongs") fluctuations, respiratory effort changes (in thorax, abdo and sum signals) and oxygen desaturations (red blocks) indicating hypopnoea (blue blocks). Note also the respiratory arousal (green block) associated with a hypopnoea. The top panel depicts 30s of monitoring, the bottom panel, 5 minutes. The vertical red line marks coinciding points between panes. A sleep hypnogram of the entire night is presented at the top of the image (marked with an arrow) where yellow is stage 1, green stage 2 and red is rapid eye movement sleep. The position of the displayed data is identified by a cursor. Note the preponderance of stage 2 sleep and the absence of slow wave (stages 3 and 4) sleep characteristic of OSA.*

2.2.2 Consequences of obstructive sleep apnoea

OSA has several serious consequences including an increase in sleep fragmentation, daytime sleepiness, metabolic disorders, cardiovascular disorders and increased all-cause mortality, each of which will be discussed in the following section.

2.2.2.1 Fragmented sleep

Sleep fragmentation is a hallmark of OSA due to an increased number and frequency of arousals from sleep in response to repetitive upper airway occlusion and is at least partly responsible for the other performance and health-related problems associated with OSA (discussed later in this section). In healthy individuals sleep begins in stage 1 sleep (sleep onset). In adults stage 2 sleep accounts for approximately half of the night, slow-wave sleep (non-REM stages 3 and 4) accounts for a further 20% and and REM sleep the balance.[260,264] NREM and REM sleep cycle approximately every 90 minutes. NREM sleep occurs more frequently in the first third of the night and REM sleep more frequently in the last third of the night. Normally, individuals have approximately 15-20 arousals per hour [265,266] and wakefulness accounts for no more than 5% of the period in bed.[264]

Increasing severity of OSA is associated with inefficient sleep with decreased sleep time, a reduced proportion of REM sleep[266,267] and an increase in the number of arousals overnight coincident with obstructive respiratory events.[266]

2.2.2.2 Daytime sleepiness and impaired quality of life

People with OSA are sleepier than those without, regardless of whether sleepiness is assessed objectively by measures of mean sleep latency or subjectively by sleep symptom questionnaires. Excessive daytime sleepiness in OSA likely results from the

increased arousal frequency and sleep fragmentation caused by repetitive upper airway obstruction. Excessive sleepiness is associated with increased morbidity including decreased productivity and increases in vehicular and work-related accidents.[268-271] Cognitive and psychomotor functioning is also impaired.[272,273] These impairments improve after treatment for OSA with continuous positive airway pressure (CPAP), the mainstay therapy for OSA.[274,275]

In addition to daytime sleepiness OSA patients have significantly lower general health and health-related quality of life than those without OSA.[276,277] The level of impairment is directly related to the extent of sleep fragmentation indicating that poor sleep quality may be the most significant factor in determining quality of life in OSA patients.[278] Treatment for OSA with CPAP results in improvement of quality of life to that of normal healthy individuals.[278-280]

2.2.2.3 Metabolic consequences

OSA is associated with alterations in metabolic function including decreased glucose tolerance and increased insulin resistance[281-283] compared with normal individuals. Several studies have reported a relationship between insulin resistance, AHI and the sleep-related hypoxemia which occurs during apnoeas and hypopnoeas.[281-283] These associations appear to be independent of obesity.[282,283]

Metabolic syndrome is a term used to describe the clustering of several proatherogenic factors including hypertension, dyslipidemia and impaired glucose tolerance.[284] Studies show that OSA patients are 6-9 times more likely to have metabolic syndrome independently of obesity than those without it.[284,285]

The exact mechanism for metabolic dysfunction in individuals with OSA is unknown, however there are several possibilities. Firstly, untreated OSA patients have increased sympathetic nerve activity indicated by increases in urinary and plasma catecholamines,[286,287] which is anti-insulin in its effects. Secondly, sleep disruption and sleep deprivation may be independently associated with metabolic dysfunction as in normal individuals it has been shown that sleep loss is associated with changes in glucocorticoid regulation and abnormal glucose tolerance.[288,289] Finally, hypoxia may independently impair glucose metabolism.[290,291] Any of these factors, alone or in combination, could facilitate the development of metabolic dysfunction in OSA. Many of these metabolic alterations in OSA patients may also lead to cardiovascular complications or increases in all-cause mortality, as discussed in the following sections.

2.2.2.4 Cardiovascular consequences

Cardiovascular disease is reported to be the most common cause of death in OSA patients.[292] Several studies have shown that individuals with OSA have a significantly increased risk of cardiovascular complications such as hypertension, ischaemic heart disease and cardiovascular disease,[293-297] with up to an 11-fold greater risk of developing such problems.[296] Severe OSA can cause significant sleep-related hypoxemia, pulmonary hypertension and right heart failure.[298-302] OSA also increases left ventricular afterload, aggravating left ventricular failure.[300,303-305] Treating OSA with CPAP in already treated heart failure patients results in further improvements in heart function.[305] While the exact mechanism for the association between OSA and cardiovascular disease remains undefined it is possible that increased generation of reactive oxygen species and initiation and amplification of the inflammatory process in OSA may play an important role.[306]

2.2.2.5 All cause mortality

Several studies have reported a significantly increased risk of death from any cause in OSA patients compared to normal individuals,[307-311] even when cardiovascular risk factors are accounted for.[309] Furthermore, treatment of OSA with continuous positive airway pressure results in reductions in mortality.[292,307,311] Two recent studies, in Busselton and Wisconsin, using well-defined and long-standing general population cohorts have reported increases in all-cause mortality in OSA patients compared to individuals without OSA.[312],[313] The 14-year follow-up of Busselton Health Survey participants found a significantly greater all-cause mortality in individuals with moderate-severe OSA than in individuals with no OSA (identified by home sleep apnoea monitoring).[312] The 18-year follow-up of the Wisconsin Sleep Cohort found that individuals with severe OSA had a 3-fold greater risk of all cause mortality than individuals with no OSA.[313]

2.2.3 Prevalence of obstructive sleep apnoea

The prevalence of OSA in Western countries is estimated to be approximately 5%.[263] In a national sleep poll in the United States of America,[314] undertaken in 2005, 6% of individuals reported having apnoeas overnight, which had been witnessed by others. Overall, 26% of the population met the criteria for being a high risk of having OSA according to questionnaire responses. Duran *et al*,[315] in a study investigating the prevalence of OSA in the general population, also found that 6% of individuals reported having witnessed apnoeas during sleep. In addition, between 11% and 36% of individuals report habitual snoring,[295,315-318] a hallmark of OSA (approximately 96% of OSA patients snore habitually).[319]

Large population based studies using polysomnography report the prevalence of OSA in men to be between 3.3% and 4.9%.[315-317,320,321] The prevalence of OSA in females is lower than that in males and estimated to be 1.2% to 2.5%.[316,320,322] Potential reasons for the difference in prevalence between males and females are discussed in section 2.2.6.2.

The prevalence of OSA reported by previous studies is likely to be underestimated as obesity is the most significant risk factor for OSA (see sections 2.2.5.1 and 2.2.6.1) and the prevalence of obesity in Australia and elsewhere in the world has increased significantly in recent years,[323-327] potentially increasing the prevalence of OSA in the general population.

2.2.4 Mechanisms of obstructive sleep apnoea

The human upper airway can be thought of as a collapsible tube. The presence of bony structures and soft tissues increase extra-luminal pressure on the tube and can predispose it to collapse. In contrast, the upper airway dilator muscles act to maintain patency via reflex pathways from the central nervous system and from receptors within the upper airway itself. Collapsibility of the upper airway in OSA may be due to either changes in the mechanical loads placed on the upper airway by surrounding structures or changes to dynamic neuromuscular responses to upper airway obstruction during sleep, or both (Figure 2.11). The anatomical and neurogenic mechanisms of upper airway collapse will be discussed below.

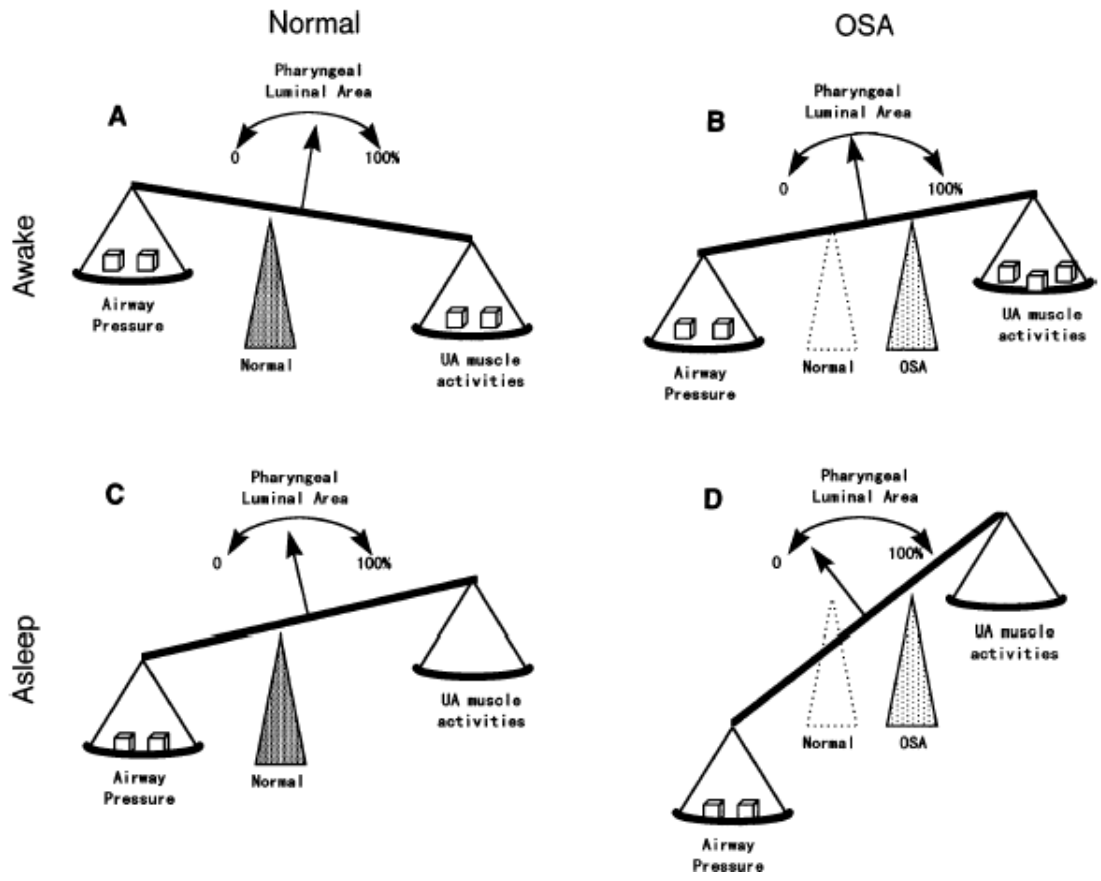

Figure 2.11. *Schematic model explaining pharyngeal airway patency. The fulcrum represents the anatomy of the pharynx (intrinsic mechanical properties). Upper airway (UA) dilator muscle activity and airway pressure are on either side of the fulcrum. The fulcrum of OSA patients is thought to be on the right hand side of normal, that is, their upper airway anatomy predisposes them to upper airway collapse. From Isono et al.*[328]

2.2.4.1 Anatomical mechanism of collapse

Anatomical changes to the upper airway may be an important determinant of upper airway collapsibility during sleep.[328,329] Conditions such as tonsillar hypertrophy,[330] acromegaly,[331] retrognathia[332] and other changes in mandibular structure[333] have been associated with OSA, likely due to narrowing of the upper airway as a result of such anatomical deviations.

Ethnic differences in craniofacial structures are thought to underlie the differing

prevalence of OSA among different ethnic groups for a given obesity level.[334] For example, Ip *et al*[317] found prevalence rates among Chinese men to be similar to that in white American males, however the mean BMI of the Chinese men was lower than that of the Americans, suggesting a strong role for craniofacial structure in the pathogenesis of OSA.

Obesity, one of the major risk factors for development of OSA[320] is associated with increased neck circumference and fat deposition around pharyngeal structures,[335-337] increasing the load on the upper airway, reducing its cross sectional area and potentially contributing to the pathogenesis of OSA. Obesity may also increase upper airway collapsibility through reductions in lung volume as it is associated with a decrease in functional residual capacity[338] which is accentuated with sleep onset.[339] This decrease in lung volume may affect upper airway collapsibility via a decrease in tracheal and pharyngeal traction.[340,341] Caudal tracheal displacement of as little as 1cm can significantly decrease upper airway collapsibility in cats[340,341] and rabbits.[342] Human studies indicate that increases in lung volume decrease sleep-disordered breathing and decreases in lung volume increase sleep-disordered breathing in OSA patients.[343,344] Moreover, human studies also show that during sleep changes in lung volume are associated with variations in upper airway mechanics.[345-347]

Mandibular advancement is a common and successful treatment for OSA in some individuals (see section 2.2.5.3), and acts by anteriorly displacing the mandible, increasing the retro-palatal space. That mandibular advancement is an anatomical adjustment and is a successful treatment for OSA highlights the importance of anatomy in the pathogenesis of OSA.[348,349] However, mandibular advancement may also have a

neurogenic effect, as upper airway muscle activity is increased with insertion of a mandibular advancement splint.[350,351]

It is very clear that the pathogenesis of OSA cannot be explained purely in terms of anatomy. Not everyone with, for example, a narrow airway will have OSA. Younes *et al*[352] recently proposed that differences in mechanical load on the upper airway account for only one third of the variability in OSA severity, suggesting that other mechanisms such as differences in neural compensatory effectiveness may also play an important role.

2.2.4.2 Neurogenic mechanism of collapse

The variable effects of a sleep-related decline in upper airway dilator muscle activity may also be an important determinant of upper airway collapse during sleep. During wakefulness, patients with OSA appear to have greater baseline levels of upper airway dilator muscle activity than normal individuals.[353] This increased activity is thought to represent a neuromuscular compensatory mechanism for a smaller or more collapsible airway. At sleep onset this augmented activity is diminished allowing the upper airway to collapse.[353,354] The mechanisms underlying the increase in wakeful muscle activity are thought to be central or reflex in origin and may include increases in wakeful drive to the dilator muscles and/or activation of the upper airway negative pressure reflex. This latter reflex is modulated by pharyngeal and laryngeal pressure sensors and causes an increase in upper airway dilator muscle activity when negative intrathoracic pressure is transmitted to the pharynx during inspiratory efforts.[355,356]

It is also possible that upper airway neural pathways are impaired in OSA, predisposing to obstruction. There are several lines of evidence to support such a contention. Firstly,

two-point discrimination and vibration sensation thresholds in the upper airway are impaired in OSA patients compared to normals,[357] an impairment which is partially reversible with continuous positive airway pressure treatment for OSA. Secondly, OSA patients have histopathologic changes to upper airway muscles compared to normal individuals.[358,359] This may indicate a process of dennervation and degeneration of upper airway muscles in OSA patients. Such changes may result from trauma induced by repetitive collapse and re-opening of the upper airway during sleep.

2.2.5 Treatment of obstructive sleep apnoea

Although there is no cure for OSA there are several successful treatments. The most common treatments are discussed in this section and include weight loss, continuous positive airway pressure (CPAP) therapy, mandibular advancement splint therapy and surgical therapy.

2.2.5.1 Weight loss

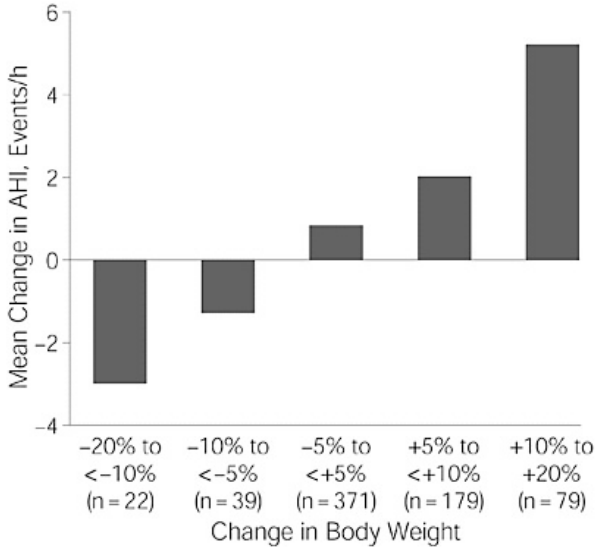

Figure 2.12. *Mean change in AHI by weight change category in 690 individuals with OSA. Note the linear relationship in weight change and change in AHI. From Peppard et al.*[360]

Many studies have demonstrated a close link between OSA and obesity[263,314,317,322,361-368] (discussed in section 2.2.6.1). Studies investigating the effect of surgical weight loss on OSA report dramatic decreases in AHI[369,370] and arousal index and improvements in sleep architecture, daytime sleepiness and quality of life.[369] Likewise, studies investigating the effect of weight loss by diet modification report significant decreases in AHI (Figure 2.12),[360,364,371-373] the number of oxygen desaturations[371-374] and daytime sleepiness.[371,372] Changes in sleep architecture with weight loss have also been reported and include a decrease in stage 1 sleep and increases in stage 2[364,372] and stages 3 and 4 (slow wave) and REM sleep.[364] In addition, weight loss results in a decrease in upper airway collapsibility.[371,375] In most OSA patients, the requirement for CPAP is abolished or the therapeutic pressure requirement decreased with sufficient weight loss.[369,370]

The mechanism by which weight loss decreases the severity of OSA most likely relates to a decrease in neck and pharyngeal fat, decreasing the compressive forces on the upper airway. It may also be due to a decrease in abdominal fat and increased lung volume increasing longitudinal traction on the upper airway and pharynx (See section 2.2.6.1).

2.2.5.2 Continuous positive airway pressure

Continuous positive airway pressure (CPAP) involves administration of air under pressure to the upper airway via a nose or face mask (Figure 2.13).

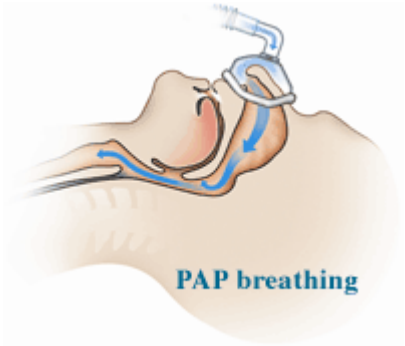

Figure 2.13. *Schematic diagram of the effect of CPAP on the upper airway. CPAP acts as a pneumatic splint, preventing the upper airway walls collapsing. PAP, positive airway pressure.*[262]

This provides a pneumatic splint for the upper airway preventing narrowing or collapse of the airway walls during sleep.[376] CPAP has been shown to reduce obstructive events, significantly improve both objective and subjective measures of daytime somnolence [274,377-380] and also improve sleep quality as it consolidates sleep (Figure 2.14) and returns oxygen saturation and arousal indices to within normal limits.[381]

A relationship has been shown between hours of CPAP use and improvements in Epworth Sleepiness Score, multiple sleep latency score and daytime functioning,[383]

indicating that the level of improvement in sleepiness symptoms is influenced by the degree of CPAP compliance.

CPAP has been shown to reverse many of the complications associated with OSA: reducing risk of cardiovascular events (fatal and non fatal)[293] or disease[296]; reducing systolic and diastolic blood pressure[384,385]; reducing nighttime mean arterial pressure[384,385]; reducing signs of atherosclerosis[386]; and returning quality of life to that of individuals without OSA.[278-280] Its proven efficacy for reducing AHI and daytime symptoms make CPAP the mainstay therapy for OSA. Despite its efficacy for treating OSA, treatment compliance is reported to be between 32% and 80%.[387-390] Compliance in recent years has improved with the development of humidifiers, auto-titrating devices, and improved nasal and oro-nasal interfaces.

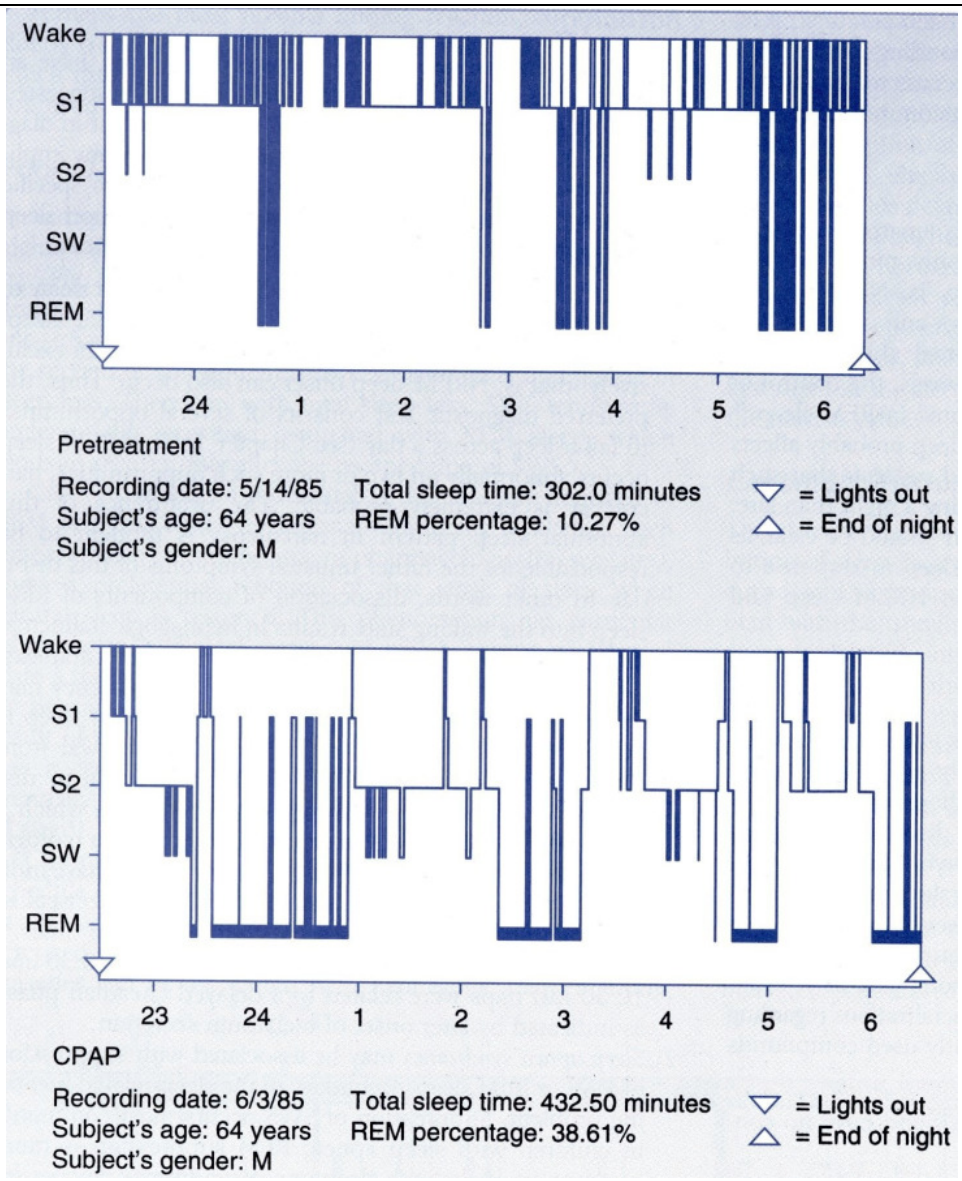

Figure 2.14. *A sleep hypnogram in one OSA patient before treatment (top) and after CPAP treatment (bottom). Note the decrease in time spent awake, the more consolidated sleep, the increase in SWS and increase in REM with CPAP treatment compared to without. From Principles and Practice of Sleep Medicine.*[382]

2.2.5.3 Mandibular advancement splint

Mandibular advancement splints (MAS) are widely used as an alternative to CPAP therapy. They are designed to maintain the upper airway patent by advancing the mandible forward and anteriorly displacing the tongue[391] (Figure 2.15). MASs increase the calibre of the upper airway[392-394] reducing its collapsibility during sleep.[395] Anterior displacement of the mandible and tongue may have neuromuscular, as well as

anatomical, effects on the upper airway. Insertion of a MAS has been shown to increase the activity of upper airway dilator muscles, such as the genioglossus, which would stiffen the airway wall, also decreasing its propensity for collapse.[350,351]

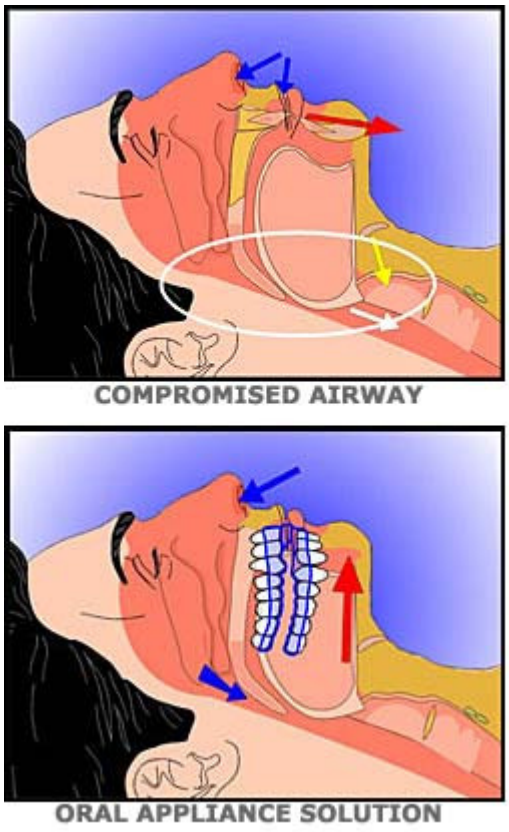

Figure 2.15. *Schematic diagram showing an obstructed upper airway (top panel) with the tongue and soft palate collapsed against the posterior pharyngeal wall and the upper airway with a mandibular advancement splint in place (bottom panel). Anterior displacement of the mandible moves the tongue away from the posterior pharyngeal wall, restoring airway patency.*[396]

In individuals with mild-moderate OSA, MAS therapy is associated with decreases in subjective daytime sleepiness[392,393,397-404] and objective daytime sleepiness.[400] Subjective and objective measures of snoring are also improved with MAS therapy,[393,398-404] as are overnight oxygen saturation measures.[392,393,395,399,400] MAS therapy significantly decreases objective measures of OSA severity,[392,393,395,397-405] with reported decreases in AHI of approximately 50%.[398,400] Beneficial effects on sleep

architecture have also been reported and include a decrease in arousal index, decrease in Stage 1 sleep and an increase in Stage 3 and 4 (slow-wave) sleep.[393,398,400,406]

MAS therapy is not tolerated by all individuals. Success rates are moderate with between 30%-65% of patients achieving complete treatment success.[395,398-401,404,405] Variable mean decreases in AHI of between 2 and 35 events per hour have been reported[380,392,393,395,397,398,400,402,403,405] suggesting design and degree of mandibular advancement are critical to its efficacy. The therapy appears most suited to those with mild to moderate OSA. Treatment success with MAS therapy may be due to the extent of mandibular advancement achieved with the device. Walker-Engstrom *et al*[401] investigated two levels of mandibular advancement (50% and 75% of maximum) and found that AHI decreased an average of 5 events more in those with 75% advancement, compared to those with 50% advancement. They also reported a significantly higher treatment success rate in the 75% group compared with the 50% group (52% and 31%, respectively).

When comparing MAS therapy to CPAP therapy, CPAP has a higher treatment success rate,[407] decreases AHI by a greater amount[380,406,407] and normalises sleep architecture more[380,406] than MAS therapy. When successful at decreasing AHI, both treatments are effective at improving daytime sleepiness.[380,406]

2.2.5.4 Surgery

The aim of surgical treatment of OSA is to increase upper airway size and prevent further obstruction. Surgical treatment has been separated into two phases, outlined below.

Phase I surgical therapy

Phase I surgery is the most conservative approach and addresses palatal and tongue base obstruction. Nasal reconstruction is used for symptomatic obstruction that interferes with nasal breathing during sleep.[408,409] Nasal reconstruction may improve snoring and daytime functioning in those with mild-moderate OSA.[410]

Uvulopalatopharyngoplasty (UPPP) and its variants are the most common procedures performed for the treatment of OSA. UPPP involves palate shortening with tonsillectomy and lateral pharyngoplasty and has been shown to improve quality of life[411] and daytime sleepiness, with up to 40% of patients being successfully treated by UPPP (*i.e.* >50% fall in AHI and an AHI <20 events.hr^{-1}).[412] However, the benefits of UPPP appear to deteriorate over time.[413,414] Variations of this procedure include laser-assisted UPPP, performed under a local anaesthetic and uvulopalatal flap surgery, which is reversible and less painful than UPPP or laser assisted UPPP.[408]

Temperature controlled radio-frequency tissue ablation (TCRFTA) is another type of Phase I surgery, which causes a sub-mucosal thermocoagulation lesion in the tongue. Subsequent wound healing leads to fibrosis and tissue contraction. TCRFTA has been shown to reduce tongue volume by approximately 20%,[415] increase airway volume and reduce upper airway obstruction.[415,416] The success rate is low, being approximately 20%, and the longevity of any beneficial effects questionable with some individuals relapsing and worsening after 2 years.

Genioglossus advancement surgery involves a small window being made in the lower jaw. This bony window along with its attachment to the genioglossus is pulled forward and down, then fastened to the outside of the lower jaw.[408,409] This increases tension on

the genioglossus, which may be sufficient to keep the region at the tongue base patent during sleep. Hyoid suspension surgery requires anterior movement of the hyoid complex and has been shown to increase upper airway cross sectional area.[408]

These surgical procedures can be performed in isolation or combined to increase treatment success. For example, combining UPPP with genioglossus advancement; hyoid suspension or radiofrequency treatment increases treatment success to 50%-76%[417-419] compared to 40% with UPPP alone.[412]

Recent developments in surgery for snoring and OSA include non-invasive procedures which can be performed under local anaesthesia such as soft palate implants which stiffen the palate.[420] These implants have been shown to reduce snoring, daytime sleepiness and AHI in both habitual snorers and individuals with mild to moderate OSA.[420-423] However, it is important to note that the reported changes in AHI are small, being a decrease of only 4-6 events per hour[421-423] which, although significant, suggest that this treatment would only be successful in those with very mild OSA.

Phase II surgical treatment

Phase II surgery involves the surgical advancement of the mandible and/or maxilla and has been used to successfully treat OSA in individuals with and without craniofacial abnormalities[424](Figure 2.16). Mandibular advancement advances the suprahyoid and tongue muscles[425] whereas maxillary advancement advances the velopharyngeal muscles.[426] Combined, these procedures significantly increase posterior air space and decrease airway collapsibility.[427] In addition, they are associated with decreases in AHI, improvements in oxygen saturation, significant decreases in stage 1 and stage 2 sleep, increases in stage 3 and 4 slow wave sleep, significant decreases in arousal index

and significant improvements in fatigue and daytime sleepiness, the equivalent to that achieved with successful CPAP therapy.[428-430] Maxillomandibular advancement has been reported to have a 95% success rate[430] with the improvements in breathing, sleep and OSA maintained after 2 years.[428] Phase II surgeries have been shown to be significantly more effective in treating OSA than phase I surgeries with the success rate exceeding 93%.[431]

Despite the high success rate, the pain and risk of complications associated with surgery and the proven efficacy of treatments such as CPAP therapy have meant that these complex surgical procedures are not widely used in the treatment of individuals with OSA.

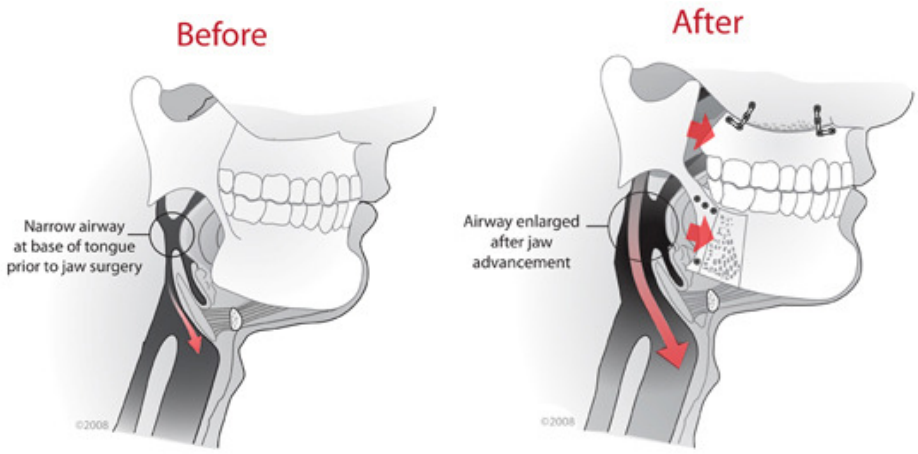

Figure 2.16. *Diagram showing the narrowed upper airway in an individual with OSA before maxillo-mandibular advancement surgery (left diagram) for OSA and the widened upper airway after surgery (right diagram).*[432]

2.2.6 Modifying factors for osbtructive sleep apnoea

Factors shown to be related to an increased risk of OSA include body weight and fat distribution, gender, age, ethnicity, alcohol consumption and sleep posture. Each of

these modifying factors and the mechanism underlying their effect on OSA will be discussed in the following section.

2.2.6.1 Body weight and fat distribution

The relationship of body mass index to OSA has been reviewed in detail previously (section 2.2.5.1). Therefore, this section will concentrate on the importance of fat distribution on OSA. Fat deposition around the neck and upper airway have been shown to have particular importance in OSA with neck circumference being independently related to OSA severity, even when BMI is accounted for.[336,433,434] OSA patients have increased upper airway fat compared to age, BMI and neck circumference matched control subjects.[435,436] These greater fatty deposits adjacent to the upper airway have been correlated with AHI.[437] A decrease in AHI has been reported with weight loss-induced reductions in these fatty deposits.[437] Fat deposition around the neck and upper airway likely precipitate OSA by a direct compressive effect on the pharyngeal lumen.

There is also evidence for an effect of abdominal obesity on OSA. Studies report an association between AHI and waist circumference, an external measure of abdominal obesity,[438,439] and intra-abdominal and subcutaneous abdominal fat.[440] As discussed in 2.2.4.1 abdominal obesity is likely to precipitate OSA via a reduction in lung volume.[339]

2.2.6.2 Gender

There is substantial evidence from both epidemiological studies and laboratory studies for an increase in OSA prevalence and severity in males compared to females[315,316,320,362,439,441-443] independently of age, BMI or neck circumference. The mechanisms underlying the gender differences in prevalence and severity of OSA are,

however, unclear. Males are known to have longer airways[444] and higher upper airway resistance[445] than females both of which would predispose males to upper airway collapse, potentially contributing to the male predominance of OSA. Sex hormones may also play a role as male hormones, primarily testosterone, have been shown to induce and exacerbate OSA.[446] Females with an excess of androgens (for example, those with polycystic ovarian syndrome) have more severe OSA and worse daytime sleepiness than their normal counterparts. Furthermore, in these women AHI correlates with testosterone levels.[447]

Female sex hormones may be protective against OSA. OSA is more prevalent in post-menopausal women than pre-menopausal women[322,442,448,449] and hormone replacement therapy normalises the risk of OSA.[322] Hormone replacement therapy has also been shown to decrease AHI and OSA prevalence in women,[450-452] suggesting a protective effect of female sex hormones. Furthermore, it appears that the male predominance of OSA is lost in individuals above 55 years of age, suggesting that when the female sex hormones are absent women may be just as likely as men to suffer OSA.[442]

2.2.6.3 Age

Increasing age is also associated with an increase in severity of OSA.[314-316,321,362] This increase may be due an age-related decrease in upper airway size[453] and increases in pharyngeal collapsibility and airway resistance.[445,454,455] The increase in pharyngeal collapsibility may be related to neuromuscular changes that result from aging. Furthermore, increasing age is associated with an increase in body mass, which may also contribute to the association. In middle-aged and elderly women who are postmenopausal, there is also the loss of the protective effect of female sex hormones

(see section 2.2.6.2) and an increase in abdominal fat,[456,457] both of which may predispose to OSA.

2.2.6.4 Ethnicity

Prevalence, severity and pathogenesis of OSA differ between ethnic groups. The prevalence of OSA in the Malaysian general population is reported to be 9% of males and 5% of females[458] compared to 4% of men and 2% of women in the Caucasian general population.[320] Furthermore, Asian individuals have more severe OSA than Caucasians for a given BMI.[459-461] African American individuals also appear to have increased risk and severity of OSA.[462] The increased prevalence and severity of OSA in Asian individuals likely relates to differences in craniofacial structure,[460,461] while the increased severity of OSA in African American individuals may be explained by differences in BMI and economic status.[463]

2.2.6.5 Alcohol consumption

Alcohol ingestion has been associated with snoring[368,464,465] and OSA[363] in most but not all[367,466,467] cross-sectional epidemiological studies. Recently, a study in Japanese truck drivers showed an association between alcohol intake and oxygen desaturation index (a marker of respiratory disturbance) overnight.[468] In addition, studies which have investigated the effect of bedtime alcohol ingestion report increases in the frequency of oxygen desaturation during sleep,[469] frequency of apnoea or hypopnoea[470,471] and an increase in the CPAP level required to eliminate snoring.[471]

Alcohol may aggravate snoring and OSA by several mechanisms. Firstly, alcohol has been shown to selectively decrease genioglossal and hypoglossal motor nerve activity, hence decreasing activity of the upper airway dilator muscles.[472-474] These changes may

decrease upper airway calibre, thereby increasing inspiratory resistance and effort, which may increase the tendency for an unstable upper airway to collapse.[475,476] Secondly, alcohol suppresses the arousal response to upper airway occlusion, potentially prolonging obstructive events.[477]

2.2.6.6 Sleep posture

Sleeping position has been shown to be an important factor in OSA. In most (but not all) patients the supine posture is associated with a greater risk of upper airway obstruction than in the left or right lateral decubitus positions.[478-481] The supine posture is associated with increased risk of sleep fragmentation with respiratory events that are of longer duration and of increased potential to end with arousal.[482] In addition, daytime sleepiness is more strongly correlated with supine AHI than AHI in any other position.[483] The mechanism underlying the effect of supine position on OSA is thought to be mechanical in nature. In the supine position the tongue and soft palate fall into the pharyngeal airspace under the influence of gravity, narrowing the airway and increasing the likelihood of collapse. This gravitational effect may also make restoration of airway patency more difficult and may explain the increased duration and likelihood of arousal with obstructive events in the supine position.

Individuals are classified as having positional sleep apnoea if they have a supine AHI at least twice that of the lateral AHI.[484] In a study of nearly 600 sleep clinic patients, Oksenberg *et al*[485] found 56% had positional sleep apnoea, the incidence being higher amongst those with mild-moderate OSA. This finding has since been replicated by others.[486] Several studies have shown that avoiding the supine position in patients with positional OSA significantly decreases AHI and snoring loudness and increases alertness, slow wave sleep and oxygen saturation.[487,488] Avoiding the supine posture in

all OSA patients (even those without positional OSA) has been shown to reduce blood pressure during the day, at night and over a 24-hour period and also significantly reduce heart rate variability, a measure of autonomic drive.[478]

2.3 GASTRO-OESOPHAGEAL REFLUX AND OBSTRUCTIVE SLEEP APNOEA

There are several lines of evidence to support a link between OSA and GOR. Firstly, patients with OSA have an increase in symptoms of GOR as well as number and length of *nocturnal*GOR episodes relative to those without OSA (Figure 2.17).[18] Secondly, nocturnal heartburn is related to snoring and symptomatic OSA.[6,489] Thirdly, a significant relationship has been reported between the severity of GORD identified by endoscopy and severity of OSA, with the occurrence of erosive GORD significantly higher in those with severe OSA.[490] Lastly, the majority of *nocturnal*GOR episodes in individuals with OSA have been found to be in close temporal relationship to either hypopnoea or apnoea.[246,259]

The link between the two conditions is further reinforced by evidence that treating one condition also significantly improves the other. For example, treating OSA with CPAP therapy significantly reduces *nocturnal*GOR episodes and GOR symptoms[20,24,28] and pharmacological treatment of GORD improves OSA.[14,491,492]

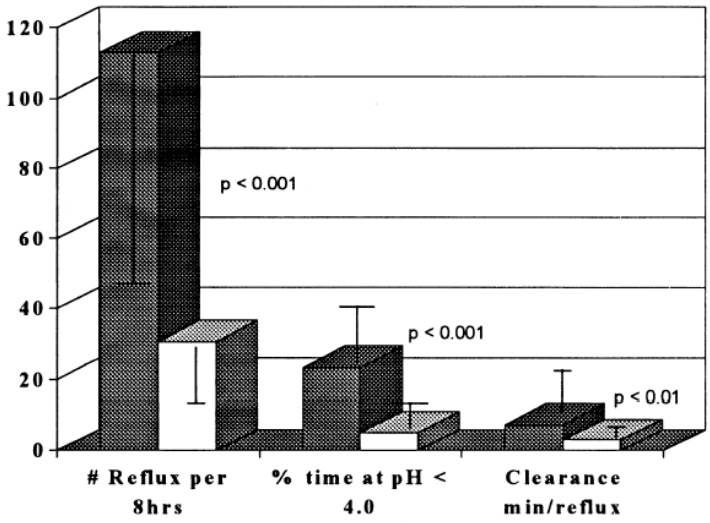

Figure 2.17. *GOR characteristics in OSA patients (shaded bars) and control subjects (white bars). Subjects were matched for age, gender, body-mass index and alcohol consumption. Note the significantly greater number of nocturnal reflux episodes and the significant increase in oesophageal acid exposure and acid clearance. From Ing et al.*[18]

GOR in OSA patients may be more serious than in non-OSA patients. It has been demonstrated that individuals with OSA have an impaired swallowing reflex, *i.e.* they take longer to swallow fluid when it is placed in the pharynx and also require a greater volume of fluid to stimulate the swallowing reflex.[493] The delay in acid clearance that results from this impairment increases oesophageal acid exposure and risk of erosive damage to the mucosa. In addition, OSA patients may be more likely to develop pulmonary complications from GOR as they have been found to aspirate more of their pharyngeal secretions during sleep than healthy individuals.[494]

The prevalence of GOR in the OSA population and possible mechanisms for the link between the two conditions are reviewed in the following section.

2.3.1 Prevalence of reflux in obstructive sleep apnoea

2.3.1.1 Daytime reflux

Studies using symptom questionnaires to determine prevalence of GOR in OSA patients have found that 60-70% of OSA patients experience symptoms such as heartburn and acid regurgitation.[19,21,495] Valipour *et al*[21] found that 60% of 230 sleep clinic patients report heartburn or acid regurgitation in the previous 12 months, with 23% reporting these symptoms at least once a week. In the largest study to date, Kim *et al*,[22] in over 1,000 sleep clinic patients, reported 22% of OSA patients to have symptomatic GORD. The most recent study using a validated questionnaire in nearly 100 sleep clinic patients reported 13% of patients attending a sleep clinic as having symptomatic GORD.[496] In summary, the prevalence of GOR symptoms in OSA patients appears to be similar to that reported in the general population where 60% of individuals report GOR symptoms in the previous 12 months and 20% at least once a week[5](Section 2.1.5.1). However Morse *et al*,[19] using a validated questionnaire, reported 61% of 174 patients referred for a sleep study to have experienced GOR symptoms more than once a week, suggesting the prevalence of symptoms may be higher in those with OSA.

No study has used objective methods of GOR diagnosis (*i.e.* pH monitoring, endoscopy or impedance monitoring) for the purpose of determining the prevalence of GOR in OSA patients. However, there are a few studies that have reported prevalence of abnormal oesophageal pH results, even though this was not their primary aim. In 17 OSA patients, Graf *et al*[497] reported that 65% of their OSA patients had abnormal oesophageal acid exposure (combined daytime and nighttime), with 41% having abnormal upright acid exposure. Penzel *et al*[246] reported that 27% of their group of 15 OSA patients had pathological oesophageal acid exposure during the day. Using

wireless pH monitoring in 77 OSA patients, Friedman *et al*[492] reported 71% of OSA patients to have an abnormal pH study. Recently, in 68 obese OSA patients Sabate *et al*[498] reported 49% of individuals had GORD diagnosed by 24-hr pH monitoring, compared to 23% of obese individuals without OSA. These limited data regarding objectively diagnosed GORD indicate a high prevalence of GORD amongst OSA patients, however there remains no direct comparison of these prevalences with the general population.

2.3.1.2 Nocturnal reflux

To date only one study has used a questionnaire-based method to determine the prevalence of *nocturnal*GOR symptoms in OSA patients[20] and found them to occur in greater than 60% of cases. However this study had several limitations, including a relatively small sample size (n=330) and a very broad definition of *nocturnal*GOR (*nocturnal*GOR was defined as being woken by heartburn or acid regurgitation 'sometimes', 'usually' or 'always'). Furthermore, the aim of the study was to investigate the effect of treatment of OSA with continuous positive airway pressure (CPAP) on *nocturnal*GOR symptoms, not to specifically examine the prevalence of *nocturnal*GOR symptoms in OSA patients. Although the prevalence of daytime or overall (i.e. daytime and nighttime combined) symptoms does not appear to differ to that in the general population, the findings of this study suggest that the prevalence of *nocturnal*GOR symptoms in individuals with OSA may be significantly greater than that in the general population.

To date, no study has used oesophageal pH monitoring to specifically determine the prevalence of abnormal *nocturnal*GOR in OSA patients. However, three studies that have used oesophageal pH monitoring to investigate the temporal relationship between

upper airway obstruction and *nocturnal*GOR episodes in small groups of patients. Penzel *et al*[246] in 15 OSA patients found 33% had pathological oesophageal acid exposure during the night. Similarly, Graf *et al*[497] in 17 OSA patients and Ozturk *et al*[259] in 19 OSA patients reported 42% and 41% of individuals had pathological oesophageal acid exposure overnight, respectively.

Despite the absence of a definitive study, the findings of these studies suggest that the prevalence of both *nocturnal*GOR symptoms and episodes is greater in OSA than in the general population (see section 2.1.9.2). Comparison of results between previous studies remains complicated by differences in questionnaires, symptom definition and subject categorisation. Furthermore, the prevalence of *nocturnal*GOR symptoms in OSA patients relative to the general population is unclear as no study has directly compared the two populations.

2.3.2 Mechanisms of reflux in obstructive sleep apnoea

Although the mechanism for the increase in GOR in individuals with OSA is unknown, several potential mechanisms have been identified. These are discussed in detail in the following section.

2.3.2.1 Similar risk factors

As evident from previous sections discussing modifying factors for GOR and OSA, risk factors such as obesity and alcohol consumption are shared by both conditions. It is possible that the increased prevalence and severity of GOR in OSA patients is due to similar predisposing factors between the two conditions.[14,18,21] However, several studies have shown an effect of OSA on GOR independent of these common risk factors.[18,498]

Ing *et al*[18] found OSA patients had significantly more GOR episodes overnight compared with normals, even when subjects were matched for gender, age, BMI and alcohol consumption. In addition, a recent study in morbidly obese patients, reported a significant association between GORD (diagnosed by oesophageal pH monitoring) and OSA independently of age, gender and BMI.[498]

2.3.2.2 Intrathoracic pressure changes

Nocturnal GOR in OSA patients may be precipitated by the generation of substantial negative intrathoracic pressures during an obstructed breath (Figure 2.18). It is possible that the consequent increased pressure gradient across the diaphragm allows the stomach contents to be "sucked" into the oesophagus.[24,489]

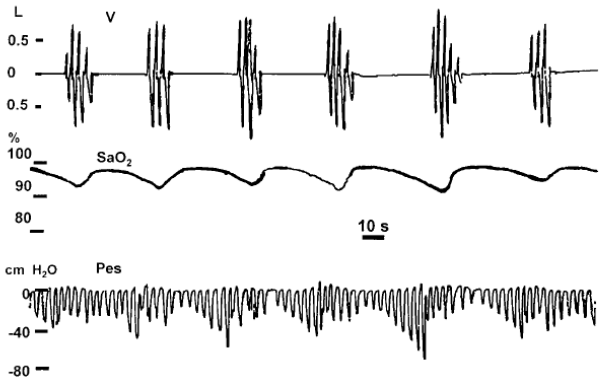

Figure 2.18. *Intrathoracic pressure changes in association with obstructive apnoea. Note the increasing respiratory efforts as indicated by progressive oesophageal pressure (P_{es}) decreases during apnoeic events. From Krieger et al.*[499]

However, the temporal relationship between *nocturnal*GOR events and either apnoea or hypopnoea has been found to be variable, with studies reporting between 53 to 70% of reflux episodes being temporally related to either an apnoea or hypopnoea.[18,246,259] Whether obstructive respiratory events precede or follow GOR episodes is unclear as results regarding this possible relationship are also variable and often not reported.

Furthermore, there is no evidence of a relationship between *nocturnal*GOR episodes and the magnitude of intrathoracic pressure changes generated during obstructive respiratory events, suggesting these may not precipitate GOR events.[259,500]

It is possible that oesophageal pH monitoring may not detect all reflux episodes. Because acid can reside in the oesophagus for lengthy periods overnight, additional reflux episodes that occur during this low pH period may not be detected. Furthermore, non-acid reflux will not be detected by conventional oesophageal pH monitoring. Indeed, pH monitoring identifies only half of reflux events that are identified by intraluminal impedance.[501] Hence it is possible that the number of reflux events that occur overnight are underestimated by pH monitoring and that a greater percentage of reflux events are temporarily related to upper airway obstruction than previously thought. For this reason, techniques such as multi-channel intraluminal impedance monitoring may be useful to more closely investigate the relationship between intrathoracic pressure changes and GOR.

2.3.2.3 Arousal and movement

OSA is characterised by repetitive arousal overnight associated with upper airway reopening. Between 76-99% of *nocturnal*GOR episodes are associated with arousal or awakening,[24,246,259] suggesting an involvement of arousal in the pathogenesis of *nocturnal*GOR in OSA. Treating OSA with CPAP has been shown to reduce reflux events in individuals with OSA, reflux disease and oesophageal disorders[20,24,25](section 2.3.4.1). CPAP may achieve this in OSA patients by simply reducing the number of arousals. However, in individuals without OSA, CPAP also reduces *nocturnal*GOR and does so without a change in arousal index,[25] suggesting a mechanism other than its effects on arousal is responsible.

During arousal from sleep it is common for movement to occur. The majority of *nocturnal*GOR events in both adults[24] and infants[502-504] correspond with gross body movements. Body movement may precipitate GOR as it is associated with an increase in gastric pressure, which may be sufficient to temporarily overcome the LOS barrier pressure and allow acid to enter the oesophagus (*i.e.* strain-related GOR). Therefore, any increased movement overnight, such as that associated with post-apnoeic arousals, may also be involved in the pathogenesis of reflux in OSA patients. To date, no study has investigated the role of movement in the pathogenesis of *nocturnal*GOR events in OSA.

2.3.2.4 Autonomic Nervous Activity

Apnoea-induced changes in autonomic nervous activity may affect GOR in several ways. Firstly, airway reopening after an obstructive apnoea is associated with temporal surges in sympathetic nervous activity.[505] This increase in sympathetic activity may precipitate GOR events by weakening the barrier to GOR, as sympathetic stimulation has been found to decrease LOS pressure in animals.[506] To date, there is no data in humans on the effect of sympathetic stimulation on the LOS. Secondly, parasympathetic (vagal) nervous activity may increase during an apnoea.[507] Because TLOSR and gastric motility are controlled by vagal nerve activity, increases in parasympathetic tone may decrease gastric motility or increase the rate of TLOSR during apnoeas, thereby increasing the likelihood of *nocturnal*GOR.

2.3.3 Relationship between the severity of obstructive sleep apnoea and gastro-oesophageal reflux

The relationship between the severity of OSA and the severity of GOR remains unclear. If there is a causal relationship between the two disorders then one might expect with increasing severity of OSA there would be an increase in the severity of GOR. However data regarding this is limited and inconsistent. Amongst studies focussing on GOR symptoms, there is evidence that severity of OSA is greater in individuals with symptomatic GORD.[495] However the majority of studies show no correlation between severity of GOR symptoms and severity of OSA.[19,21,22] The only study to report a correlation between OSA severity and *nocturnal*GOR symptom severity[20] was also the only study to specifically investigate nocturnal symptoms. In general, studies have not separated GOR into daytime and nocturnal components. Considering that OSA is a sleep-related phenomenon, an association between the severities of the two disorders may be evident if nocturnal symptoms were to be isolated from overall symptoms.

Likewise, no relationship has been shown between OSA severity and GOR or *nocturnal*GOR severity determined by oesophageal pH monitoring.[497,500,508] The only study to find a significant correlation between severity of OSA and severity of GOR was by Demeter *et al*[490] using endoscopic diagnosis of GOR. They found that erosive GORD was significantly more common in severe OSA patients compared to mild/moderate patients and that the severity of the endoscopic findings was positively correlated with severity of OSA (AHI). Consistent with other reports, they also found that while there was a correlation between severities of endoscopically-diagnosed GORD and OSA there was no difference in GOR symptoms between individuals with different severities of OSA. This study suggests that there may be a relationship

between severities of the two disorders, but that it may be confined to those with more severe GORD, or that more objective methods of diagnosis are required to define it.

2.3.4 Continuous positive airway pressure

2.3.4.1 Effect of continuous positive airway pressure on reflux

There is substantial evidence that CPAP decreases *nocturnal*GOR episodes and symptoms[20,24-27,497] in individuals with OSA. The effect appears to be dose dependent, such that the higher the CPAP pressure the greater the effect.[20] Surprisingly, CPAP not only reduces *nocturnal*GOR episodes and symptoms but also those occurring during the daytime hours (although the beneficial effect is greater overnight).[28,509] The reason for the effect of CPAP on daytime GOR events is unknown but may result from a decrease in oesophageal acid exposure overnight, leading to a decrease in oesophageal inflammation and potentially a reduction in daytime GOR symptoms.

2.3.4.2 Mechanisms of the effect of continuous positive airway pressure on reflux

Several potential mechanisms could be responsible for the effect of CPAP on *nocturnal*GOR. The decrease in *nocturnal*GOR episodes caused by CPAP may relate to mechanical effects which increase the integrity of the barrier to GOR as there is evidence to suggest CPAP causes an increase in LOS pressure.[25] CPAP also results in continuous elevation of oesophageal pressure, which may alter the pressure gradient across the LOS, therefore providing a protective effect from GOR.[510,511] Alternatively, it is possible that the decrease in nocturnal reflux is due to a decrease in arousal and/or movement frequency.[512] Arguing against this is the finding that the effect of CPAP on nocturnal reflux is not unique to patients with OSA but is also evident in those without

OSA who have GORD.[24,25] In those without OSA, CPAP exerts its effects without a change in arousal frequency.

As previously discussed, reflux episodes generally occur during periods of LOS relaxation, not during periods of stable LOS pressure. To date, there are no studies that have investigated the effect of CPAP on LOS behaviour.

2.4 NOCTURNAL GASTRO-OESOPHAGEAL REFLUX AND OBSTRUCTIVE SLEEP APNOEA IN LUNG TRANSPLANTATION.

Nocturnal GOR has been implicated in many upper and lower respiratory tract disorders as discussed in earlier sections. Bronchiolitis Obliterans Syndrome (BOS) is a marker of chronic allograft dysfunction in lung transplant patients. BOS is manifested by a decrease in forced expiratory volume in one second (FEV_1) and scar formation in the small airways.[513] Chronic allograft dysfunction due to BOS remains the main complication limiting long-term survival following lung transplantation. GOR has been implicated in the development of BOS, possibly due to pulmonary aspiration of refluxed acid. Risk of aspiration is increased during sleep and further increased by the presence of OSA. Thus far the effect of *nocturnal*GOR and OSA on allograft dysfunction in lung transplant patients is unknown. Although data are limited, the potential importance of these disorders in lung transplant patients will be reviewed in this section.

2.4.1 Gastro-oesophageal reflux in lung transplant patients

GOR is common in lung transplant patients, with 40 to 70% of post-transplant patients reported to have abnormal oesophageal acid contact time.[15,17,31,514] This increased occurrence is usually attributed to vagal nerve injury caused during transplant surgery or

to the use of immunosuppressant medications which delay gastric emptying.[515-517] The increased acid contact time in these individuals may also be due to a high occurrence of oesophageal dysmotility, which delays acid clearance.[518]

Several findings support the contention that GOR plays a role in the development of BOS. Firstly, GOR has been shown to be related to the development of diffuse bronchiolitis in the non-transplant population.[519] Secondly, post-transplant patients have a significant increase in GOR episodes and oesophageal acid contact time than pre-transplant, especially when considering *nocturnal*GOR.[514] Thirdly, lung function is negatively correlated with acid contact time in these patients.[15] Lastly, several studies have reported improvements in lung function and BOS status with Nissen Fundoplication (surgical treatment for GORD). [16,17,31,32]

Sleep may be a period of particularly high vulnerability to any aspiration-related development of BOS as it is associated with reduced oesophageal acid clearance, increased oesophageal acid contact time, decreased upper oesophageal sphincter tone[103,520] and increased risk of pulmonary aspiration.[7] Coupled with the observation that lung transplant patients have decreased mucociliary clearance[521,522] and a significant increase in supine GOR post-transplant[514] the likelihood of aspiration and prolonged acid contact with lung tissue during sleep is greatly increased. However, there is extremely limited data regarding the specific effects of *nocturnal*GOR on the development of BOS. Hadjiliadis *et al*[15] found that supine (nocturnal) GOR was more common in lung transplant patients than upright (daytime) GOR. However in this study only upright GOR correlated with lung function, suggesting no additional risk with supine GOR relative to upright. To date this is the only study to investigate the specific effects of *nocturnal*GOR on lung function.

2.4.2 Obstructive sleep apnoea in lung transplant patients

Disorders such as OSA, which are known to further increase *nocturnal*GOR and risk of aspiration, may be implicated in the development of BOS. Few studies have investigated the prevalence of OSA in lung-transplant patients. While Sanders *et al*[523] found no evidence of sleep-disordered breathing in heart-lung transplantation patients, a recent study by Malouf *et al*[33] reported OSA to be present in 40% of lung transplant patients. The mechanism behind this high prevalence of OSA is unknown, but could be related to a destabilising effect of lung transplantation surgery on the upper airway as a result of loss of longitudinal tension on the upper airway and/or to weight gain as a result of postoperative steroid use. Development of OSA post transplant may be responsible for the high occurrence of *nocturnal*GOR in this patient group.

2.4.3 Gastroesophageal reflux and obstructive sleep apnoea in lung transplant patients

Although evidence suggests that both *nocturnal*GOR and OSA are common disorders amongst individuals who have undergone lung transplantation, no study has investigated the relative importance of sleep disorders such as OSA on *nocturnal*GOR in these patients and whether they further increase the risk of lung injury or BOS.

CHAPTER THREE

The Prevalence of Nocturnal Gastro-oesophageal Reflux is Increased in Obstructive Sleep Apnoea

3.1 FOREWORD

Nocturnal GOR is associated with additional risks when compared to daytime GOR including increased oesophageal mucosal damage, increased extra-oesophageal complications and impaired quality of life. Previous studies have reported an increase in GOR events and symptoms in individuals with OSA, suggesting that OSA may precipitate reflux overnight. Despite this increased prevalence, most studies have not found an association between GOR symptoms and severity of OSA. It is likely that this is because most have investigated only daytime or overall (daytime and nocturnal combined) GOR symptoms. Considering that OSA is a sleep-related phenomenon the most significant effect on GOR is likely to be during sleep. The following study determines and compares the prevalence of *nocturnal*GOR symptoms between a general population sample and a large group of OSA patients.

This chapter has been submitted to the journal ***Sleep*** *for consideration for publication (submitted 12/09/2008).*

3.2 ABSTRACT

Background. Obstructive sleep apnoea (OSA) is thought to predispose individuals to nocturnal gastro-oesophageal reflux (*nocturnal*GOR), yet it the prevalence of *nocturnal*GOR symptoms in OSA patients compared to the general population is unclear. This study sought to compare the prevalence of *nocturnal*GOR symptoms in OSA patients with the general population.

Methods. 2,042 members of the general community (as part of the 2005-2007 Busselton Health Survey) and 1,116 patients with polysomnography-diagnosed OSA completed a validated gastro-oesophageal reflux. Risk of OSA in the general population was determined using a standardised sleep questionnaire. 137 of the OSA patients completed the questionnaire both before and after treatment with CPAP.

Results. The prevalence of *nocturnal*GOR symptoms reported more than once a week was greater in OSA patients (10.1%) than the general population (5.8%) ($p<0.001$), in individuals from the general population at high risk of OSA (11.2%) than low risk (4.5%) ($p<0.001$) and in patients with severe OSA (14.7%) than mild OSA (5.2%) ($p<0.001$). Treatment of OSA with CPAP decreased the prevalence of frequent *nocturnal*GOR from 9.0% to 3.8% ($p=0.04$).

Conclusions. The prevalence of frequent *nocturnal*GOR symptoms is greater in OSA patients than in the general community and is significantly increased in individuals with severe OSA or who are at high risk of OSA in the general population. Treatment of OSA with CPAP markedly decreases the prevalence of *nocturnal*GOR symptoms.

3.3 INTRODUCTION

Obstructive sleep apnoea (OSA) is characterised by repetitive narrowing or occlusion of the upper airway during sleep, which results in the development of large, negative intrathoracic pressures during inspiratory efforts against the obstructed airway, and repetitive arousals. It is highly likely that the pressure gradients developed during these obstructive events predispose OSA patients to heartburn and acid regurgitation, the two most commonly reported symptoms of gastro-oesophageal reflux (GOR), particularly during sleep (*nocturnal*GOR). Between 20 and 60% of OSA patients report frequent heartburn or acid regurgitation[19,21,22], the most common symptoms of GOR [46], compared to 20% of the general population[5].

Considering OSA is a sleep-related phenomenon, it is likely the largest difference in prevalence would be with specifically sleep-related GOR symptoms. Although a PubMed search using the terms "obstructive sleep apnea, gastro-oesophageal reflux" identifies 130 papers and several of these focus on the prevalence of GOR in OSA patients, to date only one paper has reported the prevalence of reflux symptoms specifically during sleep.[20] This study suggested that the prevalence of *nocturnal*GOR symptoms is substantially greater in those with OSA, with 62% of patients reporting nocturnal symptoms compared with only 10-25% of the general population.[1,6] Comparison of previously reported results regarding the prevalence of GOR and *nocturnal*GOR symptoms in those with OSA with the general population remains complicated by differences in questionnaires, symptom definition and subject categorisation. Therefore, the prevalence of *nocturnal*GOR symptoms in OSA patients relative to the general population is unclear.

Treatment of OSA with continuous positive airway pressure (CPAP) has been reported to reduce *nocturnal*GOR events and symptoms in individual cases,[20,24,27,28,509] possibly due to its effects on the primary barrier to GOR, the lower oesophageal sphincter.[25,524] However the effect of CPAP on the prevalence of *nocturnal*GOR symptoms in OSA patients remains unknown.

The primary objectives of this study were to quantify the prevalence of GOR and *nocturnal*GOR symptoms in OSA patients and the general population and to determine the effect of CPAP on prevalence in the OSA-affected group.

3.4 METHODS

3.4.1 Study populations

3.4.1.1 General Population

Busselton is a coastal town in Western Australia with a population of approximately 26,000 individuals of predominantly Western European origin. The community has been subject to repeated health studies since 1966.[312,367,525] A stratified (for sex and age) random sample of adults on the Busselton Shire electoral roll was undertaken and 2,042 subjects (61.8% response rate) completed the 2005-2007 Busselton Health Survey, which included questions about GOR symptoms and sleep-related problems (see below).

3.4.1.2 OSA Population

1,422 consecutive patients undergoing diagnostic polysomnography at Sir Charles Gairdner Hospital completed a GOR symptom questionnaire (GORQ, see below). Complete sleep and questionnaire data could not be obtained on 185 patients. Of the

remaining 1,237 patients, 1,116 were diagnosed with OSA and comprise the OSA population.

477 patients attending the Respiratory Sleep Disorders Clinic for repeat polysomnography for the purpose of optimising their CPAP therapy completed a modified version of the GORQ (see below). Of this group 137 patients completed the questionnaire both on the night of their diagnostic polysomnography and on the night of their CPAP titration study after 1-6 months of therapy.

3.4.2 Questionnaires

The questionnaire used in this study was the GORQ, developed and validated at the Mayo Clinic,[5,526] modified slightly to replace USA pharmaceutical names with Australian equivalents. The questionnaire was modified further for the 137 patients who had been using CPAP by asking about the same GOR symptoms 'since starting CPAP treatment' and by including questions regarding CPAP compliance.

A subset of six questions from the GORQ regarding frequency and severity of GOR and *nocturnal*GOR symptoms were included in the Busselton Health Survey. This questionnaire also contained questions regarding frequency of witnessed apnoeas, snoring frequency and volume, frequency of waking tired and frequency of daytime sleepiness derived from the validated Berlin questionnaire.[527]

3.4.3 Polysomnography

Standard overnight polysomnography was performed (E-Series, Compumedics, Melbourne, Australia). Sleep stage, arousals and respiratory events were scored by experienced polysomnographic technicians using standard criteria[528] without knowledge of questionnaire results.

3.4.4 Analyses

For the general population, responses to the Berlin questionnaire were used to define individuals as 'low risk' or 'high risk' for OSA.[527] In the OSA population, severity of OSA was defined by the apnoea-hypopnoea index (AHI, average number of apnoeas and hypopnoeas per hour of sleep). OSA was deemed to be mild if AHI was between 5 and 15 events.hr^{-1}; moderate if between 15 and 30 events.hr^{-1}; and severe if >30 events.hr^{-1}. Snoring frequency was defined by number of snores per minute. The arousal index (ArI) was defined as the number of arousals per hour of sleep.

For analysis of GOR symptoms heartburn or acid regurgitation experienced at least once in the last 12 months was defined as 'any GOR' and heartburn or acid regurgitation experienced at least once a week was defined as 'frequent GOR'.[5,57] The term 'GOR symptoms' refers to symptoms experienced at any time during the day or night and '*nocturnal*GOR symptoms' specifically to symptoms occurring during the night.

Data were compiled using Microsoft Access and Excel (Microsoft Corporation, Redmond, WA, USA). Statistical analyses were performed using SPSS (Version 15.0, SPSS Inc., Chicago, USA). Unpaired t-tests were used to compare anthropometric characteristics between populations. Mann-Whitney rank sum tests were performed

when data could not be normalised. Proportions of individuals in different populations reporting symptoms were compared using Chi-squared tests. Paired t-tests were used to assess changes in symptom prevalence in patients who completed the questionnaire before and after CPAP treatment. A p-value of <0.05 was considered significant for all tests.

3.4.5. Data Access and Ethical Approval

The Human Research Ethics Committee of Sir Charles Gairdner Hospital approved this study. The 2005-2007 Busselton Health Survey was approved by the Human Research Ethics Committee of the University of Western Australia. The Busselton Population Medical Research Foundation approved inclusion of the GORQ questions into the survey and access to survey data.

3.5 RESULTS

Compared with the general population, the OSA population was younger, had a greater BMI, a higher proportion of males and more individuals taking acid suppressive medications (Table 3.1). The prevalence of frequent GOR symptoms, any *nocturnal*GOR symptoms and frequent *nocturnal*GOR symptoms was greater in the OSA population than the general population by 10.9%, 5.7% and 4.5%, respectively ($p<0.05$ for each).

Table 3.1. Subject characteristics and prevalence of gastro-oesophageal reflux symptoms in the general population and an OSA population.

	General Population (n=2,042)	**OSA Population** (n=1,116)
Age, years	57.6 (17.7)	49.5 (13.2)*
BMI,kg.m^{-2}	27.0 (4.6)	31.8 (7.5)*
Males, %	48.5	67.7*
Acid suppressive medications, %	14.0	28.5*
Gastro-oesophageal Reflux†		
Any GOR, %	63.0	59.7
Frequent GOR, %	14.3	25.2*
Nocturnal Gastro-oesophageal Reflux		
Any *nocturnal*GOR, %	27.0	32.7*
Frequent *nocturnal*GOR, %	5.8	10.3*

*Data are presented as mean (SD) or percent of population. *p<0.05, OSA vs General Population. †Day- and night- GOR combined. Abbreviations: OSA = obstructive sleep apnoea; BMI = body mass index, calculated as weight divided by square of height in meters; GOR = gastro-oesophageal reflux; nocturnalGOR = nocturnal gastro-oesophageal reflux.*

In the general population, 18.8% of individuals were considered to be at high risk for OSA[527] (Table 3.2). Compared with the low risk group, those at high risk had more than twice the prevalence of frequent GOR and frequent *nocturnal*GOR symptoms ($p<0.05$).

In the OSA population the prevalence of any or frequent *nocturnal*GOR symptoms was increased in those with moderate or severe OSA (Table 3.2). The prevalence of GOR symptoms was similar between those with mild, moderate and severe disease.

Treatment of OSA with CPAP (for between 1 and 6 months) had a substantial effect on the prevalence of GOR symptoms, especially nocturnal symptoms. The prevalence of any *nocturnal*GOR symptoms decreased from 44.8% before treatment to 6.1% after treatment ($p<0.001$) and of frequent *nocturnal*GOR symptoms from 9.0% to 3.8% ($p<0.04$) (Table 3.3). Despite this reduction in symptoms, the proportion of individuals taking acid suppressive medications remained unchanged.

Table 3.2. Effect of OSA severity on the prevalence of gastro-oesophageal reflux symptoms in the general population and an OSA population

	General Population		**OSA Population**		
	Low risk (n=1,657)	**High risk** (n=385)	**Mild** (n=302)	**Moderate** (n=322)	**Severe** (n=492)
Age, years	57.6 (18.0)	57.3 (16.3)	47.6 (14.0)	49.9(12.9)‡	50.5 (12.7)‡
BMI, $kg.m^{-2}$	25.9 (3.9)	31.5 (4.9)*	30.9 (7.4)	31.0 (6.8)	33.0 (7.9)†§
Males, %	46.4	57.4*	55.6	69.6‡	73.4‡
Acid suppressive medications, %	12.8	20.0*	23.5	28.0	27.1
	Gastro-oesophageal *Reflux*†				
Any GOR, %	61.3	73.8*	56.4	62.4	60.8
Frequent GOR,%	11.6	24.9*	20.8	26.5	27.3
	Nocturnal Gastro-oesophageal *Reflux*				
Any *nocturnal*GOR, %	23.7	41.4*	22.9	32.8‡	39.4‡
Frequent *nocturnal*GOR, %	4.5	11.2*	5.2	8.7	14.7‡§

*Data are presented as mean (SD) or percent of population. *p<0.05 vs low risk (within general population). ‡p<0.05 vs mild OSA (within OSA population). §p<0.05 vs moderate OSA (within OSA population). †Day- and night- GOR combined. Abbreviations: OSA = obstructive sleep apnoea; BMI = body mass index, calculated as weight divided by square of height in meters; GOR = gastro-oesophageal reflux; nocturnalGOR = nocturnal gastro-oesophageal reflux.*

Table 3.3. Effects of CPAP treatment for OSA on GOR Symptoms

	Pre-treatment (n=137)	**Post-treatment** (n=137)	***p-value***
BMI, ,kg.m^{-2}	32.3 (6.4)	33.3 (7.4)	*0.18*
AHI, events.hr^{-1}	38.2 (25.3)	12.7 (13.7)	*<0.001*
ArI, arousals.hr^{-1}	39.3 (24.0)	24.4 (13.1)	*<0.001*
Snoring, snores.min^{-1}	5.0 (3.8)	1.4 (2.0)	*<0.001*
Acid suppressive medications, %	32.1	30.7	*0.8*
Gastro-oesophageal *Reflux*†			
Any GOR, %	72.6	54.5	*<0.001*
Frequent GOR, %	27.6	18.2	*<0.001*
Nocturnal Gastro-oesophageal *Reflux*			
Any *nocturnal*GOR, %	44.8	6.1	*<0.001*
Frequent *nocturnal*GOR, %	9.0	3.8	*0.04*

Data are presented as mean (SD) or percent of group. †Day- and night- GOR combined. Abbreviations: BMI = body mass index, calculated as weight divided by square of height in meters; AHI = apnoea-hypopnoea index, number of apnoeas and hyponeas per hour of sleep; ArI = arousal index, number of arousals per hour of sleep; GOR = gastro-oesophageal reflux; nocturnalGOR = nocturnal gastro-oesophageal reflux.

3.6 DISCUSSION

This is the first study to utilise standardised definitions of GOR and *nocturnal*GOR in an OSA population and a sample of the general population in order to determine and compare the prevalences of GOR symptoms in these groups. The major findings of this study are that the prevalence of *nocturnal*GOR symptoms is greater both in individuals at high risk of OSA in the general population and in those with diagnosed OSA and that it decreases substantially with treatment of OSA by CPAP.

A very high proportion of the general population (63%) reported reflux symptoms at least once in the previous 12 months. This is similar to prevalence estimates from other

studies[5] and to that of our OSA population (60%). Differences between the general population and those with OSA become apparent when comparing the prevalence of frequent GOR and *nocturnal*GOR symptoms, both of which were significantly greater in the OSA population.

The prevalences of 27% for any and 6% for frequent *nocturnal*GOR symptoms that we found in the general population are consistent with previous findings.[1,6] The prevalences of any and frequent *nocturnal*GOR symptoms in our OSA population of 32% and 10% respectively were significantly greater than in the general population. However, these were substantially less than the 62% of OSA patients with *nocturnal*GOR symptoms reported in the only other comparative study.[20] The reason for this difference may be due to the use of a different definition of *nocturnal*GOR: in the present study we were careful to use a well-validated questionnaire to elicit the relevant symptoms. Furthermore, in the present study the frequency of symptoms was estimated and related to OSA risk (in the general population) or its severity (in the OSA group). Using the Berlin questionnaire,[527] which has been found to be both sensitive and specific in identifying individuals with an AHI >5 events.hr^{-1},[314] we found that 19% of the general population sample were at "high risk" of OSA, similar to results reported in a large population-based study from North America. [314] The prevalences of any and frequent GOR and *nocturnal*GOR symptoms were significantly greater in this high risk group, particularly for nocturnal symptoms where it was 1.7 and 2.5 times that of the low risk group for any and frequent *nocturnal*GOR symptoms, respectively. It was notable that the prevalence estimates for the high risk group of 41.4% and 11.2% for any and frequent *nocturnal*GOR symptoms, respectively, were similar to the estimates in those with severe OSA, which were 39% and 15%, respectively. Consistent with these findings in the general population, a 'dose response' relationship was evident

between OSA severity and *nocturnal*GOR symptoms in our OSA group (Table 3.2), suggesting that OSA predisposes to *nocturnal*GOR.

There are several possible reasons for this predisposition. Firstly, the generation of substantial negative intrathoracic pressures during upper airway obstructions may result in the breach of the lower oesophageal sphincter, the primary barrier to reflux. Secondly, these obstructive events are terminated by disruption of sleep [529] which could result in both increased awareness of events and their frequency as *nocturnal*GOR episodes usually occur during brief arousal or awakening from sleep.[106,113,246-248]

Previous studies have suggested that application of CPAP reduces GOR in individuals with and without OSA[20,24-28,497,509]. These studies applied CPAP for between 1 night and 39 months, suggesting 1-6 months of therapy (*i.e.* the time frame for which our CPAP group was receiving treatment before completing the post-treatment questionnaire) was sufficient time for CPAP to impact on *nocturnal*GOR symptoms. Indeed there was a striking decrease in the prevalence of *nocturnal*GOR in OSA patients after treatment with CPAP, to levels similar to or lower than that observed in the low risk group in the general population. This may relate to an associated decrease in arousal frequency [512] or mechanical effects which act to increase the integrity of the barrier to GOR.[25,524] It was notable that the number of individuals on acid suppressive medication was unchanged before and after treatment. This finding suggests that acid suppressive medications in patients with OSA be re-evaluated after commencement of CPAP therapy.

Despite its large size, there are several potential limitations to this study. Firstly, in any epidemiologic study there is a possibility of selection bias. However, there is no *a*

priori reason to believe selection bias was an issue as we used a random sample of the general population and all patients who attended the sleep clinic for either diagnostic or CPAP titration polysomnographic study were presented with and completed the GORQ before polysomnography. Secondly, the data used in these analyses were largely based on self-report thus there is the possibility of error in the ascertainment of GOR or sleep symptoms. It is unlikely, however, that there was a systematic bias in the assessment of these factors. Thirdly, the analyses undertaken in the study do not account for potential confounders such as age and BMI, which may be responsible, at least in part for the apparent association between risk and severity of OSA and *nocturnal*GOR symptoms.

3.7 ACKNOWLEDGEMENTS

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CHAPTER FOUR

Obstructive sleep apnoea is an independent risk factor for nocturnal gastro-oesophageal reflux

4.1 FOREWORD

The prevalence of *nocturnal*GOR symptoms in individuals with either polysomnography-diagnosed OSA or those at high risk of OSA in the general population is increased (Chapter Three). However it remains unclear whether the apparent association between *nocturnal*GOR symptoms and presence or severity of OSA occurs independently of other risk factors for the two disorders such as age and BMI. This question was addressed in Chapter Four, which presents univariate and multivariate analyses of demographic and sleep-related risk factors affecting the prevalence or frequency of *nocturnal*GOR symptoms in the general population and a large group of OSA patients.

This chapter is in preparation for submission to the journal ***Chest*** *for consideration for publication.*

4.2 ABSTRACT

Background: Obstructive Sleep Apnoea (OSA) is associated with an increase in gastro-oesophageal reflux (GOR) symptoms and events, however epidemiological studies have not provided data in support of an association between the severity of OSA and GOR. Considering OSA is a nocturnal phenomenon, one would expect the strongest association to be evident when looking at nocturnal GOR (*nocturnal*GOR) symptoms, however most studies have not specifically investigated nocturnal symptoms. This study sought to determine the sleep-associated risk factors for *nocturnal*GOR symptoms in the general population and OSA patients using standardised, validated questionnaires.

Methods: 2,042 individuals from the general community who participated in the 2005-2007 Busselton Health Survey and 1,116 patients with polysomnography-diagnosed OSA completed a validated GOR symptom questionnaire. Risk of OSA was determined in the general population using the validated Berlin questionnaire. Severity of OSA in the OSA population was defined by the apnoea-hypopnoea index (AHI-number of apnoeas or hypopnoeas per hour of sleep). Univariate and multivariate logistic regression were performed with *nocturnal*GOR symptoms as the main outcome

Results: In the general population, waking tired (odds ratio 1.34 (1.18, 1.52; p<0.001)) and high risk of OSA (odds ratio 2.42 (1.58, 3.73; p<0.001)) were independently associated with increased risk of more than weekly *nocturnal*GOR symptoms. In the OSA population, severity of OSA was independently associated a significantly increased risk of more than weekly *nocturnal*GOR symptoms (odds ratio 1.71 (1.31, 2.29; p<0.001)).

Conclusions: In both a general population and in an OSA population symptoms and severity of OSA are associated with increased *nocturnal*GOR symptoms.

4.3 INTRODUCTION

Heartburn and acid regurgitation are the most commonly described symptoms of gastro-oesophageal reflux (GOR)[46] and are reported as frequent in 20% of the general population[5] and up to 60% of individuals with obstructive sleep apnoea (OSA).[19] It is thought that repetitive collapse of the upper airway, repetitive arousal and generation of negative intrathoracic pressure during occluded inspirations associated with sleep may predispose individuals with OSA to sleep-related events and symptoms (*nocturnal*GOR). Indeed, approximately 60% of OSA patients report *nocturnal*GOR symptoms[20] compared with approximately 10% of the general population.[1]

The increased prevalence of GOR and *nocturnal*GOR symptoms in individuals with OSA compared with the general population suggests an association between the two conditions. Surprisingly, the majority of epidemiological studies investigating such an association have found no evidence of a relationship between symptoms of GOR and the presence or severity of OSA.[19,21,22] However, these studies have not separated *nocturnal*GOR symptoms from daytime or 'overall' symptoms. Considering that OSA is a sleep-related phenomenon it is reasonable to hypothesise that any association, if present, would be most apparent when specifically examining *nocturnal*GOR symptoms. Such an association is suggested in a study by Fass *et al*,[6] who investigated factors contributing to nocturnal heartburn in the general population and reported significant associations between all sleep variables (including symptomatic OSA defined by snoring and daytime sleepiness) and nocturnal heartburn. However, this study did not include the other typical symptom of GOR, acid regurgitation, nor did it use a validated sleep questionnaire for the assessment of OSA and therefore may have overestimated the risk of OSA in their population.

To date, no study has investigated the associations between sleep variables and *nocturnal*GOR symptoms (specifically heartburn and acid regurgitation) in either the general population or individuals with OSA using standardised, validated questionnaires to assess *nocturnal*GOR symptoms and risk of OSA. This study sought to determine if sleep-related symptoms, such as snoring, sleepiness and OSA risk or severity, independently affect the presence or frequency of *nocturnal*GOR symptoms in these populations.

4.4 METHODS

4.4.1 Study populations

4.4.1.1 General Population

Busselton is a coastal town in Western Australia with a population of approximately 26,000 individuals of predominantly Western European origin. The community has participated in repeated health studies since 1966.[525] A stratified (for sex and age) random sample of adults on the Busselton Shire electoral roll was invited to attend the 2005-2007 Busselton Health Survey, which included questions about GOR symptoms and sleep-related problems (see below). 2,042 subjects (61.8% response rate) completed the study.

4.4.1.2 OSA Population

1,422 consecutive patients undergoing diagnostic polysomnography at Sir Charles Gairdner Hospital completed a GOR symptom questionnaire (GORQ). Complete sleep data could not be obtained on 185 patients. Of the remaining 1,237 patients, 1,116 were diagnosed with OSA and comprise the OSA population.

4.4.2 Questionnaires

The questionnaire used in this study was the GORQ, developed and validated at the Mayo Clinic,[5,526] modified slightly to replace USA pharmaceutical names with Australian equivalents. The modified GORQ was administered to the OSA group and a subset of six questions regarding frequency and severity of GOR and *nocturnal*GOR symptoms were included in the Busselton Health Survey administered to the general population sample. This questionnaire also contained questions regarding frequency of witnessed apnoeas, snoring frequency and volume, frequency of waking tired and frequency of daytime sleepiness derived from the validated Berlin questionnaire.[527]

4.4.3 Polysomnography

Standard overnight polysomnography (E-Series, Compumedics, Melbourne, Australia) was performed on all individuals in the OSA group. Sleep stage, arousals and respiratory events were scored by experienced polysomnographic technicians using standard criteria[528] without knowledge of questionnaire results.

4.4.4 Analyses

For the general population, responses to the Berlin questionnaire were used to define individuals as 'low risk' or 'high risk' for OSA.[527] In the OSA population, severity of sleep-disordered breathing was defined by the average number of apnoeas and hypopnoeas per hour of sleep (apnoea-hypopnoea index, AHI). Mild OSA was defined as an AHI >5-15 events.hr^{-1}; moderate OSA as an AHI >15-30 events.hr^{-1}; and severe OSA as an AHI >30 events.hr^{-1}. Snoring frequency was defined as minimal if there were <1 snores per minute, intermittent if there were 1-2 snores per minute or continuous if there were >2 snores per minute. The arousal index (ArI) was defined as

the number of arousals per hour of sleep. ArI was categorised into quartiles (0-20, >20-40, >40-60 and >60 arousals.hr^{-1}) for the purpose of analysis.

*Nocturnal*GOR symptoms were defined as 'any' if heartburn or acid regurgitation were experienced at least once in the last 12 months or as 'frequent' if heartburn or acid regurgitation were experienced at least once a week.[5,57]

Data were compiled using Microsoft Access and Excel (Microsoft Corporation, Redmond, WA, USA). Statistical analyses were performed using SPSS (Version 15.0, SPSS Inc., Chicago, USA). Unpaired t-tests were performed to compare anthropometric characteristics between populations. Where the data could not be normalised a Mann-Whitney Rank Sum Test was performed. The proportions of individuals who reported symptoms were compared using Chi squared tests. Logistic regression was used to examine significant associations between *nocturnal*GOR symptoms and sleep variables. Odds ratios and their 95% confidence intervals (CIs) were calculated for these associations based on appropriate reference categories. Regardless of univariate association the following variables were forced into the adjusted model because of a known association with GOR: age; gender; and BMI. Other risk factors were examined for independent association with any or frequent *nocturnal*GOR symptoms if they exhibited evidence of a univariate association ($p<0.1$). Two multivariate models were developed for the general population sample, the first including individual sleep variables and the second including risk of OSA according to the Berlin score (derived from the individual sleep variables). Subjects with missing data were excluded from analysis. A p-value of < 0.05 was considered significant for all statistical tests.

4.4.5 Data Access and Ethical Approval

The Human Research Ethics Committee of Sir Charles Gairdner Hospital approved this study. The 2005-2007 Busselton Health Survey was approved by the Human Research Ethics Committee of the University of Western Australia. The Busselton Population Medical Research Foundation approved inclusion of the GORQ questions into the survey and access to survey data.

4.5 RESULTS

Of the 2,042 individuals in the general population, complete data were available on 1,895 individuals. Of the 1,116 OSA patients, complete data were available on 1,093 individuals.

Compared with the general population, individuals with OSA were younger, had a higher BMI, a greater proportion of males and increased proportion of individuals taking acid suppressive medications (Table 4.1). A greater proportion of the OSA group reported symptoms compared with the general population.

Table 4.1. Population characteristics and occurrence of nocturnalGOR symptoms

	General population	**OSA population**
n	2042	1116
Males, %	48	68*
Age, years	58 (18)	50 (13)*
BMI, $kg.m^{-2}$	27 (5)	32 (8)*
Any *nocturnal*GOR, %	27	34*
Frequent *nocturnal*GOR, %	6	10*
Acid suppressive medication, %	14	28*

*Data presented as mean (SD) or percent of population. BMI= body mass index (weight/height^2, $kg.m^{-2}$); nocturnalGOR= nocturnal gastro-oesophageal reflux. *p<0.05 vs general population.*

4.5.1 General population

Male gender, increasing age and increasing BMI, increasing frequencies of snoring, witnessed apnoeas, daily waking tired and daytime sleepiness were associated with increased risk of any *nocturnal*GOR symptoms (Table 4.2). Similar associations were observed for frequent *nocturnal*GOR. Compared with those at low risk for OSA, individuals at high risk had more than a 2-fold increased risk of any *nocturnal*GOR or frequent *nocturnal*GOR symptoms ($p<0.001$)

Multivariate analyses of factors associated with risk of any *nocturnal*GOR symptoms showed that age category, BMI category, snoring frequency and waking tired (Table 3) but not gender, frequency of witnessed apnoeas or daytime sleepiness were significant. If high risk of OSA was entered into the multivariate model in the place of the other sleep symptoms, it remained significant, with a 1.9-fold increased risk of any *nocturnal*GOR symptoms compared with those at low risk of OSA, along with age and BMI categories (Table 4.3).

Multivariate analyses of factors associated with risk of frequent *nocturnal*GOR symptoms showed significant associations with age and frequency of waking tired (Table 4.3). These variables remained significantly associated with frequent *nocturnal*GOR symptoms regardless of whether age and BMI were considered as continuous variables or if sleep variables were categorised according to presence or absence of snoring, apnoea, waking tired or daytime sleepiness. If sleep symptoms were combined and used to calculate risk of OSA (Berlin Score) those at high risk were 2.4 times more likely to experience frequent *nocturnal*GOR symptoms than those at low risk (Table 4.3).

Table 4.2. General population: Univariate associations with nocturnalGOR symptoms.

	Any *nocturnal*GOR (n=1,895) **OR (95% CI)**	**Frequent *nocturnal*GOR** (n=1,895) **OR (95% CI)**
	Demographic variables	
Gender		
Male	1.0	1.0
Female	0.79 (0.64, 0.97)*	1.03 (0.70, 1.53)
Age category		
<30	1.0	1.0
30-40	2.67 (1.27, 5.66)†	2.02 (0.43, 9.47)
40-50	4.32 (2.08, 9.01)‡	2.00 (0.42, 9.56)
50-60	5.21 (2.53, 10.71)‡	4.04 (0.93, 17.60)
>60	6.30 (3.15, 12.58)‡	4.89 (1.18, 20.23)*
BMI category		
Normal weight	1.0	1.0
Overweight	1.80 (1.41, 2.30)‡	1.55 (0.95, 2.51)
Obese	2.11 (1.56, 2.85)‡	2.01 (1.14, 3.55)*
Morbidly obese	2.63 (1.68, 3.92)‡	1.56 (0.63, 3.88)
	Sleep variables	
Snore		
No	1.0	1.0
Yes	2.04 (1.64, 2.54)‡	2.24 (1.42, 3.53)‡
Snoring frequency		
None	1.0	1.0
1-2 times/month	1.67 (1.19, 2.35)†	3.15 (1.73, 5.73)‡
1-2 times/week	2.01 (1.52, 2.66)‡	2.07 (1.16, 3.69)*
3-4 times/week	2.17 (1.56, 3.02)‡	2.54 (1.34, 4.81)†
Every day	2.02 (1.49, 2.73)‡	2.26 (1.23, 4.12)†
Apnoea frequency		
None	1.0	1.0
1-2 times/month	2.87 (1.93, 4.28)‡	1.34 (0.60, 2.98)
1-2 times/week	2.12 (1.33, 3.38)†	1.30 (0.51, 3.30)
3-4 times/week	1.88 (1.08, 3.25)*	2.65 (1.16, 6.04)*
Every day	2.02 (1.26, 3.22)†	1.56 (0.67, 3.74)
Wake tired		
None	1.0	1.0
1-2 times/month	0.90 (0.66, 1.22)	0.76 (0.38, 1.50)
1-2 times/week	1.25 (0.94, 1.68)	1.60 (0.92, 2.75)
3-4 times/week	1.42 (0.98, 2.06)	1.04 (0.46, 2.36)
Every day	1.52 (1.11, 2.08)†	2.63 (1.56, 4.34)‡
Daytime sleepiness		
None	1.0	1.0
1-2 times/month	1.28 (0.95, 1.71)	0.90 (0.48, 1.69)
1-2 times/week	1.31 (0.98, 1.74)	1.07 (0.60, 1.90)
3-4 times/week	1.08 (0.75, 1.56)	0.91 (0.42, 1.94)
Every day	1.74 (1.28, 2.37)‡	2.35 (1.39, 3.98)‡
OSA risk		
Low risk OSA	1.0	1.0
High risk OSA	2.23 (1.74, 2.86)‡	2.40 (1.57, 3.69)‡

*Data presented as Odds Ratios (OR) with 95% confidence intervals (CI). BMI= body mass index (weight/height^2, kg.m^{-2}); OSA= obstructive sleep apnoea. *p<0.05; † p<0.01; ‡ p<0.001.*

Table 4.3. General Population: Multivariate associations with nocturnalGOR symptoms.

	Any *nocturnal*GOR (n=1,895) **OR (95% CI)**	**Frequent *nocturnal*GOR** (n=1,895) **OR (95% CI)**
	Demographic variables	
Age category	1.39 (1.27,1.52)‡	1.53 (1.27, 1.85)‡
BMI category	1.27 (1.12, 1.43)‡	ns
	Sleep variables	
Snoring frequency	1.12 (1.04, 1.20)†	ns
Wake tired	1.16 (1.08, 1.25)‡	1.34 (1.18, 1.52)‡
	Demographic variables	
Age category	1.36 (1.25, 1.49)‡	1.42 (1.18, 1.71)‡
BMI category	1.16 (1.01, 1.34)*	ns
	Sleep variables	
High risk OSA	1.92 (1.43, 2.58)‡	2.42 (1.58, 3.73)‡

*Data presented as Odds Ratios (OR) with 95% confidence intervals (CI). Top panel: significant associations with any and frequent nocturnalGOR symptoms with sleep symptoms included as individual categories (i.e. snoring frequency, witnessed apnoea frequency, frequency of waking tired and frequency of daytime sleepiness). Bottom panel: significant associations with any and frequent nocturnalGOR symptoms with sleep symptoms combined and used to calculate risk of OSA (Berlin score). nocturnalGOR= nocturnal gastro-oesophageal reflux; BMI= body mass index (weight/height^2, kg.m^{-2}); OSA= obstructive sleep apnoea; ns = p>0.05. * p<0.05; † p<0.01; ‡ p<0.001.*

4.5.2 OSA population

In the OSA population, univariate analyses showed that morbid obesity (BMI>35 kgm^{-2}), severity of OSA and a very high ArI (>60) were associated with significantly increased risk of both any *nocturnal*GOR and frequent *nocturnal*GOR symptoms (Table 4.4).

Multivariate analyses of factors associated with any *nocturnal*GOR showed only gender and severity of OSA to be significant risk factors (Table 4.5). OSA severity was independently associated with an odds ratio of 1.5 for any *nocturnal*GOR symptoms.

Multivariate analyses of factors associated with frequent *nocturnal*GOR showed OSA severity to be the only significant risk factor, with an odds ratio of 1.7 (Table 4.5). Again, these findings were unchanged if age and BMI or sleep variables were entered as continuous rather than categorical variables.

Table 4.4. OSA population: Univariate associations with nGOR symptoms.

	Any nGOR (n=1,093) OR (95% CI)	**Frequent nGOR (n=1,093) OR (95% CI)**
	Demographic variables	
Gender		
Male	1.0	1.0
Female	1.22 (0.94, 1.59)	0.97 (0.73, 1.67)
Age category		
<30	1.0	1.0
30-40	1.35 (0.76, 2.39)	1.02 (0.38, 2.76)
40-50	1.49 (0.86, 2.58)	1.56 (0.63, 3.90)
50-60	1.25 (0.72, 2.16)	1.48 (0.59, 3.68)
>60	1.30 (0.74, 2.28)	1.44 (0.57, 3.65)
BMI category		
Normal weight	1.0	1.0
Overweight	1.28 (0.85, 1.94)	1.83 (0.86, 3.90)
Obese	1.39 (0.91, 2.14)	2.09 (0.97, 4.49)
Morbidly obese	1.67 (1.09, 2.54)*	2.21 (1.04, 4.73)*
	Sleep variables	
OSA severity		
Mild	1.0	1.0
Moderate	1.75 (1.22, 2.50)†	1.90 (1.00, 3.62)*
Severe	2.24 (1.62, 3.10)‡	3.02 (1.69, 5.40)‡
Arousal category		
<20	1.0	1.0
20-40	1.14 (0.82, 1.60)	1.01 (0.64, 1.92)
40-60	1.22 (0.81, 1.83)	1.44 (0.76, 2.72)
>60	1.87 (1.21, 2.88)†	1.98 (1.03, 3.80)*
Snoring frequency		
None	1.0	1.0
Intermittent	1.17 (0.68, 2.02)	0.57 (0.22, 1.48)
Continuous	1.11 (0.78, 1.58)	0.89 (0.53, 1.51)

*Data presented as Odds Ratios (OR) with 95% confidence intervals (CI). BMI= body mass index (weight/height^2, kg.m^{-2}); OSA= obstructive sleep apnoea. * p<0.05; † p<0.01; ‡ p<0.001.*

Table 4.5. OSA Population: Mulitvariate associations with nocturnalGOR symptoms.

	Any *nocturnal*GOR (n=1,093) OR (95% CI)	**Frequent *nocturnal*GOR (n=1,093) OR (95% CI)**
	Demographic variables	
Gender	1.38 (1.04, 1.80)*	ns
	Sleep variables	
OSA severity	1.51 (1.29, 1.78)‡	1.71 (1.31, 2.29)‡

*Data presented as Odds Ratios (OR) with 95% confidence intervals (CI). nocturnalGOR= nocturnal gastro-oesophageal reflux; OSA= obstructive sleep apnoea; ns = p>0.05. * p<0.05; † p<0.01; ‡ p<0.001.*

4.6 DISCUSSION

This is the first study to investigate the risk factors for *nocturnal*GOR symptoms in a general population sample and a large group of OSA patients. Using standardised, validated questionnaires significant associations between risk and severity of OSA and *nocturnal*GOR symptoms in both the general population and OSA patients were found. These findings support the notion of a causal association between OSA and *nocturnal*GOR, the mechanism of which requires clarification.

4.6.1 Nocturnal gastro-oesophageal reflux in the general population

Very few studies have investigated the risk factors associated with *nocturnal*GOR symptoms in the general population. Fass *et al*[6] characterised risk factors for nocturnal heartburn in a sample of 15,000 members of the general population and showed significant relationships between reported snoring and sleepiness (symptomatic OSA) and insomnia and symptoms of nocturnal heartburn. The present study differs from this in that it includes a definition of *nocturnal*GOR symptoms which includes both

nocturnal heartburn and acid regurgitation. In addition it uses the validated Berlin questionnaire to define risk of OSA in the general population.

Multivariate analyses showed that gender did not independently (of age, BMI or OSA symptoms) affect risk of any or frequent *nocturnal*GOR symptoms in the general population. This finding is consistent with previous reports investigating either *nocturnal*GOR or GOR symptoms[6,79,123,124]. There was an increased risk of any or frequent *nocturnal*GOR symptoms with increasing age. Previous reports regarding the effect of age on GOR and *nocturnal*GOR symptoms are conflicting with either no effect of age[5,123,200] or a small increased risk of GOR symptoms with increasing age.[87,124]

Epidemiological studies consistently report an association between BMI and GOR symptoms.[6,123,168,174] In the present study, multivariate analyses showed that increasing BMI is associated with increased risk of any *nocturnal*GOR symptoms. The mechanism by which increased BMI predisposes to GOR may relate to the increased intragastric pressure in obese individuals[176-178] contributing to an increased gastro-oesophageal pressure gradient.[179,180] Furthermore, obese individuals are more likely to have hiatus hernia,[83,185] an independent risk factor for GOR.[92,186] The presence of hiatus hernia was not investigated in the present study.

In univariate analyses all sleep variables including snore, snoring frequency, frequency of witnessed apnoeas, frequency of waking tired, frequency of daytime sleepiness and high risk of OSA were associated with any *nocturnal*GOR and frequent *nocturnal*GOR. Unlike BMI and age there was not an increasing risk (odds ratio) with increasing frequency of sleep abnormalities. Multivariate analyses showed that only snoring frequency and frequency of waking tired were independently associated with any

*nocturnal*GOR symptoms. Frequency of waking tired was independently associated with frequent *nocturnal*GOR symptoms. Risk of OSA was assessed using the Berlin questionnaire which has been found to be both sensitive and specific in identifying individuals with an AHI >5 events.hr^{-1}.[314] Within the general population 19% were at "high risk" of OSA, similar to results reported in a large population-based study from North America.[314] When 'high risk' for OSA replaced individual sleep symptoms in the multivariate model, those at high risk had a 1.9-fold increased risk of any *nocturnal*GOR and a 2.4-fold increased risk of frequent *nocturnal*GOR symptoms than those at low risk. Although snoring was a significant risk factor for any *nocturnal*GOR symptoms, the present analyses did not show a significant association between witnessed apnoeas and *nocturnal*GOR symptoms. Such a relationship might be expected if there were an association between *nocturnal*GOR and OSA. However this result may well have been due to a Type II error, as only 16% of the general population sample reported having witnessed apnoeas.

4.6.2 Nocturnal gastro-oesophageal reflux in an OSA population

Unlike the general population, female gender showed a trend for increasing risk of any *nocturnal*GOR symptoms in the OSA population in the univariate analysis which became significant in multivariate analysis, with a 40% increased risk of *nocturnal*GOR symptoms in females compared with males (Table 4.5). This finding is consistent with that of Valipour *et al*[21] who reported a 60% increased risk of overall GOR symptoms for females compared with males (although their result failed to reach significance, likely due to a Type II error). While morbid obesity (BMI>35kgm^{-2}) was associated with approximately a two-fold increased risk of any *nocturnal*GOR or frequent

*nocturnal*GOR symptoms in the univariate analysis, this association was not statistically significant in any of the multivariate models.

OSA severity was a strong independent (of gender age and BMI) risk factor for both any *nocturnal*GOR and frequent *nocturnal*GOR symptoms with odds ratios of 1.5 and 1.7 for any and frequent *nocturnal*GOR symptoms, respectively.

These data strongly support an independent causal relationship between upper airway obstruction and *nocturnal*GOR as even when age, gender and BMI are taken into account the association between OSA severity and *nocturnal*GOR symptoms remains. Despite the high prevalence of GOR symptoms and the increased number of GOR events reported in individuals with OSA, previous epidemiological studies have generally not found an association between presence or severity of OSA and GOR.[19,21,22] This is possibly because the majority of studies have not investigated nocturnal symptoms specifically, concentrating instead on daytime symptoms or a combination of daytime and nocturnal symptoms. Notably, when the analyses were performed without separating nocturnal from daytime GOR symptoms (data not presented) OSA severity was not significantly associated with GOR symptoms, a finding in agreement with most previous studies.[19,21,22]

Given that OSA is a sleep-related phenomenon it is logical to expect the largest association to be with nocturnal symptoms and our data support this hypothesis. Previously Green *et al*[20] noted a weak association between AHI and *nocturnal*GOR symptoms in their study investigating the effect of treatment of OSA with continuous positive airway pressure, however their definition of *nocturnal*GOR was broad (all

those who reported being woken by heartburn or acid regurgitation 'sometimes', 'usually' or 'always').

There are several possibilities for the association between OSA and GOR. Firstly, both disorders share similar risk factors such as obesity and male gender.[14,18,21] Secondly, negative intrathoracic pressure swings which occur during upper airway obstruction may disturb the barrier provided by the lower oesophageal sphincter allowing acid to be 'sucked' out of the stomach. Lastly, obstructive events are terminated by disruption of sleep[529] which could result in both increased awareness of events and their frequency as *nocturnal*GOR episodes usually occur during brief arousal or awakening from sleep.[106,113,246-248] While the mechanisms underlying any association between OSA and GORD remain to be defined the findings of the present study and previous studies[6,18,489,490,495] provide increasingly strong evidence for an association between the two disorders.

Although associations between OSA and *nocturnal*GOR in both the general and OSA populations were evident, there were important differences between these two samples. In the general population age, male gender and BMI were associated with increased risk of *nocturnal*GOR symptoms (in univariate analysis) and age and BMI remained related to *nocturnal*GOR symptoms, independently of sleep variables. On the other hand, in the OSA population, age and BMI were not related to *nocturnal*GOR symptoms and female gender was associated with increased risk of *nocturnal*GOR symptoms. These results highlight the importance of a reference population when examining risk factors.

There are several potential limitations to this study. Firstly, in any epidemiologic study there is a possibility of selection bias. However, there is no *a priori* reason to believe selection bias was an issue as we used a random sample of the general population and

all patients who attended the sleep clinic for either diagnostic or CPAP titration polysomnographic study were presented with and completed the GORQ before polysomnography. Secondly, the data used in these analyses were largely based on self-report thus there is the possibility of error in the ascertainment of GOR or sleep symptoms. It is unlikely, however that there was a systematic bias in the assessment of these factors.

4.7 ACKNOWLEDGEMENTS

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CHAPTER FIVE

Impact of Continuous Positive Airway Pressure on the Lower Oesophageal Sphincter

5.1 FOREWORD

Population-based analyses demonstrate that CPAP has a profound effect on *nocturnal*GOR symptoms (Chapter Three). However the mechanisms underlying such a decrease in *nocturnal*GOR symptom prevalence remains unclear. Generally, GOR does not occur during periods of stable LOS pressure but during periods of transient relaxation, however the effect of CPAP on LOS relaxation is unknown. This chapter examined the effect of CPAP on LOS relaxation in awake, healthy individuals.

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5.2 ABSTRACT

Background. The lower oesophageal sphincter (LOS) is the primary barrier to gastro-oesophageal reflux. Reflux is associated with periods of LOS relaxation, as occurs during swallowing. Continuous positive airway pressure (CPAP) has been shown to reduce reflux in individuals with and without sleep apnoea, by an unknown mechanism. The aim of this study was to determine the effect of CPAP on swallow-induced LOS relaxation.

Methods. Measurements were made in 10 healthy, awake, supine individuals. Oesophageal (P_{oes}), LOS (P_{LOS}), gastric (P_g) and barrier pressure to reflux (P_b=P_{LOS}-P_g) were recorded using a sleeve catheter during 5 swallows of 5 ml of water. This was repeated at 4 levels of CPAP (0, 5, 10 and 15 cmH_20). Pressures were measured during quiet breathing and during the LOS relaxation associated with a swallow. Duration of LOS relaxation was also recorded.

Results. During quiet breathing CPAP significantly increased end-expiratory P_{oes}, P_{LOS}, P_g and P_b ($p<0.05$). The increase in P_b was due to a disproportionate increase in P_{LOS} compared to P_g ($p<0.05$). During a swallow, CPAP increased nadir P_{LOS}, P_g and P_b and decreased the duration of LOS relaxation (4.1 s with 0 cmH_20 CPAP to 1.6 s on 15 cmH_20 CPAP, $p<0.001$).

Conclusions. P_b increased with CPAP by virtue of a disproportionate increase in P_{LOS} compared to P_g. This may be due to either reflex activation of LOS smooth muscle, or non-specific transmission of pressure to the LOS. The findings suggest CPAP may make the LOS less susceptible to reflux by increasing P_b and decreasing the duration of LOS relaxation.

5.3 INTRODUCTION

Gastro-oesophageal reflux is common with approximately 20% of the general community reporting reflux symptoms on a weekly basis.[5] Nocturnal reflux has been reported to occur in 9-11% of the population[1] and may be particularly harmful to the oesophagus because of the associated prolonged acid clearance time.[9] Obstructive sleep apnoea (OSA) is an aggravating factor for nocturnal reflux, presumably because of the development during obstructive events of pressure gradients across the lower oesophageal sphincter (LOS) that favour reflux.

The LOS is a high-pressure zone located between the oesophagus and stomach, which acts as a barrier to reflux. Pressure within the sphincter is generated by contraction of oesophageal smooth muscle and of the crural diaphragm during inspiration. Baseline LOS pressure fluctuates with respiration, increasing during inspiration as a consequence of diaphragm contraction. In normal, healthy individuals relaxation of the LOS is initiated by swallowing and lasts until the oesophageal peristaltic contraction reaches the sphincter segment. Such relaxation is essential in order to allow passage of the swallowed bolus from the oesophagus to the stomach but may also result in stomach contents entering the oesophagus. The LOS may also relax in the absence of oesophageal peristaltic contraction. Such transient LOS relaxations, which usually occur in response to gastric distension,[114] underlie the majority of reflux events that occur during both wakefulness and sleep.[106]

Continuous positive airway pressure (CPAP), the mainstay therapy for OSA, has been shown to reduce reflux events and improve symptoms of overnight reflux in individuals with OSA, reflux disease and achalasia.[20,24-26] While the mechanism by which CPAP

reduces reflux is unknown several theories have been proposed. It is possible that CPAP exerts its effects by simply reducing the number of arousals from sleep, as reflux episodes are known to occur during periods of arousal rather than during stable sleep.[106,246] This consideration could be particularly applicable in OSA where sleep is fragmented by upper airway obstruction-related arousals that are abolished by CPAP therapy. However, the finding that CPAP also reduces reflux in subjects without OSA,[25] in whom it has no effect on arousal frequency, suggests that its primary effect on reflux may not be mediated by this mechanism.

Other potential mechanisms by which CPAP could reduce reflux relate to its effects on pressure gradients across the LOS and possibly to changes in the intrinsic function of the LOS itself. Abolition of negative intrathoracic pressure swings accompanying upper airway obstruction is likely to be important in patients with OSA. More generally, CPAP increases intrathoracic pressure, which may mechanically compress the oesophagus[510] and decrease the pressure gradient across the diaphragm. Both of these changes could potentially reduce reflux. There is also some evidence to suggest CPAP causes a reflex increase in basal LOS pressure,[25] however the mechanism of such an increase is unknown. Further, the relevance of such changes is unclear, given that reflux events usually occur during relaxation of the LOS.[106]

To date there has been no study investigating the effect of CPAP on LOS pressure during periods of transient relaxation, when reflux is known to occur. Thus the primary aims of this study were to determine whether varying levels of CPAP influenced LOS pressure during periods of swallow-induced LOS relaxation and to examine the possible mechanisms underlying any such change.

5.4 METHODS

5.4.1 Subjects

Studies were performed on 10 normal (5 male, 5 female) healthy volunteers with no history of gastro-oesophageal or pulmonary disease. Subjects were 31 (7) yrs of age with a BMI of 24 (3) $kg.m^{-2}$. Written informed consent was obtained prior to participating in the study, which was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital.

5.4.2 Measurements

5.4.2.1 Manometry

A purpose built multilumen silicone manometry catheter (O.D. 2.5 mm) (Dentsleeve Pty Ltd., SA, Australia) was passed via the nares into the oesophagus to simultaneously record pressure changes within the oesophagus, LOS and stomach. The catheter incorporated a 6 cm sleeve sensor for measuring LOS pressure, 5 side holes above the sleeve to measure oesophageal pressure and 2 side holes below the sleeve to measure gastric pressure. Side holes were spaced at 4 cm intervals. All manometric channels were continuously infused with distilled water at a rate of 0.15 $ml.min^{-1}$ using a low compliance capillary infusion pump (Dentsleeve Pty Ltd). The infusion system was connected to pressure transducers (Abbott Australasia Pty Ltd, NSW, Australia) that were calibrated prior to each study. The sleeve was positioned across the LOS using a slow pull-through technique.[103] Absolute pressures for the sleeve and side holes were referenced to atmospheric pressure.

5.4.2.2 Airway Pressure

Subjects breathed via a tight fitting nasal mask (Sullivan Mirage, ResMed Ltd, North Ryde, NSW) for the duration of the study. Pressure was measured at the mask via a sideport (model 143 PC, microswitch, Honeywell Morristown, NJ). Prior to each study the pressure transducer was calibrated against a water manometer.

5.4.3 Protocol

Subjects were asked to limit fluid intake for two hours before the study, abstain from caffeine and high fat foods, and to have only a light meal 2-3 hours beforehand. All measurements were made in the supine position during wakefulness. CPAP of 0, 5, 10 and 15 cmH_20 were applied in random order via a nasal mask (BiPAP, Respironics Inc.). At each level of CPAP subjects were asked to perform 5 swallows of 5 ml of water. Each swallow was preceded by at least 30 s of stable LOS pressure, which was monitored continuously. The time at which each swallow was initiated was recorded using an event marker. Double swallows were excluded from subsequent analysis. Throughout each study all signals were recorded continuously on a computerised data acquisition and analysis system (Powerlab 16S, ADInstruments, Castle Hill, New South Wales, Australia).

5.4.4 Analysis

5.4.4.1 Data analysis

End-expiratory oesophageal pressure (P_{oes}), lower oesophageal sphincter pressure (P_{LOS}), gastric pressure (P_g), transdiaphragmatic pressure ($P_{di}=P_g-P_{oes}$) and barrier pressure ($P_b=P_{LOS}-P_g$) were measured for each of the 5 breaths preceding a swallow.

During each swallow-induced LOS relaxation, measurements of nadir P_{LOS}, P_g and nadir P_b were obtained. Duration of LOS relaxation was defined as the time the LOS was less than 20% of baseline pressure.[114] Peristaltic wave amplitude was defined as the peak P_{oes} in each oesophageal pressure channel referenced to basal intraoesophageal pressure. Peristaltic wave velocity was calculated by measuring the time between the onset of contractions taking into account the distance between the most proximal oesophageal side hole and the most distal oesophageal side hole (*i.e.* a total distance of 16cm). Intrabolus pressure (the pressure within the water bolus) was defined as the average of the plateau/ramp pressure before the onset of the peristaltic contraction wave referenced to basal intraoesophageal pressure.[530,531] The border between these pressure regions was visually determined by the investigators.

5.4.4.2 Statistical analysis

Differences in P_{oes}, P_{LOS}, P_g, P_{di} and P_b among levels of CPAP were compared using one-way repeated measures ANOVA. Differences in intrabolus pressure, peristaltic wave amplitude and velocity and duration of LOS relaxation were also compared using one way-repeated measures ANOVA. A two-way repeated measures ANOVA was used to compare the magnitude of changes in P_{oes}, P_g and P_{LOS} with CPAP application. Post hoc analyses were performed using the Student-Neuman-Keuls test. Results are presented as mean (standard deviation). A p-value <0.05 was considered statistically significant.

5.5 RESULTS

5.5.1 Effect of CPAP on basal LOS pressure

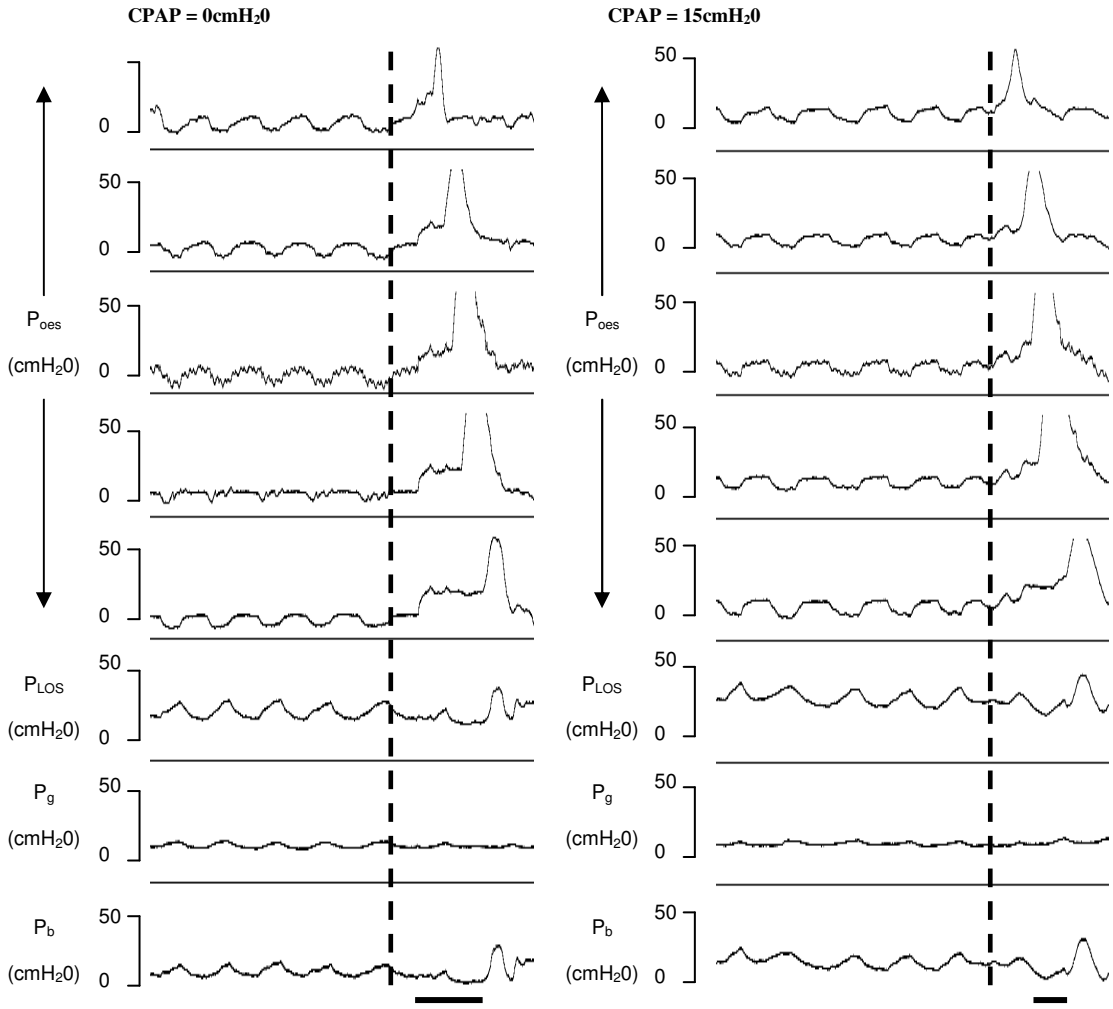

Figure 5.1. *Representative polygraph example showing the effect of swallowing 5ml of water on oesophageal pressure (P_{oes}), lower oesophageal sphincter pressure (P_{LOS}), gastric pressure (P_g) and barrier pressure (P_b) with 0 cmH_20 CPAP (left example) and with 15 cmH_20 CPAP (right example). The dashed line shows initiation of the swallow. The solid line shows the duration of sphincter relaxation. The subject was supine.*

Application of increasing levels of CPAP systematically increased P_{oes}, P_{LOS}, P_g and P_b (Figures 5.1 and 5.2). Compared to breathing at atmospheric pressure (0 cmH_20) a

CPAP of 15 cmH_20 increased P_{oes}, P_{LOS}, P_g and P_b by 10.1, 7.9, 3.4 and 4.1 cmH_20, respectively ($p<0.05$ for all). The absolute values are summarised in Table 5.1. At each level of CPAP the magnitude of increase in P_{oes} was greater than the magnitude of increase in P_{LOS} ($p<0.05$), which in turn was greater than the magnitude of increase in P_g ($p<0.05$). A CPAP of 15 cmH_20 significantly decreased P_{di} by 6.7 cmH_20 ($p<0.05$).

Table 5.1. Absolute pressures with CPAP application

CPAP (cmH_20)	0	5	10	15
Baseline LOS function:				
P_{LOS} (cmH_20)	15.4 (5.3)	18.5 (4.8)	20.9 (4.3)	23.3 (5.8)
P_g (cmH_20)	6.4 (4.4)	7.6 (4.3)	8.4 (4.4)	9.8 (4.8)
P_b (cmH_20)	8.5 (4.0)	10.7 (4.5)	11.9 (4.6)	12.6 (5.9)
Swallow-induced LOS relaxation:				
P_{LOS} (cmH_20)	8.3 (4.7)	10.8 (4.6)	12.4 (3.1)	15.6 (4.9)
P_g (cmH_20)	6.7 (4.1)	8.1 (4.1)	8.7 (3.7)	10.6 (4.2)
P_b (cmH_20)	-0.6 (4.2)	1.2 (5.2)	2.4 (5.0)	4.0 (6.0)
Duration of LOS relaxation (s)	4.1 (1.1)	2.6 (1.2)	1.9 (1.1)	1.6 (1.7)
Oesophageal body:				
P_{oes} (basal) (cmH_20)	-1.3 (2.1)	2.9(3.1)	5.7 (3.8)	8.8 (4.4)
Intrabolus pressure (distal)(cmH_20)	10.1 (3.2)	7.8 (3.1)	7.1 (2.1)	6.5 (2.1)
Peristaltic wave amplitude (cmH_20)	102.0 (48.8)	100 (49.8)	99.2 (41.3)	98.7 (40.6)
Peristaltic wave velocity ($cm.s^{-1}$)	2.5 (0.5)	3.0 (0.6)	3.5 (0.9)	3.7 (0.9)
Diaphragm:				
Diaphragm (P_{di}) (cmH_20)	7.7 (5.4)	4.7 (4.4)	2.7 (4.4)	1.0 (4.4)

Subjects awake, supine. Results presented as mean (SD).

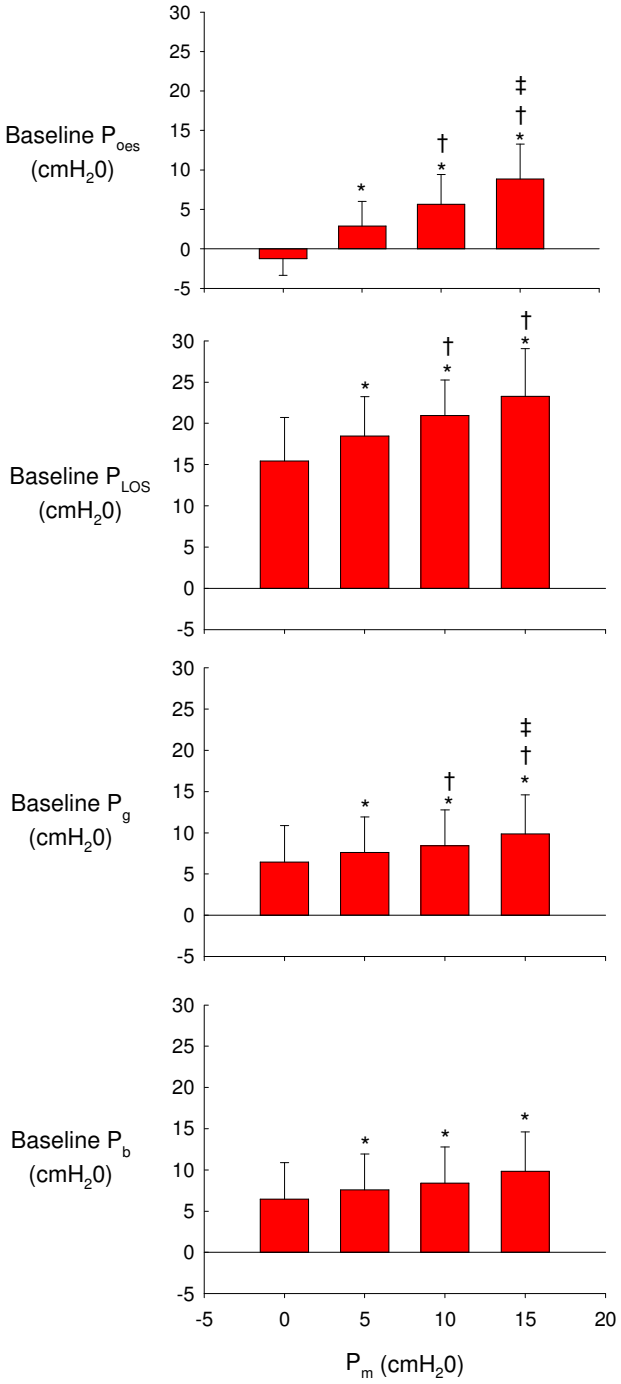

Figure 5.2. *Change in lower oesophageal sphincter pressure (P_{LOS}), gastric pressure (P_g) and barrier pressure (P_b=P_{LOS}-P_g) with increasing levels of mask pressure (P_m, cmH_20) during quiet breathing (5 breaths before each swallow). Mean of 5 trials. Mean ± SD, n=10. *p<0.05 vs P_m=0 cmH_20; †p<0.05 vs P_m=5 cmH_20; ‡p<0.05 vs P_m=10 cmH_20.*

5.5.2 Effect of CPAP during swallow-induced LOS relaxation

Progressively increasing CPAP also systematically increased the nadir P_{LOS}, P_g and P_b during a swallow-induced LOS relaxation (Table 5.1, Figure 5.1, Figure 5.3). Compared to a swallow performed at atmospheric pressure, a CPAP of 15 cmH_20 significantly increased nadir P_{LOS}, P_g and P_b during swallow-induced LOS relaxation by 7.3, 3.9 and 4.6 cmH_20, respectively ($p<0.05$). At a CPAP of 15 cmH_20 the magnitude of increase in nadir P_{LOS} was greater than the increase in nadir P_g ($p<0.05$). A CPAP of 15 cmH_20 significantly decreased the duration of LOS relaxation by 2.5 s ($p<0.001$, Table 5.1, Figure 5.4).

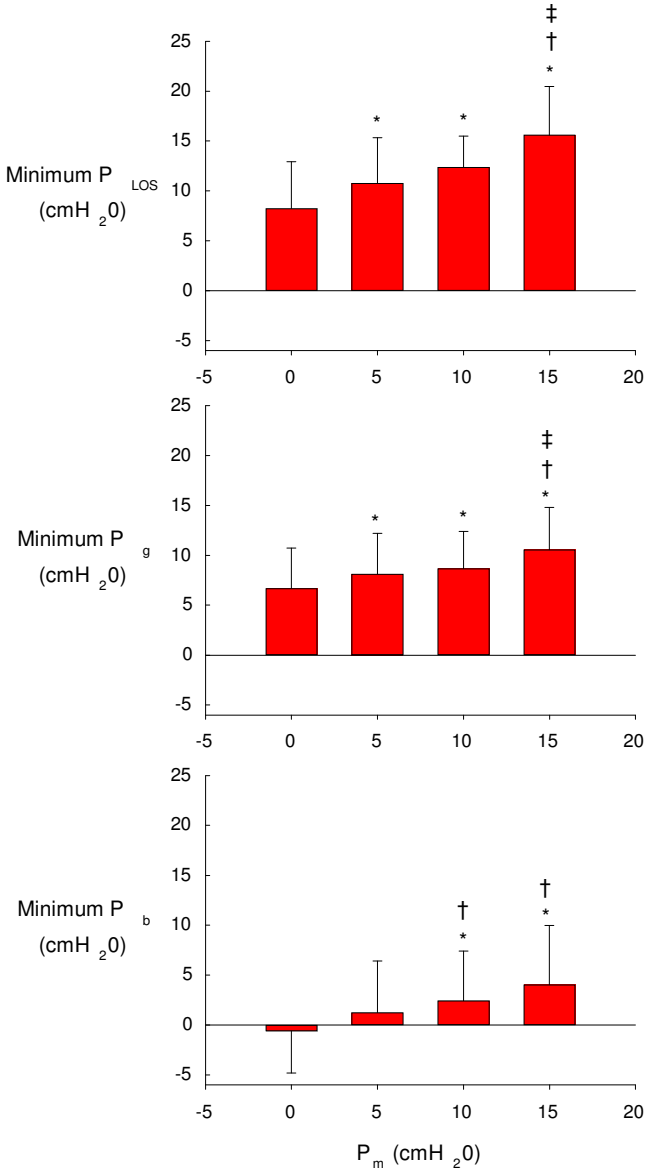

Figure 5.3. *Change in nadir lower oesophageal sphincter pressure (P_{LOS}), gastric pressure (P_g) and barrier pressure (P_b=P_{LOS}-P_g) with increasing levels of mask pressure (P_m, cmH_20) during swallow-induced LOS relaxation. Mean of 5 trials. Mean ± SD, n=10. *p<0.05 vs P_m=0 cmH_20; †p<0.05 vs P_m=5 cmH_20; ‡p<0.05 vs P_m=10 cmH_20.*

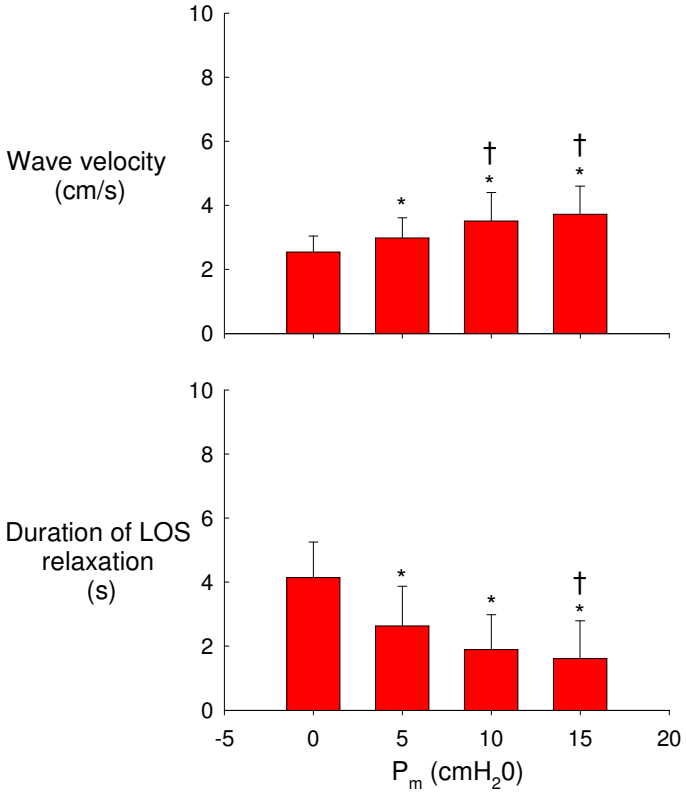

Figure 5.4. *Change in peristaltic wave velocity and change in duration of LOS relaxation with increasing levels of mask pressure (P_m). Mean of 5 trials. Mean ± SD, n=10. $^{*}p<0.05$ vs $P_m=0$ cmH_20; $^{\dagger}p<0.05$ vs $P_m=5$ cmH_20.*

Mean peristaltic wave amplitude over all 5 recording sites was 102.0 (48.8) cmH_20 and was unaffected by CPAP application (data not shown). In contrast, peristaltic wave velocity progressively increased with increasing levels of CPAP, with a 15 cmH_20 CPAP increasing peristaltic wave velocity by 1.2 $cm.s^{-1}$ compared to a CPAP of 0 cmH_20. CPAP decreased intrabolus pressure by 3.6 cmH_20 with 15 cmH_20 CPAP compared to a CPAP of 0 cmH_20 ($p<0.05$)(Table 5.1).

5.6 DISCUSSION

The major findings of this study in healthy, asymptomatic individuals were that nasal CPAP: (i) systematically increased both basal end-expiratory P_b during quiet breathing and nadir P_b during swallow-induced LOS relaxation; (ii) systematically increased the velocity of swallow-induced oesophageal peristalsis; and (iii) decreased the duration for which the LOS was relaxed following a swallow. To the extent that these findings reflect physiological function in individuals with gastro-oesophageal reflux, they suggest that the beneficial effects of CPAP on reflux[20,24-26] may be mediated by an increased gastro-oesophageal anti-reflux barrier during swallow-induced relaxation and decreased time of LOS relaxation.

5.6.1 The effect of CPAP on the Lower Oesophageal Sphincter

The strength of the LOS to act as a barrier to reflux is reflected in the difference in pressure between the pressure generated within the LOS (P_{LOS}) and the pressure generated below it (P_g), the LOS barrier pressure ($P_b=P_{LOS}-P_g$). Accordingly, an increase in P_b, indicative of an increased capacity of the LOS to act as a barrier to reflux, could occur as a result of either a decrease in P_g in excess of P_{LOS} or by a greater increase in P_{LOS} than P_g. The present study shows that increasing levels of CPAP systematically increases end-expiratory P_{LOS}, P_g and P_b during quiet breathing and nadir P_{LOS} and P_b during swallow-induced LOS relaxation. In both circumstances the increase in P_b was the result of a disproportionate increase in P_{LOS} compared to P_g.

There are several potential mechanisms for the effect of CPAP on LOS pressure. Contraction of the crural diaphragm during inspiration has been shown to contribute to P_{LOS}.[532] It is therefore possible that the CPAP-induced increases in P_{LOS} and P_b may

relate to CPAP-induced shortening of the crural diaphragm.[533] However we believe this to be unlikely given that all measurements were obtained at end-expiration when the diaphragm is electrically and mechanically quiet.[534] Further, end-expiratory P_{di}, which reflects passive tension within the diaphragm, decreased rather than increased with increasing levels of CPAP.

The CPAP-induced increases in P_{LOS} and P_b may be a consequence of the increase in P_g which occurs as a result of downward displacement of the diaphragm and compression of the stomach.[535] Several studies have shown that an increase in P_g can result in a reflex increase in LOS tone.[536-539]

Other potential mechanisms for the CPAP-induced increases in P_{LOS} and P_b relate to the effect of CPAP on intraoesophageal pressure and oesophageal shortening and peristalsis. Non-specific transmission of positive pressure from the oesophagus to the LOS could increase P_{LOS}, for example via oesophageal compression.[510] Supporting this hypothesis is the finding that at all levels of CPAP, P_{oes} increased more than P_{LOS}. CPAP may also affect oesophageal shortening during swallow-induced LOS relaxation by preventing axial movement of the LOS and therefore inhibiting complete sphincter opening, increasing nadir P_{LOS} and P_b. Last, nadir P_b could also be increased a result of an increase in intrabolus pressure, which would impose a pressure on the LOS pressure sensor during LOS relaxation. However this is unlikely given that intrabolus pressure decreased rather than increased during CPAP.

While the present study is the first to examine the effect of CPAP on LOS function during swallow-induced relaxation, several earlier studies have examined the effect of CPAP on basal LOS pressure. In normal, healthy individuals during wakefulness,

Fournier *et al* reported a small (2 cmH_20) but non-significant increase in LOS pressure with a CPAP of 8 cmH_20 CPAP.[510] Kerr *et al* [25] reported a 13.2 cmH_20 increase in basal LOS pressure at a CPAP of 8 cmH_20 in sleeping individuals with reflux disease. In the present study we recorded a 3 cmH_20 increase in P_{LOS} with 5 cmH_20 CPAP, and a 5.5 cmH_20 increase in P_{LOS} with 10 cmH_20 CPAP. The reason for the differences between the findings of these studies is not immediately clear, but may relate to differences in the phase of respiratory cycle at which P_{LOS} was measured, whether changes in P_{LOS} were expressed relative to P_g, differences in patient groups and whether the study was performed during wakefulness or sleep.

5.6.2 Effect of CPAP on the oesophageal body

CPAP also caused an increase in the velocity of the swallow-induced oesophageal peristaltic wave. Such a finding is consistent with those of Fournier.[510] We also noted a decrease in the duration of LOS relaxation. This change may be related to the increase in peristaltic wave velocity, as the swallow-induced LOS relaxation will persist for as long as the peristaltic contraction takes to reach the distal oesophageal segment.[540-542]

The mechanism underlying the effect of CPAP on peristaltic wave velocity is unclear. It may be that increased oesophageal pressures resulting from CPAP application are responsible for the increase in peristaltic wave velocity. It may also be related to its effect on oesophageal smooth muscle and/or gastric pressure. In much the same way that the force-velocity relationship of circular oesophageal smooth muscle is dependent upon the preload, or the amount the muscle is stretched (bolus size),[543] it is possible that the CPAP-related increase in lung volume and associated downward displacement of the diaphragm and mediastinal contents[535] exerts a longitudinal stretching force on the

oesophagus, increasing preload on longitudinal muscle fibres and increasing the velocity of force propagation along the oesophagus. Alternatively, application of CPAP effectively leads to increased oesophageal outflow resistance. [536] Based on previous studies, one might therefore have expected peristaltic velocity to slow rather than increase.[540,544] The reason for the increase in velocity observed in our study and the discrepancy with the previous findings remains unclear.

5.6.3 Implications for gastro-oesophageal reflux

This study suggests that CPAP may decrease reflux by two mechanisms: (i) by increasing the mechanical barrier to reflux and (ii) by decreasing the length of time the LOS is relaxed and therefore susceptible to being breached by abdominal contents. It is also possible that the increase in oesophageal pressure limits proximal acid migration and accelerates oesophageal clearance. Considering that the majority of reflux events occur during periods of transient relaxation it appeared important to investigate the effect of CPAP under such a condition. Our data shows that CPAP increased P_b and decreased relaxation duration in a dose-dependent fashion. This implies that a greater reduction in reflux might be expected with a higher level of CPAP. Consistent with this hypothesis the findings of Green *et al*[20] in 189 subjects with OSA and nocturnal reflux showed a strong correlation between improvements in reflux symptoms and the magnitude of applied CPAP.

Several potential limitations exist when extrapolating the observations from the present study to the circumstances surrounding spontaneous reflux events. First, we studied healthy, asymptomatic individuals, not individuals with reflux disease. While this may be an important distinction, it is notable that Kerr *et al*[25] reported a similar effect of

CPAP on baseline P_{LOS} in individuals with and without reflux disease. However this may not be the case for all patient groups as Shoenut *et al*[26] has previously shown that CPAP reduces reflux in individuals with achalasia but not with scleroderma. Second, we investigated the effect of CPAP on swallow-induced LOS relaxation, not during transient LOS relaxations, which usually accompany reflux events. Whilst transient LOS relaxations share elements of the swallow-induced relaxation neural pathway, specific studies on transient LOS relaxations are needed to confirm the observations on swallow-induced LOS relaxation. Finally, we studied our subjects during wakefulness rather than at night during sleep when CPAP is usually applied. However, it is notable that the pressure changes surrounding reflux events during wakefulness and sleep have previously been shown to be similar[106], suggesting that the findings from the present study may indeed be directly referable to any changes that may occur during sleep.

5.7 ACKNOWLEDGEMENTS

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CHAPTER SIX

Characteristics of Nocturnal Gastro-oesophageal Reflux Events in Obstructive Sleep Apnoea

6.1 FOREWORD

The prevalence of nocturnal GOR symptoms is significantly greater in OSA patients or those at high risk of OSA in the general community (Chapter Three). The mechanisms underlying this increase are investigated in this chapter by determining the effect of sleep-related upper airway obstruction on the primary barrier to GOR, the LOS, and undertaking a careful examination of the temporal relationship between obstructive respiratory events and *nocturnal*GOR events.

Continuous Positive Airway Pressure significantly reduces *nocturnal*GOR symptoms (Chapter Three). This may be due to an increase in the mechanical barrier to GOR (Chapter Five). These previous studies were undertaken in awake, healthy individuals, thus extrapolation of these findings to sleeping individuals with OSA is limited. Therefore, the studies in this Chapter investigated the effect of CPAP on LOS function in OSA patients during sleep.

This chapter is in preparation for submission to the ***Journal of Applied Physiology*** *for consideration for publication.*

6.2 ABSTRACT

Background. Obstructive Sleep Apnoea (OSA) is associated with an increase in nocturnal gastro-oesophageal reflux (*nocturnal*GOR) events and symptoms. Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to reduce *nocturnal*GOR in patients with OSA. This study sought to determine the mechanism(s) underlying the increase in *nocturnal*GOR in OSA patients and the effect of CPAP on *nocturnal*GOR events.

Methods. Eight patients with OSA and *nocturnal*GOR symptoms underwent polysomnography with oesophageal manometry and dual oesophageal pH monitoring. The first half of the night was spent without CPAP and the second half with 10cmH_20 CPAP.

Results: During the first half of the night there was an average of 2.7±1.8 *nocturnal*GOR events per hour compared to 70±39 obstructive respiratory events per hour. Of these *nocturnal*GOR events 57% occurred either during an apnoea/hypopnoea or within 10 s of airway reopening. Upper airway obstruction did not affect the barrier pressure provided by the LOS. CPAP significantly reduced oesophageal acid exposure (15±12% and 4±8%, $p<0.05$) and tended to decrease the number of *nocturnal*GOR events (2.7±1.8 and 1.3±2.3 per hour, $p=0.15$). CPAP decreased the duration of LOS relaxation and tended to increase the nadir pressure during LOS relaxation.

Conclusion. There was no convincing evidence of a direct causal relationship between upper airway obstruction and *nocturnal*GOR events. Furthermore, upper airway obstruction had no effect on the LOS, suggesting that the generation of negative intrathoracic pressures does not precipitate GOR. Finally, CPAP appears to reduce *nocturnal*GOR by increasing the mechanical barrier to GOR.

6.3 INTRODUCTION

Gastro-oesophageal reflux (GOR) is a common condition, characterised by symptoms such as heartburn and acid regurgitation.[46] When awake, GOR events are usually brief because of the effects of powerful protective mechanisms such as swallowing and oesophageal peristalsis. When asleep these protective mechanisms are abolished, resulting in GOR events which are usually only cleared with return of swallowing and peristalsis on arousal from sleep. These longer events increase oesophageal acid exposure and risk of oesophageal injury.[8,9]

Nocturnal GOR (*nocturnal*GOR) may be a particular problem for patients with obstructive sleep apnoea (OSA). OSA is characterised by repetitive narrowing or collapse of the upper airway during sleep with the development of large negative intrathoracic pressures during inspiratory efforts against the occluded airway, until restoration of airway patency with arousal from sleep. OSA is associated with increased occurrence of nocturnal symptoms of GOR[20] as well as increased number and length of overnight GOR episodes.[18] While OSA and GOR share common risk factors, a recent study in morbidly obese patients has reported a significant association between GOR disease and OSA, independently of age, gender and BMI.[498]

The precise mechanism underlying the increase in *nocturnal*GOR in OSA patients remains unclear. Possibilities include the generation of negative intrathoracic pressures during an obstructive event sufficient to overcome the barrier provided by the lower oesophageal sphincter (LOS),[24,489] or the effect of the repetitive arousals which terminate the obstructive event, as *nocturnal*GOR events have been shown to occur during arousal from sleep.[106,113,246-248] If GOR is precipitated by obstructive events then

one would expect to observe a close temporal relationship with the apnoea itself or the apnoea-related arousal. However studies report variable results in this regard.[18,246,259]

Continuous positive airway pressure (CPAP), the mainstay therapy for OSA, has been shown to reduce reflux events and improve symptoms of *nocturnal*GOR in patients with OSA, reflux disease and oesophageal disorders.[20,24,25] Potential mechanisms by which CPAP could reduce reflux include its effects on LOS pressure or function.[25,524]

The present study sought to: i) determine the temporal relationship of *nocturnal*GOR events with apnoea/hypopnoea and arousal; ii) determine the effect of upper airway obstruction on the barrier function of the LOS; iii) characterise the mechanism of LOS failure for each nocturnal GOR event; (iv) determine the effect of CPAP on LOS function during sleep; and v) determine the mechanism underlying the decrease in GOR with CPAP treatment.

6.4 METHODS

6.4.1 Subjects

Eight patients who had been diagnosed with OSA and symptomatic *nocturnal*GOR attended our sleep laboratory for overnight polysomnography with simultaneous oesophageal manometry and pH monitoring. These patients had been identified from their responses to a GOR symptom questionnaire completed by all sleep clinic patients. Specifically, each patient had reported *nocturnal*GOR symptoms (either nocturnal heartburn or acid regurgitation) at least once a week for the previous 12 months.[5] All patients were undergoing CPAP therapy for their OSA at the time of the study.

6.4.2 Protocol

For 48 hours before the study subjects were required to cease any proton-pump inhibitors, H_2-receptor antagonists or antacids and abstain from caffeinated, acidic and high-fat foods and drinks. Each subject was required to fast for 5 hours before the study.

Measurements of neck, waist and hip circumference; height, weight; and spirometry were obtained on arrival to the sleep laboratory (approximately 5pm). Two catheters were inserted into the oesophagus via the nares, one for oesophageal manometry and the other to monitor oesophageal pH. Each subject then underwent manometry to assess oesophageal motility, determine LOS position and measure oesophageal and gastric pressures. These measurements were obtained while supine and awake. Patients then were fed a standardised meal consisting of meat or fish, potatoes, cooked vegetables, ice cream and milk (50% fat, 30% carbohydrate, 20% protein, totaling approximately 800 calories) following which they were instrumented for overnight polysomnography. The monitoring period was divided into the 'postprandial period', defined as the 2 hour period following completion of the meal and the 'nocturnal period', defined as the time between 'lights out' at night and 'lights on' the next morning.

In all subjects the first half of the night was spent without CPAP. During the second half of the night 10 cmH_20 CPAP was applied via a nasal mask. Oesophageal manometry and pH monitoring were performed throughout the night. All manometry and pH signals were recorded on a computerised data acquisition and analysis system (Powerlab 16S, ADInstruments, Castle Hill, New South Wales, Australia).

The study was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital and written informed consent was obtained from each patient prior to participation.

6.4.3 Measurements

6.4.3.1 Oesophageal manometry

A purpose built manometry catheter (O.D. 2.5 mm) (Dentsleeve Pty Ltd., SA, Australia) was passed via the nares into the oesophagus to simultaneously record pressure changes within the oesophagus, LOS and stomach. The catheter incorporated a sleeve sensor for measuring LOS pressure (P_{LOS}), and side holes to measure pharyngeal (P_{ph}), oesophageal (P_{oes}) and gastric pressure (P_g). The barrier pressure (P_b) of the LOS was defined as P_{LOS} relative to P_g (*i.e.* $P_b=P_{LOS}-P_g$). The pharyngeal side hole was perfused with air at a rate of 0.08ml.min^{-1}. All other manometric channels were continuously infused with distilled water at a rate of 0.15 ml.min^{-1} using a low compliance capillary infusion pump (Dentsleeve Pty Ltd). The infusion system was connected to pressure transducers (Abbott Australasia Pty Ltd, NSW, Australia) that were calibrated prior to each study. The sleeve was positioned across the LOS using a slow pull-through technique.[103] Absolute pressures for the sleeve and side holes were referenced to atmospheric pressure.

Before the meal, manometry was used to determine oesophageal motility both on and off CPAP. Oesophageal motility was determined, while supine, by asking each subject to swallow 5 ml of water a total of 10 times, both with and without application of 10 cmH_20 of CPAP. Each swallow was preceded by at least 30s of stable oesophageal function. P_b was measured for each of the 5 breaths preceding a swallow; the mean of the end-expiratory pressures for these 5 breaths was then used to define basal P_b. Peristaltic wave

amplitude and velocity were measured for each swallow. Peristaltic wave amplitude was defined as the peak P_{oes} in each oesophageal side hole, referenced to baseline P_{oes}. Ineffective oesophageal motility was defined as a distal P_{oes} amplitude during a peristaltic wave of <30mmHg (41 cmH_20) or if >30% of peristaltic waves in the distal oesophagus occurred simultaneously.[545] The LOS was defined as hypotonic if the baseline P_b was <10mmHg (13.7 cmH_20).[546]

During the nocturnal period, manometry was used to identify LOS relaxations while off and on CPAP. These were classified as transient LOS relaxations (TLOSR) or swallow-induced LOS relaxations (swallow-induced LOSR). A TLOSR was defined if all of the following criteria were met: i) the absence of swallowing for 4 s before to 2 s after the onset of LOS relaxation; ii) a relaxation rate of ≥1 $mmHg.s^{-1}$; iii) time from onset to complete relaxation of ≤ 10 s; and iv) a nadir pressure of ≤ 2 mmHg.[114] A swallow-induced LOSR was defined as a LOS relaxation which occurred during a primary peristaltic wave resulting from a swallow. Only LOS relaxations associated with single, isolated swallows were analysed. The duration of each TLOSR or swallow-induced LOSR was defined as the time the LOS pressure was less than 20% of baseline pressure.[114] Nadir P_b during an LOS relaxation was also measured, defined as the minimum pressure recorded during the relaxation.

6.4.3.2 Oesophageal pH monitoring.

Oesophageal pH monitoring was performed using a dual-pH catheter (O.D. 1.4 mm, Versaflex pH catheters, Alpine Biomed, Fountain Valley, CA) with antimony pH electrodes placed 15 cm apart. The catheter was inserted into the oesophagus via the nares and positioned so that the pH electrodes were 5 cm (distal pH) and 20 cm (proximal pH) above the LOS, the position of which had been determined previously from

oesophageal manometry. Prior to insertion the pH electrodes were calibrated against solutions of pH 4 and 7. The catheter was connected to an acid reflux monitor (RepHlux Tracer™, Alpine Biomed, Fountain Valley, CA).

Normal pH values for the postprandial and nocturnal periods for the distal and proximal electrodes were derived as follows. Postprandial distal pH values were taken from Mason *et al*[547] (% time below pH 4 <8.4%; number of episodes <11; number of episodes more than 5 mins <2; longest episode <10.5 mins). Postprandial proximal pH values were taken from Vincent *et al*[548] (% time below pH 4 <0.3%; number of episodes <2; number of episodes more than 5 mins = 0; longest episode <1 mins). Nocturnal distal pH values were taken from the supine values reported by Johnson *et al*[549] (% time below pH 4 <1.2%; number of episodes <4; number of episodes more than 5 mins = 0; longest episode <4 mins). Nocturnal proximal pH values were taken from the supine values reported by Dobhan *et al*[550] (% time below pH 4 <0%; number of episodes = 0; number of episodes more than 5 mins = 0; longest episode = 0 mins).

GOR events (whether distal or proximal) were defined according to standard criteria.[111] Specifically, a GOR event was defined by a decrease in oesophageal pH to <4 for longer than 4 s, or an abrupt decrease of more than 1 pH unit if the pH was already <4. Duration of a GOR event was defined as the time from the onset of the event (defined above) to the time when the refluxate was cleared from the oesophagus (defined by an increase in oesophageal pH to >4 for longer than 15 s).

All GOR events in the postprandial and nocturnal periods were identified and manometry used to classify the mechanism of each event as being either due to TSLOR, swallow-induced LOSR, strain or low P_b. Reflux occurring during LOS relaxations

which were independent of swallowing were classified as occurring during TLOSR. Reflux occurring in association with swallow-induced LOSR was classified as swallow-induced. Strain-induced GOR occurred in association with sharp and brief simultaneous positive elevations in gastric and oesophageal pressure. GOR occurring during periods of absent basal P_b were classified as due to low P_b .[45] The mechanism of an event was classified as 'uncertain' if it met none of these criteria.

6.4.3.3 Polysomnography.

Overnight polysomnography included monitoring of: electroencephalogram (C4-A1 and C3-A2); left and right electrooculograms; submental and tibial electromyograms; electrocardiogram; abdominal and thoracic motion; nasal and oral airflow; nasal pressure; oxygen saturation; body position; and sound. These data were collected on a computerised data acquisition system (E-Series, Compumedics, Melbourne, Australia).

Categorisation of sleep stage and respiratory events were performed according to standard criteria.[261,528] The severity of sleep-disordered breathing was defined by the apnoea-hypopnoea index (AHI), which is defined as the number of apnoeas and hypopnoeas per hour of sleep. An apnoea was defined as a reduction in airflow of >80% lasting for more than 10 s and a hypopnoea was defined as either a reduction in airflow of >50%, lasting more than 10 s[261] or a reduction in airflow of <50% plus a 3% oxygen desaturation lasting more than 10 s.[261]

6.4.4 Analyses

6.4.4.1 Data analyses.

The effect of upper airway obstruction on P_b was investigated by measuring end-expiratory P_b for the three breaths before, the final 3 breaths during, and the first 3 breaths after an apnoea or hypopnoea.

During the nocturnal period, the sleep stage in which each reflux event occurred was defined by the sleep stage of the epoch in which the *nocturnal*GOR event began. The temporal relationship between upper airway obstruction and GOR events was determined by recording the presence of an arousal, movement, swallow or obstructive respiratory event in the 10 s, 30 s or 1 min before and after the onset of each reflux event.

6.4.4.2 Statistical analyses

Results are presented as mean ± standard deviation. Statistical analyses were performed using SigmaStat (SysStat Software Inc., San Jose, USA). Paired t-tests were used to compare measurements obtained from the nocturnal period with and without CPAP. One way repeated measures ANOVA was used to compare nadir pressures and duration of LOS relaxation between sleep stages and positions. One way ANOVA was used to compare LOS pressures before, during and after an apnoea and the proportions of GOR events due to each mechanism. Post hoc analyses were performed using the Student-Neuman-Keuls test. Linear regression analyses were used to determine correlations between measures of GOR and sleep variables. A p-value of <0.05 was considered significant for all tests.

6.5 RESULTS

6.5.1 Subjects

Seven males and 1 female aged 52±10 yrs with a BMI of 35±7 $kg.m^{-2}$ were studied (Table 6.1). All had at least moderately severe OSA with a mean of 70±39 $events.hr^{-1}$ in the first half of the night, an increased arousal index and reduced sleep efficiency (Table 6.1). Most obstructive events were hypopnoeas (69±40 $events.hr^{-1}$) with apnoeas relatively few in number (2±3 $events.hr^{-1}$). In the second half of the night, with administration of CPAP, AHI decreased to 5±2 $events.hr^{-1}$ (all hypopnoeas), arousal index returned to within the normal range (≤ 20 arousals per hour) and sleep efficiency improved (Table 6.1).

6.5.2 Manometry during wakefulness and sleep

Manometric measurements while on and off CPAP are shown in Table 6.2. Relative to measurements obtained off CPAP, application of 10 cmH_20 CPAP while awake decreased the duration of swallow-induced LOSR (p=0.028) but had no effect on baseline P_b (p=0.58) or nadir P_b during a swallow-induced LOSR (p=0.38). Five subjects were classified as having a hypotonic LOS[546] (Subjects 1,3,4,6,8) and five as having ineffective oesophageal motility[545] (Subjects 1,4,5,6,8).

During sleep, application of CPAP decreased the duration of swallow-induced LOSR (p=0.002) but had no effect on basal P_b (p=0.25), nadir P_b during swallow-induced LOSR (p=0.15), nadir P_b during a TLOSR (p=0.60) or duration of TLOSR (p=0.76) (Table 6.2). Neither the magnitude of nadir P_b or duration of relaxation of a swallow-induced LOSR or a TLOSR were affected by sleep stage or body position. The

magnitude of end-expiratory P_b was similar, regardless of whether measured before, during or after an obstructive respiratory event (15.4±14.7, 15.8±15.5 and 15.7±16.4 cmH_20, respectively, p=0.95).

Table 6.1. Subject characteristics, sleep architecture and severity of sleep-disordered breathing

				Nocturnal Period													
				Without CPAP							*With CPAP*						
Subject	**Gender**	**Age**	**BMI**	**SE**	**St 1**	**St 2**	**SWS**	**REM**	**ArI**	**AHI**	**SE**	**St 1**	**St 2**	**SWS**	**REM**	**ArI**	**AHI**
		yrs	kgm^{-2}	%	%	%	%	%	$events.hr^{-1}$	$events.hr^{-1}$	%	%	%	%	%	$events.hr^{-1}$	$events.hr^{-1}$
1	M	48	31	52	18	80	0	3	49	38	55	10	78	3	9	19	2
2	M	36	41	76	4	88	0	8	68	83	69	5	70	0	25	21	9
3	M	69	47	36	3	86	10	0	90	93	58	6	46	20	28	18	5
4	M	60	30	80	6	84	0	11	78	93	83	3	58	2	37	12	3
5	F	47	42	70	14	86	0	0	131	140	93	0	56	10	34	11	4
6	M	54	29	66	0	85	10	5	22	30	58	1	73	4	22	17	6
7	M	50	30	76	0	86	0	13	35	26	85	0	86	0	14	10	4
8	M	53	28	72	22	55	8	15	65	58	84	6	34	16	44	10	9
Average		52	35	66	8	81	4	7	67	70	73	4	63*	7	27*	15*	5*
SD		10	7	14	8	11	4	6	34	39	15	4	17	8	12	4	3

*BMI (Body mass index, kg/m^2); Nocturnal (from 'lights off' at night to 'lights on' in the morning); SE (sleep efficiency); St 1 (% of night spent in stage 1 sleep); St 2 (% of night spent in stage 2 sleep); SWS (% of night spent in stage 3 and 4 sleep); REM (% of night spent in rapid eye movement sleep); ArI (arousal index, number of arousals per hour of sleep); AHI (apnea-hypopnea index; number of apneas and hypopneas per hour of sleep). * $p<0.05$ vs without CPAP.*

Table 6.2. Lower oesophageal sphincter manometry

	Awake						**Nocturnal Period**									
	Without CPAP			***With CPAP***			***Without CPAP***					***With CPAP***				
		Swallow-induced LOSR			**Swallow-induced LOSR**			**Swallow-induced LOSR**		**TLOSR**			**Swallow-induced LOSR**		**TLOSR**	
Subject	**Baseline P_{LOS}** (cmH_20)	**nadir P_{LOS}** (cmH_20)	**Length LOSR** (s)	**Baseline P_{LOS}** (cmH_20)	**nadir P_{LOS}** (cmH_20)	**Length LOSR** (s)	**Baseline P_{LOS}** (cmH_20)	**nadir P_{LOS}** (cmH_20)	**Length LOSR** (s)	**nadir P_{LOS}** (cmH_20)	**Length LOSR** (s)	**Baseline P_{LOS}** (cmH_20)	**nadir P_{LOS}** (cmH_20)	**Length LOSR** (s)	**nadir P_{LOS}** (cmH_20)	**Length LOSR** (s)
1	9.0	1.7	4.9	12.2	0.5	2.9	22.3	1.7	5.2	0.1	22.5	36.4	1.2	4.1	-0.3	19.3
2	25.2	1.4	3.9	22.9	2.7	2.4	18.7	4.6	4.8	-1.3	19.7	10.2	2.1	2.5	0.8	24.9
3	13.5	-1.3	1.8	n/a	n/a	n/a	7.7	1.6	2.9	0.7	18.7	19.2	7.2	1.6	3.0	17.0
4	2.3	1.0	4.7	2.8	1.4	3.7	1.9	0.8	5.2	0.5	11.6	9.0	7.9	2.3	0	0
5	24.0	9.6	2.2	24.7	16.8	2.9	12.9	2.4	2.1	-1.0	19.4	24.3	16.3	2.2	5.1	14.6
6	13.4	6.2	2.6	16.0	7.8	1.5	27.7	13.3	5.2	3.3	17.8	14.8	6.6	2.1	2.6	11.1
7	51.9	13.6	3.4	27.2	10.6	1.6	38.3	7.6	3.7	1.5	18.7	45.4	20.2	2.2	2.4	13.8
8	10.3	0.0	6.6	16.2	1.4	2.4	6.0	2.3	4.3	0.7	20.1	19.6	5.4	1.9	0.3	30.9
Average	18.7	4.0	3.8	17.4	5.9	2.5*	16.9	4.3	4.2	0.6	18.1	22.4	8.4	2.4	2.0	16.4
SD	15.4	5.3	1.6	8.4	6.1	0.8	12.3	4.2	1.2	1.4	2.8	12.7	6.6	0.8†	1.9	9.2

*Awake = during oesophageal motility testing at beginning of study, subjects were awake, supine and fasted. Nocturnal period = from 'lights out' at night to 'lights on' the following morning; swallow-induced LOSR = swallow-induced lower oesophageal sphincter relaxation; TLOSR = transient lower oesophageal sphincter relaxation.; P_{LOS} = lower oesophageal sphincter pressure; length LOSR = duration for which the LOS was relaxed. * $p<0.05$ vs Awake, without CPAP. † $p<0.05$ vs Nocturnal, without CPAP.*

6.5.3 Severity of gastro-oesophageal reflux during postprandial and nocturnal Periods

During the postprandial period a total of 66 GOR events were recorded (Table 6.3). Reflux events were observed in all subjects, with an average of 8±4 events per subject, each lasting 73±79 s. Two patients had abnormally high postprandial acid contact time in the distal oesophagus (subjects 4, 5). Subject 7 had abnormally high postprandial acid contact time in the proximal oesophagus (data not shown).

During the first half of the nocturnal period a total of 107 GOR events were recorded. Events were observed in all subjects, averaging 13±10 events per subject, each lasting 230±211 s. All subjects had abnormally high acid contact time in the distal oesophagus (Table 6.3). Seven subjects had abnormally high acid contact time in the proximal oesophagus (subjects 1-6, 8) (data not shown).

During the second half of the nocturnal period, when on CPAP, a total of 23 GOR events were recorded in three subjects (Table 6.3). No reflux events were detected in five of the subjects. Relative to the first half of the night, during the second half of the night the number of *nocturnal*GOR events, duration of longest *nocturnal*GOR event, the number of *nocturnal*GOR events lasting > 5minutes and the average time spent < pH 4.0 in the distal oesophagus were significantly reduced ($p<0.05$ for all). In addition, the number of *nocturnal*GOR events in the proximal oesophagus and the duration of the longest of these events were decreased ($p<0.05$, data not shown). There was no change in the number of events >5 mins ($p=1.0$) and although % time with pH <4.0 was reduced, this did not reach statistical significance ($p=0.26$). Two of the 8 subjects had abnormally high acid contact time in the distal and proximal oesophagus (subjects 1, 8).

Table 6.3. Gastro-oesophageal reflux events during the postprandial and nocturnal periods

	Postprandial period					Nocturnal period									
						Without CPAP					*With CPAP*				
Subject	**No. events**	**Av. Length** s	**No. > 5min**	**Longest Event** (s)	**Time pH <4.0** %	**No. events**	**Av. Length** s	**No. > 5min**	**Longest Event** (s)	**Time pH <4.0** %	**No. events**	**Av. Length** s	**No. > 5min**	**Longest Event** (s)	**Time pH <4.0** %
1	10	34	0	111	5	19	178	5	594	18	10	148	2	601	22
2	5	22	0	16	2	8	92	1	315	4	0	0	0	0	0
3	5	12	0	18	1	6	246	1	1035	7	0	0	0	0	0
4	14	261	6	869	51	35	95	2	648	17	0	0	0	0	0
5	16	61	0	212	14	12	28	0	129	2	1	4	0	4	0.03
6	4	68	0	221	4	6	149	2	482	6	0	0	0	0	0
7	8	58	0	257	6	6	682	2	2872	28	0	0	0	0	0
8	4	65	0	184	4	13	367	4	2254	35	13	107	1	380	12
Average	8	73	1	236	13	13	230	2	1041	15	3*	32*	0.4*	123*	4*
SD	4	79	2	271	10	10	211	2	989	12	5	60	1	234	8

*Postprandial (2 hour period after the completion of meal); Nocturnal (from 'lights off' at night to 'lights on' in the morning); Distal pH electrode (5cm above proximal border of lower oesophageal sphincter); Proximal pH electrode (20cm above proximal border of lower oesophageal sphincter); Number >5mins (number of reflux episodes greater than 5 minutes); % time < 4.0 (percentage of period spent below a pH of 4.0). * p<0.05 vs without CPAP.*

6.5.4 Mechanisms of gastro-oesophageal reflux during postprandial and nocturnal Periods

Comparisons within each period showed that during the postprandial period a significantly greater proportion of GOR events were due to TLOSR than swallow-induced LOSR ($p<0.001$), low P_{LOS} ($p<0.001$) and strain ($p<0.001$). Swallow-induced LOSR, low P_{LOS} and strain accounted for a similar proportion of GOR events (Table 6.4). Within the first half of the nocturnal period (off CPAP), the results were similar, with TLOSR accounting for significantly more GOR events than swallow-induced LOSR ($p=0.003$), low P_{LOS} ($p=0.017$) or strain ($p=0.012$). Within the second half of the nocturnal period (on CPAP), there were no differences in the proportion of GOR events induced by each mechanism ($p=0.59$). Comparisons between the postprandial, nocturnal period (off CPAP) and nocturnal period (on CPAP) showed no differences in the proportion of events induced by each mechanism between the postprandial, nocturnal period (off CPAP) or nocturnal period (on CPAP).

Not all occurrences of swallow-induced LOSR and TLOSR were associated with episodes of GOR. A total of 62 TLOSRs were recorded off CPAP and 34 on CPAP, of which 67±22% and 23±37%, respectively, were associated with GOR ($p=0.003$). A total of 1,292 swallows were recorded when off CPAP and 400 when on CPAP, of which 0.8±0.6% and 0.8±0.7%, respectively, were associated with a GOR event ($p=0.99$). Nadir P_b and duration of swallow-induced LOSR were not different between relaxations that were associated with GOR and those that were not, either off or on CPAP. Duration of TLOSR was not different between those associated with GOR and those that were not, either off or on CPAP. Off CPAP, nadir P_b during TLOSRs associated with GOR was significantly lower than that during TLOSRs not associated with GOR (-0.7±0.9 cmH_20 and 1.9±2.2 cmH_20, respectively, $p=0.028$)).

Table 6.4. Mechanisms of gastro-oesophageal reflux

Subject	Postprandial period						Nocturnal period											
							Without CPAP						*With CPAP*					
		Reflux Mechanism					Reflux Mechanism						Reflux Mechanism					
	No. Events	TLOSR	Swallow-induced	Low P_{LOS}	Strain	Un-certain	No. Events	TLOSR	Swallow-induced	Low P_{LOS}	Strain	Un-certain	No. Events	TLOSR	Swallow-induced	Low P_{LOS}	Strain	Un-certain
		%	%	%	%	%		%	%	%	%	%		%	%	%	%	%
1	10	70	0	0	20	10	21	71	0	10	14	5	9	78	22	0	0	0
2	5	80	0	0	20	0	8	66	12	0	25	12	0	0	0	0	0	0
3	5	100	0	0	0	0	6	66	33	0	0	0	0	0	0	0	0	0
4	14	14	7	50	29	0	35	17	6	57	20	0	0	0	0	0	0	0
5	16	58	19	19	6	0	12	33	8	42	17	0	1	100	0	0	0	0
6	4	50	0	25	25	0	6	33	0	0	67	0	0	0	0	0	0	0
7	8	75	0	12	12	0	6	50	17	17	17	17	0	0	0	0	0	0
8	4	50	50	0	0	0	13	38	15	31	15	0	13	62	8	15	15	0
Average	8	62	10	14	11	1	13	47	11	20	22	2	3	80	10	5	5	0
SD	5	26	18	11	11	4	10	20	11	22	20	4	5	19	11	9	9	0

Data are presented as a proportion of the number of gastro-oesophageal reflux events recorded for that period. No. events = number of gastro-oesophageal reflux events; Postprandial period = 2 hours after the meal; Nocturnal period = from 'lights out' at night to 'lights on' the following morning; TLOSR = transient lower oesophageal sphincter relaxation.

6.5.5 Relationships between reflux and obstructive events

During the first half of the nocturnal period 78% of events occurred during periods of extended wakefulness, 6% during Stage 1, 15% during Stage 2 sleep and 1% during REM sleep. On CPAP, 82% of events occurred during wakefulness, 4% during Stage 1 sleep, 9% during Stage 2 sleep and 4% during REM sleep.

During the first half of the nocturnal period, when off CPAP, the rate of obstructive events (AHI, 70±39 events.hr^{-1}) greatly exceeded the rate of *nocturnal*GOR events (2.7±1.8 events.hr^{-1}). There were no statistically significant relationships between severity of OSA, arousal index or sleep efficiency and any measure related to GOR.

Of the 107 reflux events observed across all patients during the first half of the nocturnal period, 84 occurred during periods of extended wakefulness. Approximately one third of these occurred at the beginning of the wakeful period, with an obstructive respiratory event or arousal occurring in the preceding 60 s in 28% and 33% of these reflux events, respectively. Of the 23 reflux events occurring during sleep, 33% occurred during a hypopnoea and none during an apnoea. An obstructive event or arousal was present in the 10 s preceding these reflux events on 57% and 14% of occasions, respectively. An obstructive event or arousal was present in the 60s preceding these reflux events on 76% and 76% of occasions, respectively. In the 10 s immediately following the onset of *nocturnal*GOR events there was an obstructive event, arousal or swallow in 23%, 10% and 7% of *nocturnal*GOR events. In the 60 s following the onset events there was an obstructive event, arousal or swallow in 76%, 50% and 33% of cases, respectively.

Of the 23 reflux events observed across all subjects during the second half of the nocturnal period (on CPAP), 19 occurred during periods of extended wakefulness. Four of these 19 events occurred at the beginning of the wakeful period, with an obstructive respiratory event or arousal occurring in the preceding 60 s in 10% and 21% of these reflux events, respectively. Of the 4 GOR events that occurred during sleep, there were no obstructive events or arousals in the 10 s preceding a *nocturnal*GOR event, but an arousal was present in the 60 s preceding *nocturnal*GOR events in 3 of the cases. In the 10 s immediately following the onset of reflux events there was an arousal and swallow in one case. In the 60 s immediately following onset an obstructive event was present in 2 cases.

6.6 DISCUSSION

The major findings of this study were that: (i) there was no convincing evidence of a direct temporal (cause and effect) relationship between *nocturnal*GOR events and either obstructive respiratory events or arousals from sleep, although most events occurred in close association with upper airway obstruction or during periods of wakefulness, some of which were initiated by upper airway obstruction; (ii) upper airway obstruction did not alter the barrier pressure of the LOS; and (iii) CPAP abolished *nocturnal*GOR in most subjects due to a CPAP-related increase in the barrier pressure of the LOS.

6.6.1 Mechanism of *nocturnal*GOR in OSA

If apnoeas or hypopnoeas were precipitating factors for *nocturnal*GOR events in patients with OSA then a close temporal relationship between them would be expected. The present study found that 57% of *nocturnal*GOR events occurred either during an

obstructive respiratory event or within 10s of airway reopening. This finding is consistent with other studies reporting between 54% and 70% of *nocturnal*GOR episodes to be associated with an apnoea or hypopnoea.[18,246,259] While suggestive of a causal relationship between obstructive respiratory events and *nocturnal*GOR events these findings could also reflect the large number of apnoea/hypoponeas that occur during the night in patients with OSA and the high probability, by chance, of a *nocturnal*GOR event occurring in proximity to any given respiratory event. We believe this to be likely for several reasons.

Firstly, in the present study the rate of obstructive respiratory events (70±39 events.hr^{-1}) greatly exceeded the rate of *nocturnal*GOR events (2.7±1.8 events.hr^{-1}), indicating a high probability that a *nocturnal*GOR event would occur in proximity to a respiratory event. Secondly, only 14% of *nocturnal*GOR events had an arousal in the preceding 10 s. This suggests that the arousal that accompanies re-establishment of upper airway patency *after* occlusion and the associated surges in sympathetic nervous activity are unlikely to precipitate *nocturnal*GOR events by weakening the barrier to GOR.[505,506,551,552] Thirdly, we found no association between AHI or ArI and severity of *nocturnal*GOR which would be expected if obstructive respiratory events were precipitating *nocturnal*GOR events. Fourthly, upper airway obstruction had little effect on the barrier pressure of the LOS, indicating that that negative intrathoracic pressures generated within the thorax during occluded inspirations do not overwhelm the capacity of the LOS to act as a barrier and "suck acid" out of the stomach.[524] The observation that the barrier pressure provided by the LOS is also maintained during expiration also suggests that obstructive respiratory events are unlikely to precipitate *nocturnal*GOR events. Fifthly, approximately half of the *nocturnal*GOR events within each subject occurred during a TLOSR, with swallow-induced LOSR, strain and low P_b accounting

for 11%, 22% and 20%, respectively. This is a very similar pattern to that reported by others in patients with reflux disease without OSA,[102,113] suggesting that OSA patients with reflux disease do not exhibit a different mechanism of *nocturnal*GOR from those without OSA. Lastly, the frequency of TLOSR in the first half of the night (1.2±0.4 per hour) was similar to that previously reported in healthy subjects and GORD patients without OSA (0.5-3.7 per hour).[45,233] This finding argues against a role of increased parasympathetic (vagal) nervous activity *during* an apnoea[507] in the genesis of TLOSR and *nocturnal*GOR in patients with OSA.

It was notable that a high proportion of the subjects studied had low P_b indicative of a hypotonic LOS and that, relative to healthy normal individuals[546] a higher proportion of GOR episodes were due to low P_b.[106] While this may simply reflect that these subjects were preselected for reflux disease, it is also possible that chronic OSA and the generation of repetitive negative intrathoracic pressures may affect the integrity of the LOS by repetitively loading the diaphragm and phrenoesophageal ligament (which couples the crural diaphragm to the LOS) and weakening the barrier provided by the LOS. To date, the effect of chronic, repetitive upper airway obstruction on the integrity of the LOS or the development of hiatus hernia in individuals with OSA remains unknown.

6.6.2 Mechanism of CPAP in *nocturnal*GOR

CPAP eliminated *nocturnal*GOR in 6 of the 8 subjects and whilst not eliminating it, decreased oesophageal acid exposure in one. One subject had an increase in oesophageal acid exposure with CPAP application. Such a beneficial effect of CPAP has been reported previously.[20,24-28,497,509] When off CPAP, the majority of

*nocturnal*GOR events in these OSA patients occurred during relaxation of the LOS (50% during TLOSR and 10% during swallow-induced LOSR). In the six patients whose *nocturnal*GOR was abolished with application of CPAP, relative to measures obtained off CPAP: (i) the duration of LOS relaxation during swallow-induced LOSR (during wakefulness and sleep) was decreased; (ii) the nadir P_b during both swallow-induced LOSR (during wakefulness and sleep) and TLOSR (during sleep) tended to increase; and (iii) basal LOS pressure (during sleep) tended to increase. These findings are consistent with data previously reported by our group in normal healthy individuals during wakefulness[524] suggesting that CPAP reduces *nocturnal*GOR by increasing the mechanical barrier to GOR.

The CPAP-induced increase in P_b may be due to direct mechanical effects on the LOS either due to non-specific transmission of positive pressure from the oesophagus to the LOS, or to effects on oesophageal shortening during swallow-induced LOS relaxation preventing axial movement of the LOS and therefore inhibiting complete sphincter opening, increasing nadir P_b. Alternatively, the increase in P_b may be reflex-driven, as several studies have shown that an increase in P_g can result in a reflex increase in LOS tone.[536-539]

It was notable that one patient had an increase in oesophageal acid exposure on CPAP. In this patient, CPAP application did not result in an increase in nadir P_b during either swallow-induced LOSR or TLOSR. It is possible that this patient had an impaired reflex response to the CPAP-induced increase in P_g, perhaps as a consequence of repetitive stress on the gastro-oesophageal junction during upper airway occlusion. While evidence to support such a hypothesis is limited, Urata *et al*[507] have suggested that OSA may effect neural control of the gastrointestinal system with impaired gastric

motility in these patients. Furthermore, other reflexes, such as the swallow reflex have been shown to be impaired in patients with OSA.[493]

6.6.3 Limitations

This study has several limitations. Firstly, subjects abstained from acid suppressive medications for 48 hrs, whereas other studies have done so for 5 days prior to a study to avoid acid rebound. However, there is little evidence for rebound acid hypersecretion[553,554] and gastric pH was approximately 2 in all patients prior to commencement of the study arguing against a prolonged effect of proton pump inhibitor therapy on gastric acid secretion. Secondly, the order of CPAP application was not randomised. There is evidence that *nocturnal*GOR occurs significantly more often early in the night due to the proximity to the evening meal.[555] Hence the effect of CPAP on *nocturnal*GOR reported here may not be due to CPAP itself but due to an order-effect. However, the primary focus of this study was not to characterise the influence of CPAP on number or length of *nocturnal*GOR events but to investigate the mechanism of its effect on them. Thirdly, there may have been non-acid reflux episodes which occurred during the night in relation of obstructive events which we were unable to detect with conventional pH monitoring. Fourthly, all subjects were administered 10cmH_20 CPAP, which may have been subtherapeutic in some individuals. While this may explain the variable effects on GOR seen in this study we think it unlikely as 6/8 subjects were controlled with an AHI of <5 events.hr^{-1} with the remaining 2 subjects having an AHI of just 9 events.hr^{-1}. In addition, the two subjects who were not adequately controlled had no GOR on CPAP suggesting inadequate OSA control is unlikely to explain the variability in results. Finally, the relatively small number of subjects in this complex

study introduces the possibility of a Type II error into analyses. However, even with this small group of subjects, differences in LOS function were apparent.

6.6.4 Conclusions

In conclusion, these data do not support the notion of a direct causal relationship between upper airway obstruction and *nocturnal*GOR events. It is the first study to show that upper airway obstruction does not effect the mechanical barrier to GOR, the LOS, suggesting that the generation of negative intrathoracic pressures does not precipitate GOR. The association between OSA and *nocturnal*GOR may be due to more chronic effects of OSA rather than individual obstructive respiratory events. Finally, CPAP appears to reduce *nocturnal*GOR by increasing nadir P_b and decreasing the duration for which the LOS is relaxed during swallow-induced LOSR and TLOSR.

6.7 ACKNOWLEDGEMENTS

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CHAPTER SEVEN

Obstructive Sleep Apnoea and Nocturnal Gastro-oesophageal Reflux are Common in Lung Transplant Patients

7.1 FOREWORD

The association between OSA and *nocturnal*GOR may be of particular importance in individuals who have undergone lung transplantation. GOR has been implicated in the development of BOS, the major limitation to survival after lung transplant, likely due to pulmonary aspiration of refluxed acid. However, given the increased oesophageal acid exposure and risk of aspiration during sleep, *nocturnal*GOR may be of more damage to lung tissue than daytime GOR. The risk of *nocturnal*GOR may be further increased if OSA were also present (Chapters Three and Four).

To date the effect of *nocturnal*GOR and OSA on allograft health in lung transplant patients is unknown. The relative importance of OSA on worsening *nocturnal*GOR in these patients and whether they further increase the risk of lung injury or BOS is also unknown. The studies in this chapter investigated the potential interaction of *nocturnal*GOR and OSA in development of lung injury in lung transplant patients.

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7.2 ABSTRACT

Background. Gastro-oesophageal reflux (GOR) has been implicated in the pathogenesis of bronchiolitis obliterans syndrome (BOS), possibly due to pulmonary aspiration of refluxed acid. Risk of aspiration of gastric contents is increased during sleep due to decreased oesophageal clearance mechanisms and may be further increased by the presence of obstructive sleep apnoea (OSA). This study sought to investigate the relationship between nocturnal GOR, OSA and BOS in a group of lung transplant patients.

Methods. Fourteen lung transplant patients underwent overnight polysomnography with simultaneous dual oesophageal pH monitoring.

Results. Patients had a FEV_1 of 84±15% of their best post-transplant FEV_1. Six of the 14 patients were in various stages of BOS. The average proportion of time spent overnight with a pH of below 4 was 1.7±3.1%. Increased GOR was evident in 8/14 patients during the postprandial period and/or overnight in the distal and/or proximal oesophagus. All patients had OSA (apnoea-hypopnoea index, AHI > 5 events.hr^{-1}). There were no relationships between severity of OSA or GOR and severity of BOS.

Conclusion. Both nocturnal GOR and OSA were common in this group of patients but their occurrences were not related. Neither was there any relationship between the presence of nocturnal GOR or OSA and severity of BOS.

7.2 INTRODUCTION

Gastro-oesophageal reflux (GOR) in lung transplant patients is common, with abnormal oesophageal acid contact time reported in up to 70% of post-transplant patients.[15,17,31,514] It has been suggested that GOR with pulmonary aspiration could be a cause of post-transplant Bronchiolitis Obliterans Syndrome (BOS), the main complication limiting long-term survival. Several findings support this contention. Firstly, GOR has been implicated in the development of diffuse bronchiolitis in the non-transplant population.[519] Secondly, post-transplant patients have significantly more GOR episodes and increased oesophageal acid contact time than pre-transplant, especially when supine.[514] Thirdly, increased acid contact time is associated with decreased lung function in these patients.[15] Finally, lung function and BOS status are improved following surgical treatment for GOR.[16,17,31,32]

Sleep represents a period of high vulnerability to pulmonary aspiration of stomach contents as it is associated with decreased upper oesophageal sphincter tone,[520] reduced oesophageal acid clearance, increased oesophageal acid contact time, increased proximal acid migration[7] and increased pharyngeal aspiration.[556] Therefore, any increase in nocturnal reflux (*nocturnal*GOR) following lung transplantation could potentially increase vulnerability to pulmonary aspiration-related development of BOS.

The risk of nocturnal pulmonary aspiration could also be increased if obstructive sleep apnoea (OSA) were present, as OSA has been associated with an increased number of GOR events and increased severity and frequency of GOR symptoms.[18,20] Compounding this risk is the possibility that lung transplant increases the risk of OSA itself.[557-559]

The aims of this study were to determine: (i) the occurrence of *nocturnal*GOR after lung transplantation; (ii) the occurrence of OSA after lung transplantation; (iii) the relationship between respiratory-related obstructive events and *nocturnal*GOR events; and (iv) the interrelationships, if any, between GOR, OSA and the presence or absence of BOS.

7.4 METHODS

7.4.1 Patients

Fourteen consecutive patients attending a lung transplant clinic were recruited to participate in the study (Table 7.1). Written informed consent was obtained from each patient prior to participation in the study, which was approved by the Hospital's Human Research Ethics Committee.

7.4.2 Protocol

On arrival at the sleep laboratory measurements were obtained of neck circumference, waist circumference, hip circumference, waist-to-hip ratio, height, weight and BMI. While supine and awake each patient underwent oesophageal manometry to test oesophageal motility and determine the location of the lower oesophageal sphincter (LOS). The manometry catheter was then removed, an oesophageal pH catheter inserted and the patient instrumented for overnight polysomnography. Patients were then fed a standardised meal consisting of meat or fish, potato, cooked vegetables, icecream and milk (50% fat, 30% carbohydrate, 20% protein, totaling approx 800 calories). The polysomnographic study was started a short time after dinner.

For 48 hours before the study, patients were required to cease any proton-pump inhibitor, H_2-receptor antagonist or antacid and abstain from caffeinated, acidic and high fat foods and drinks. For 5 hrs prior to the study patients were required to fast.

7.4.3 Measurements

7.4.3.1 Spirometry

Standard spirometry was performed at the patient's most recent lung transplant clinic appointment. These spirometry values were used to determine the severity of BOS, defined according to standard criteria.[513]

7.4.3.2 Oesophageal manometry

A purpose built manometry catheter (O.D. 2.5 mm) (Dentsleeve Pty Ltd., SA, Australia) was passed via the nares into the oesophagus to simultaneously record pressure changes within the oesophagus, LOS and stomach. The catheter incorporated a sleeve sensor for measuring LOS pressure (P_{LOS}), and side holes to measure pharyngeal (P_{ph}), oesophageal (P_{oes}) and gastric pressure (P_g). All pressures were referenced to atmospheric pressure.

While supine, patients were asked to perform 10 swallows of 5 ml of water. Each swallow was preceded by at least 30 s of stable oesophageal function. P_{LOS}, expressed relative to P_g, was measured for each of the 5 breaths preceding a swallow; the mean of these 5 breaths was then used for baseline manometry analysis. Duration of each swallow-induced LOS relaxation was defined as the time the LOS was less than 20% of baseline pressure.[114] The LOS was defined as hypotonic if the baseline P_{LOS} was <10 mmHg (13.7 cmH_20).[546] Peristaltic wave amplitude was defined as the peak P_{oes} in each oesophageal side hole, referenced to baseline P_{oes}. Ineffective oesophageal motility was

defined as a distal P_{oes} amplitude during a peristaltic wave of <30 mmHg (41 cmH_20) or if >30% of peristaltic waves in the distal oesophagus occurred simultaneously.[545,560]

7.4.3.3 Oesophageal pH monitoring

Overnight oesophageal pH monitoring was performed using a dual-pH catheter (O.D. 1.4 mm, Versaflex pH catheters, Alpine Biomed, Fountain Valley, CA) with antimony pH electrodes placed 15 cm apart. The pH catheter was inserted into the oesophagus via the nares and positioned so that the pH electrodes were 5 and 20 cm above the LOS, which had been determined previously from oesophageal manometry. Prior to insertion the pH catheter was calibrated against solutions of pH 4 and 7. The catheter was connected to an acid reflux monitor (RepHlux Tracer™, Alpine Biomed, Fountain Valley, CA). GOR events (whether distal or proximal) and acid clearance were defined according to Dent *et al*.[111] The oesophageal pH monitoring period was divided into the 'postprandial period', defined as the 2 hr period following completion of the meal and the 'nocturnal period', defined as the time between 'lights out' at night and 'lights on' the next morning.

All pH and manometry signals were recorded continuously on a computerised data acquisition and analysis system (Powerlab 16S, ADInstruments, Castle Hill, New South Wales, Australia).

7.4.3.4 GOR Symptoms

Patients completed a validated GOR questionnaire[526] prior to polysomnography. Heartburn and acid regurgitation indices were derived from the product of event frequency and severity.[19]

7.4.3.5 Polysomnography

Overnight polysomnography included monitoring of: electroencephalogram (C4-A1 and C3-A2); left and right electrooculograms; submental and tibial electromyograms; electrocardiogram; abdominal and thoracic motion; nasal and oral airflow; nasal pressure; oxygen saturation; body position; and sound. All data were collected on a computerised data acquisition system (E-Series, Compumedics, Melbourne, Australia).

Analysis of sleep stage and respiratory events were performed according to standard criteria.[261,528] Severity of sleep-disordered breathing was defined by the apnoea-hypopnoea index (AHI), which is defined as the number of apnoeas and hypopnoeas per hour of sleep.

7.4.5.6 Radiographs

Pre- and post-transplant posteroanterior chest radiographs were used to determine the effect of transplant on diaphragm position and tracheal length, and thereby potential effects on upper airway stability.[561] Measurements were obtained of the distance between: apex of 1st rib to carina; apex of 1st rib to apex of hemi-diaphragm; carina to apex of hemi diaphragm; horizontal distance from spinous processes to ribs tangential to the apex of the hemi diaphragm; and horizontal distance from the carina to the ribs. Pre- and post-transplant lateral chest radiographs were used to measure the distances between the apex of lung to midline of diaphragm and the distance from the anterior to posterior costophrenic angles.

7.4.4 Statistical analysis.

Results are presented as mean±standard deviation. A p-value <0.05 was considered statistically significant. Linear regression analyses were used to investigate correlations between variables.

7.5 RESULTS

Patients were 59±6 yrs old, 38±47 months post-transplant with a FEV_1 (% of best post-transplant FEV_1) of 84±15% (Table 7.1). Six patients had BOS. One was on supplemental oxygen (patient 14). There were no relationships between FEV_1 and any anthropometric measure, severity of OSA (AHI) or severity of postprandial or nocturnal GOR, regardless of which GOR measure was used.

Table 7.1. Subject characteristics and summary data

Subject	Gender	Age (yr)	BMI (kg/m^2)	Neck Circ. (cm)	Waist Circ. (cm)	Hip Circ. (cm)	Tx type	Reason for Tx	FEV_1 %	BOS category
1	M	62	28	N/a	N/a	N/a	BLST	COPD	49	2
2	M	47	20	37	73	88	HLT	PPH	93	1
3	M	49	29	42	102	102	SLT (L)	IPF	91	0
4	F	58	30	36	99	106	BLST	ILD	92	0
5	M	61	30	40	116	112	BLST	COPD	92	0p
6	M	63	29	51	114	113	BLST	COPD	79	1
7	M	64	26	39	100	106	SLT (L)	IPF	95	0
8	F	65	25	37	98	111	SLT (R)	COPD	81	1
9	F	54	25	39	95	104	SLT (L)	ILD	90	0
10	M	58	28	46	102	103	SLT (R)	IPF	104	0
11	M	61	27	47	111	112	SLT (R)	IPF	93	0
12	M	50	28	42	104	99	HLT	Eisenmengers	76	0
13	M	62	32	44	98	174	SLT (R)	COPD/ILD	86	0
14	M	65	20	38	88	91	SLT (R)	COPD	59	2
Average (SD)		**59 (6)**	**27 (4)**	**41 (5)**	**100 (11)**	**109 (21)**			**84 (15)**	

BMI (body mass index); Neck circ. (neck circumference); Waist circ. (waist circumference); Hip circ. (hip circumference); Tx; (Transplant); FEV_1 (forced expiratory volume in one second), expressed as a percentage of the best post Tx FEV_1; BOS (Bronchiolitis Obliterans Syndrome); BSLT (Bilateral sequential lung transplant); HLT (Heart-Lung transplant); SLT (Single lung transplant (L) left, (R) right); COPD (Chronic Obstructive Pulmonary Disease); PPH (Primary Pulmonary Hypertension); IPF (Idiopathic Pulmonary Fibrosis); ILD (Interstitial Lung Disease, non classifiable); Eisenmengers (Eisenmengers syndrome); N/a (data not available).

7.5.1 Polysomnography

Results of the overnight polysomnography for the 14 patients are summarised in Table 7.2. Patients spent the majority of their sleep time in Stage 2 sleep, the proportion of which was increased (76%) relative to normal individuals (approximately 50%).[260] Sleep efficiency (normally >80%)[260] was reduced in all patients.

All 14 patients had OSA (AHI>5events.hr^{-1}), with 50% having severe OSA (AHI>30). The majority of obstructive events were hypopnoeas rather than apnoeas in all but one patient (patient 6). In addition, three patients (patients 6,7,13) had more than 5 central apnoeas an hour, however in all patients the number of obstructive events greatly outweighed the number of central events by at least a factor of 3. Two patients had mean oxygen saturations of <90% during sleep (patients 6 and 14) reflecting disordered gas exchange that was also evident during wakefulness. One of these patients was on long-term oxygen therapy (patient 14).

Arousal index was increased was increased relative to normal values[265] although only 4 patients reported excessive daytime sleepiness (patients 6,12,13,14). AHI was significantly related to neck circumference (r^2=0.33,p=0.04), but not to any other anthropometric variable. There was no relationship between the type of transplant and severity of OSA.

Table 7.2. Sleep data

Subject	AHI	HI	ArI	SE	SaO_2	ESS	Sleep Stages (%TST)		
				%	%		NREM 1 and 2	NREM SWS	REM
1	50	50	39	68	91	5	91	1	8
2	14	13	16	89	98	3	60	16	24
3	14	13	17	79	98	6	65	1	34
4	11	10	16	82	95	6	67	8	25
5	44	42	39	69	96	8	70	10	20
6	82	16	61	76	78	12	92	0	9
7	50	38	37	66	90	3	70	12	18
8	13	13	8	68	95	4	69	16	15
9	17	17	21	85	94	6	83	0	17
10	40	40	13	57	94	4	91.6	3	6
11	27	19	37	85	94	7	67	15	19
12	18	18	19	72	93	11	73.3	14	13
13	52	43	32	68	93	15	77	8	16
14	55	54	69	48	89	9	87	3	9
Average (SD)	**35 (22)**	**28 (16)**	**30 (18)**	**72 (11)**	**93 (5)**	**7 (4)**	**76 (11)**	**8 (6)**	**17 (8)**

AHI (apnoea-hypopnoea index, number of apnoeas and hypopnoeas per hour of sleep); HI (hypopnoea index, number of hypopnoeas per hour of sleep); ArI (arousal index, number of arousals per hour of sleep); SE (sleep efficiency); SaO2 (average oxygen saturation during nocturnal period); ESS (Epworth sleepiness scale); % TST (percentage of total sleep time); NREM 1 and 2 (non-rapid eye movement sleep stages 1 and 2 combined); NREM SWS (non-rapid eye movement slow-wave sleep, stages 3 and 4 combined); REM (rapid eye movement sleep).

7.5.2 Radiographic Analyses

There were no relationships between any anatomical distance measured on the chest radiographs or change in anatomical distances from pre- to post- transplant and AHI, even when the distances were normalised for height.

7.5.3 Oesophageal manometry

Baseline P_{LOS} was 11.4±11.0 cmH_20. Nadir P_{LOS} during a swallow-induced LOS relaxation was 1.0±6.7 cmH_20. 9 of 14 patients had a hypotonic LOS.[546]

The average peristaltic amplitude in the distal oesophagus during a 5ml water swallow was 85.4±50.1 cmH_20. Average peristaltic wave velocity was 2.7±0.8 $cm.s^{-1}$ in the distal oesophagus and the average duration of LOS relaxation during a water swallow was 3.3±1.0 s. 4 of 14 patients were classified as having ineffective oesophageal motility (patients 1,2,12,14).[545,560]

Table 7.3. Postprandial gastro-oesophageal reflux data

Subject	*DISTAL PROBE*				*PROXIMAL PROBE*			
	No. events	**No. >5mins**	**Longest event** (s)	**% time pH <4.0** %	**No. events**	**No. >5 mins**	**Longest event** (s)	**% time pH <4.0** %
1	4	0	170	2.8	0	0	0	0.0
2	2	0	60	2.0	0	0	0	0.0
3	2	0	19	0.3	0	0	0	0.0
4	4	0	204	5.6	0	0	0	0.0
5	8	0	200	6.5	0	0	0	0.0
6	2	0	68	1.3	0	0	0	0.0
7	1	0	12	0.2	0	0	0	0.0
8	3	0	94	1.5	0	0	0	0.0
9	1	0	6	0.1	0	0	0	0.0
10	5	0	170	4.0	0	0	0	0.0
11	2	0	14	0.3	0	0	0	0.0
12	1	0	6	0.1	0	0	0	0.0
13	5	0	72	1.8	2	0	95	1.5
14	7	1	392	8.9	0	0	0	0.0
Average (SD)	**4 (2)**	**0.1 (0.3)**	**106 (110)**	**2.5 (2.8)**	**0.1 (0.5)**	**0 (0)**	**7 (25)**	**0.1 (0.4)**

Postprandial (2 hour period after the completion of meal); Distal sensor (5cm above proximal border of lower oesophageal sphincter); Proximal sensor (20cm above proximal border of lower oesophageal sphincter); Number >5mins (number of reflux episodes greater than 5 minutes); % time < 4.0 (percentage of period spent below a pH of 4.0).

7.5.4 Oesophageal pH monitoring

7.5.4.1 Postprandial period

Abnormal postprandial GOR was found in two patients,[547] with acid reaching the proximal oesophagus in one[548] (Table 7.3). Specifically, patient 14 had abnormally high postprandial acid contact time in the distal oesophagus while patient 13 had abnormally high acid contact time in the proximal oesophagus, but normal distal acid contact time.

Two patients (patients 6,13) were symptomatic for GOR according to their heartburn and acid regurgitation indices.[19] Only one of these individuals (patient 13) had abnormal results for any pH measure during the postprandial period.

7.5.4.2 Nocturnal period

Eight patients had abnormal *nocturnal*GOR [549] (patients 2,4,5,7,9,10,13,14)(Table 7.4). Five had abnormally high supine acid contact time (patients 2,5,9,10,14) and 3 had abnormal *nocturnal*GOR determined by number of GOR episodes recorded in the nocturnal period (patients 4,7,13). Of these 8 patients, acid reached the proximal oesophagus to an abnormal extent in 3[562] (patients 2,5,14). Measures of GOR during the nocturnal period were not related to any anthropometric or sleep variable.

Table 7.4. Nocturnal gastro-oesophageal reflux data

Subject	*DISTAL PROBE*				*PROXIMAL PROBE*			
	No. events	**No. >5 mins**	**Longest event (s)**	**% time pH <4.0 %**	**No. events**	**No. >5 mins**	**Longest event (s)**	**% time pH <4.0 %**
1	3	0	12	0.1	0	0	0	0.0
2	8	1	485	1.9	2	0	163	0.7
3	0	0	0	0.0	0	0	0	0.0
4	7	0	9	0.1	0	0	0	0.0
5	47	1	576	10.3	5	0	42	0.5
6	1	0	7	0.0	0	0	0	0.0
7	9	0	12	0.2	0	0	0	0.0
8	2	0	10	0.1	0	0	0	0.0
9	3	1	575	1.9	0	0	0	0.0
10	17	0	116	1.4	0	0	0	0.0
11	0	0	0	0.0	0	0	0	0.0
12	1	0	91	0.3	0	0	0	0.0
13	7	0	16	0.3	0	0	0	0.0
14	30	2	439	7.4	1	1	1327	4.1
Average (SD)	**10 (13)**	**0.4 (0.6)**	**168 (235)**	**1.7 (3.1)**	**0.6 (1.4)**	**0.1 (0.3)**	**109 (353)**	**0.4 (1.1)**

Nocturnal (from 'lights off' at night to 'lights on' in the morning); Distal sensor (5cm above proximal border of lower oesophageal sphincter); Proximal sensor (20cm above proximal border of lower oesophageal sphincter); Number >5mins (number of reflux episodes greater than 5 minutes); % time < 4.0 (percentage of period spent below a pH of 4.0).

Of the 134 GOR events that occurred during the nocturnal period, 70% occurred during periods of prolonged wakefulness and/or brief arousals from sleep. Of the 36 events that occurred during sleep, 75% occurred during Stage 2 sleep, 6% during Stage 4 sleep and 17% during REM sleep. Sleep stage could not be determined in 2% of the events due to EEG artifact. In the minute preceding a *nocturnal*GOR event an arousal was present on 67% of occasions, a swallow on 56%, a hypopnoea on 89%, and a central apnoea on 6%. In the 10s preceding a *nocturnal*GOR event a hypopnoea was present on 70% of occasions and a central apnoea on 3%. In the minute following a *nocturnal*GOR event a hypopnoea was present on 56% of occasions.

7.6 DISCUSSION

An association between lung disease and GOR has been recognised for some time.[29] In lung transplant patients a major limitation to long-term survival is the development of BOS, identified by a persistent drop in FEV_1 after transplant, affecting 50-60% of patients at five years after transplant.[30] Aspiration of stomach contents has been implicated in allograft dysfunction, in particular in relation to the early development of BOS.[15-17,31,32] This is the first study to investigate the interrelationships between OSA, *nocturnal*GOR and BOS in patients who have undergone a lung transplant. While the study revealed a surprisingly high incidence of OSA with all 14 patients having OSA, half of who were severe (AHI >30), it did not demonstrate a clear relationship between *nocturnal*GOR and BOS or between GOR, OSA and BOS.

7.6.1 OSA and sleep architecture in transplant patients

All fourteen patients studied had clinically significant OSA based on standard criteria, 50% of them with severe disease (AHI>30 events.hr^{-1}). There are several potential mechanisms for the high incidence of OSA in this and other studies.[557-559] Obesity is strongly associated with OSA, especially in males and it is common for individuals to gain weight after transplant, most likely due to chronic corticosteroid use. While the lack of a correlation between BMI and AHI in this study does not support weight gain as a cause, it could be the distribution of obesity that is most critical, with fat deposition around the upper airway being an important factor because of its direct compressive effect. Such regional fat deposition is reflected in neck circumference measurements.[434,563,564] Indeed, we found neck circumference to be significantly correlated to AHI in our study population.

It is also possible that donor-recipient organ size mismatch or uncoupling of the upper airway from mediastinal structures through the surgery itself could result in a decrease in longitudinal traction on the pharynx and increase its collapsibility. It has previously been shown that caudal tracheal displacement of as little as 1cm can significantly decrease upper airway collapsibility in cats.[340,341] However, even when normalised for height we did not find a relationship between radiologically derived anatomical distances and AHI, suggesting that changes in tracheal traction may not be responsible for the high occurrence of OSA in this group. However we did not have a pre-transplant AHI for our patients and so remain unsure of the degree to which OSA was the result of surgery or a pre-existing problem.

7.6.2 GOR in transplant patients

Abnormal postprandial GOR was uncommon in our study participants, with only two of 14 patients presenting with an abnormal postprandial pH study. However eight patients had abnormal pH findings during the nocturnal period. These findings are consistent with other studies, which report between 40 and 70% of lung transplant patients as having abnormal supine GOR.[15,17,31,514] The development of OSA post-transplant is a plausible cause of this increase in nocturnal, supine reflux.

Nocturnal GOR is associated with increased acid contact time (some events having been observed to last up to 45 mins), increased proximal migration[7] and increased oesophageal injury.[565] Compounding this is the high prevalence of oesophageal dysmotility in post-transplant patients, being 29% in the present study and 33% in a previous study[518] and the fact that mucociliary clearance is impaired in these patients.[521,522] Both lengthy acid

contact time and increased proximal acid migration increase the risk of aspiration and, potentially, the risk of development of BOS.

7.6.3 GOR, OSA and BOS

Despite the high occurrence of both *nocturnal*GOR and OSA, and the increase in aspiration risk with both conditions, we found no relationship between severity of BOS and either severity of OSA (AHI) or nocturnal oesophageal pH parameters. Further, while many GOR events occurred in close proximity to hypopnoeic or apnoeic events, the lack of a consistent order effect between respiratory and reflux events and the lack of a correlation between pH parameters and AHI suggest that obstructive events do not consistently precipitate GOR events. It remains possible that OSA increases GOR by increasing arousal frequency during sleep or by modulating LOS barrier pressure by virtue of the generation of substantial intrathoracic pressure changes during obstructive events.

7.6.4 Limitations

The study has several potential limitations. Firstly, nocturnal pH but not ambulatory (daytime) pH was monitored. Although it is the latter, which is commonly used to document the presence of GOR the primary focus of this study was the nocturnal period, when vulnerability to aspiration is increased because of recumbency and sleep. This is equivalent to the 'supine' period for an ambulatory test and the normal values published for the supine period of a 24hr ambulatory test should be comparable to our nocturnal pH values. Secondly, our patients ceased proton pump inhibitors 48 hrs before the study. While other studies have done so for 5 days prior to a study to avoid acid rebound, there is little evidence for rebound acid hypersecretion.[553,554] Furthermore the finding that gastric

pH was approximately 2 in all patients prior to commencement of the study argues against a prolonged effect of proton pump inhibitor therapy on gastric acid secretion in these patients. Thirdly, it is possible that non-acid reflux played a role in the development of BOS[566] but our system was only able to detect acid reflux. Lastly, the small sample size of patients and the heterogeneity of transplant types introduced the likelihood of a type II error when investigating relationships between OSA severity, BOS and GOR.

7.6.5 Conclusions

In conclusion, this is the first study to investigate the potential interrelationships between OSA, *nocturnal*GOR and BOS status in lung transplant patients. Both GOR and OSA were extremely common in this group of patients. However the small size and heterogeneity of the patient group precludes drawing any definitive conclusions regarding the relationships between the severity of GOR, severity of OSA and the presence of BOS. These findings suggest that lung transplant patients are at increased risk for both GOR and OSA. Routine polysomnography and pH monitoring could be considered as part of the pre- and post-transplant assessment of these individuals.

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CHAPTER EIGHT

General Discussion and Overview

This thesis incorporates a series of novel studies which were undertaken to investigate the relationship between gastro-oesophageal reflux and obstructive sleep apnoea and determine the mechanism of interaction between the two conditions. This final Chapter summarises the findings of these studies and their implications for clinical practice.

Previous studies report that OSA patients have an increase in number and severity of GOR events and an increased prevalence of GOR and *nocturnal*GOR symptoms compared to healthy individuals, suggestive of a relationship (perhaps even cause and effect) between OSA and GOR. However, most previous epidemiological studies which have specifically looked for this potential association have failed to find evidence in support of such a relationship. This is likely because these studies have not distinguished between daytime and nocturnal GOR symptoms. Considering that OSA is a sleep-related phenomenon, Chapter Three hypothesised that an association would be evident if nocturnal symptoms were specifically concentrated upon. The findings of this study supported the hypothesis, showing that the prevalence of frequent *nocturnal*GOR symptoms was greater in those either at high risk of OSA in the general population (11.2%) compared to those at low risk (5.8%) or in those with severe OSA (14.7%) compared to mild OSA (5.2%). Notably, the prevalence of combined daytime and nocturnal GOR symptoms reported in Chapter Three was not different between these groups, a finding which has been reported by most other epidemiological studies,

highlighting the importance of assessing *nocturnal* symptoms when investigating the relationship between these two disorders.

The potential confounding role of other risk factors, such as age and BMI in this association was investigated in Chapter Four which showed, in a general community sample, that being at 'high risk' of OSA as judged by the validated Berlin questionnaire was independently associated with a significantly increased risk of *nocturnal*GOR symptoms. Consistent with this, study of an OSA population demonstrated that severity of OSA was directly associated with increased risk of *nocturnal*GOR symptoms, OSA severity having an adjusted odds ratio of 1.7 for frequent *nocturnal*GOR symptoms. There was no association between overall GOR symptoms and OSA. These results further supported the notion of a strong association between OSA and *nocturnal*GOR. These findings suggest that routine questioning regarding *nocturnal*GOR symptoms be undertaken in individuals under investigation for OSA.

The two studies described in Chapters Three and Four relied on self-reported GOR symptoms in both populations and self reported OSA symptoms in the general community sample. A useful extension of these would be to use objective measures of OSA (*i.e.* polysomnography), GOR and *nocturnal*GOR (such as ambulatory pH monitoring) to further characterise these relationships.

While the studies in Chapters Three and Four revealed a strong association between *nocturnal*GOR symptoms and OSA presence and severity this does not necessarily imply a 'cause and effect' relationship between the two conditions. Chapter Six describes a study that attempted to determine causality by carefully examining the temporal relationship between obstructive respiratory events and *nocturnal*GOR events

and to characterise the mechanism of each *nocturnal*GOR event. Although most *nocturnal*GOR events occurred in close association with obstructive respiratory events and arousal, there was no consistent order to the association. Furthermore, the observation that the primary barrier to GOR, the lower oesophageal sphincter was unaffected by upper airway obstruction and the resultant intrathoracic pressure generation, suggests that negative pressure generation does not cause *nocturnal*GOR events. It is likely that the obstructive respiratory events and *nocturnal*GOR events are closely related because OSA patients have many obstructive events overnight, therefore the probability of a *nocturnal*GOR event occurring near an apnoea or hypopnoea is extremely high. The present study is the first to confirm that the association between OSA and *nocturnal*GOR is not due to negative intrathoracic pressure generation 'sucking' acidic stomach contents into the oesophagus. While the underlying mechanism remains undefined, this study suggests that the acute or temporal effects of upper airway occlusion, such as negative intrathoracic pressure generation, arousal or surges in sympathetic nervous drive do not directly precipitate *nocturnal*GOR events. It is possible that the association between OSA and GOR is due to chronic effects of OSA, rather than the direct influence of individual obstructive events.

There was a high occurrence of hypotonic LOS amongst the 8 OSA patients (5/8), suggesting that chronic OSA may affect the integrity of the LOS, possibly by placing repetitive stress on the diaphragm and phrenoesophageal ligament, which couples the crural diaphragm to the LOS (figure 2.1), during upper airway occlusion thereby weakening the barrier and/or predisposing to hiatus hernia. The effect of chronic, repetitive upper airway obstruction on the integrity of the LOS and its influence on the development of hiatus hernia in those with OSA is unknown and may play a role in the pathogenesis of GOR in these patients. Alternative possibilities for the increase in GOR

in individuals with OSA include potential effects on the LOS of autonomic nervous and hypoxic changes which result from upper airway obstruction.

The primary therapy for OSA is CPAP. Previous studies have shown CPAP to have beneficial effects on both *nocturnal*GOR events and *nocturnal*GOR symptoms. The findings of the studies in Chapter Three and Six support and extend these previous studies by showing that: (i) the prevalence of *nocturnal*GOR symptoms is lower in individuals after treatment with CPAP therapy than before; and (ii) in OSA patients overnight, there is a significant decrease in both oesophageal acid contact time and number of *nocturnal*GOR events on CPAP compared to off CPAP. The mechanism underlying the reduction in *nocturnal*GOR events and symptoms was examined in Chapters Five and Six by investigating the effect of CPAP on LOS relaxation, during which time the majority of GOR and *nocturnal*GOR events are known to occur.

In normal healthy individuals during wakefulness CPAP increased the nadir P_{LOS} during an LOS relaxation and shortened the length of LOS relaxation associated with swallowing, thereby increasing the mechanical barrier to GOR, decreasing the probability of its occurrence. The observation that P_{LOS} increased significantly more than P_g suggests a reflex increase may be involved, possibly in response to the increase in P_g. In OSA subjects during sleep CPAP also decreased the duration of LOS relaxation associated with a swallow and tended to increase nadir P_{LOS} during both swallow-induced and inappropriate transient LOS relaxation, changes which also suggest an increase in the mechanical barrier to GOR.

It is likely, therefore, that the decrease in *nocturnal*GOR when on CPAP is due to its mechanical effects on the LOS. A potentially novel application of CPAP may be in

individuals who have persistent *nocturnal*GOR symptoms on acid-suppressive medications. Given that these are the first studies to investigate the effect of CPAP on LOS relaxation and a relatively small number of OSA subjects were studied during sleep, further work is needed in OSA patients and other patient groups during wakefulness and sleep to substantiate these findings.

The association between OSA and *nocturnal*GOR may be of particular importance in individuals who have undergone lung transplantation. GOR has been implicated in the development of BOS, the major challenge to survival after lung transplant, likely due to pulmonary aspiration of refluxed acid. Given the increased oesophageal acid exposure and risk of aspiration during sleep, *nocturnal*GOR may be more threatening to lung tissue than daytime GOR. Data in Chapter Seven of this thesis suggest that the risk of *nocturnal*GOR may be particularly high as both OSA and *nocturnal*GOR were common in the lung transplant patients studied, with all subjects having OSA and over half having an abnormal amount of *nocturnal*GOR. Despite these high occurrences, there were no significant associations between the presence and severity of BOS and OSA or *nocturnal*GOR. These data suggest that lung transplant patients are at increased risk for both GOR and OSA, but do not support a link between these events and BOS. It is possible that OSA and *nocturnal*GOR were present before lung transplant, rather than being a consequence of the transplantation surgery.

Given the small and heterogeneous nature of the group studied future studies should include much larger patient group spanning all types of transplantation and underlying pathologies and include a longitudinal analysis of individuals pre-transplantation and at several points post-transplantation, to track the development of BOS. Regardless, these findings have practical implications, given the high prevalence of OSA and

*nocturnal*GOR, that routine polysomnography and pH monitoring should be considered in the management of these individuals.

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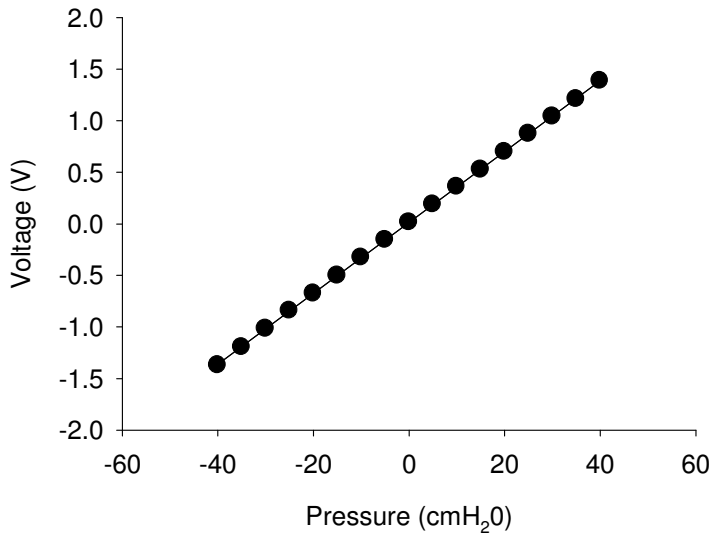
APPENDIX ONE

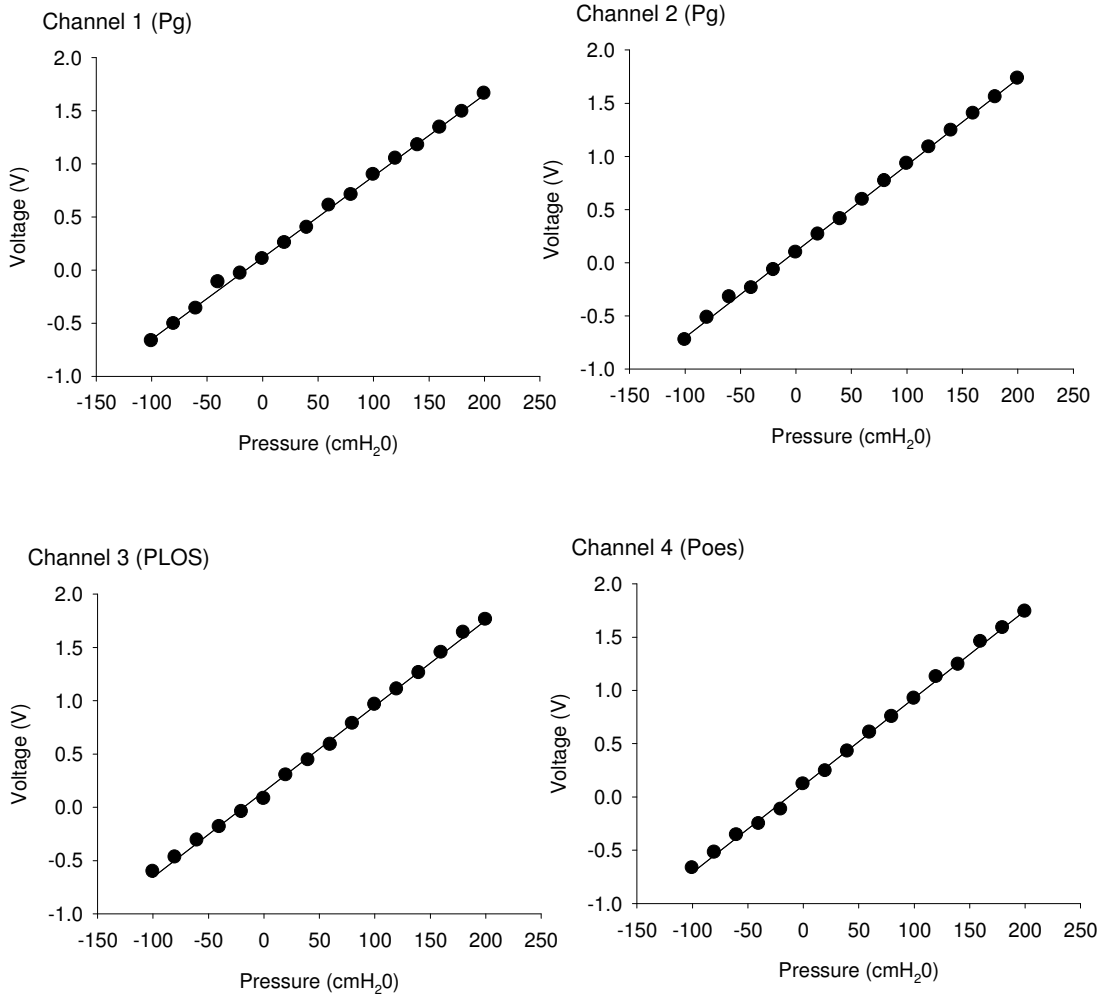
Linearity check of the differential pressure transducer (Honeywell, Morrison, NJ, USA) used to assess mask pressure during the application of CPAP in subjects with OSA. A water manometer was used to deliver known pressures and the voltage output of the transducer recorded and plotted against these pressures.

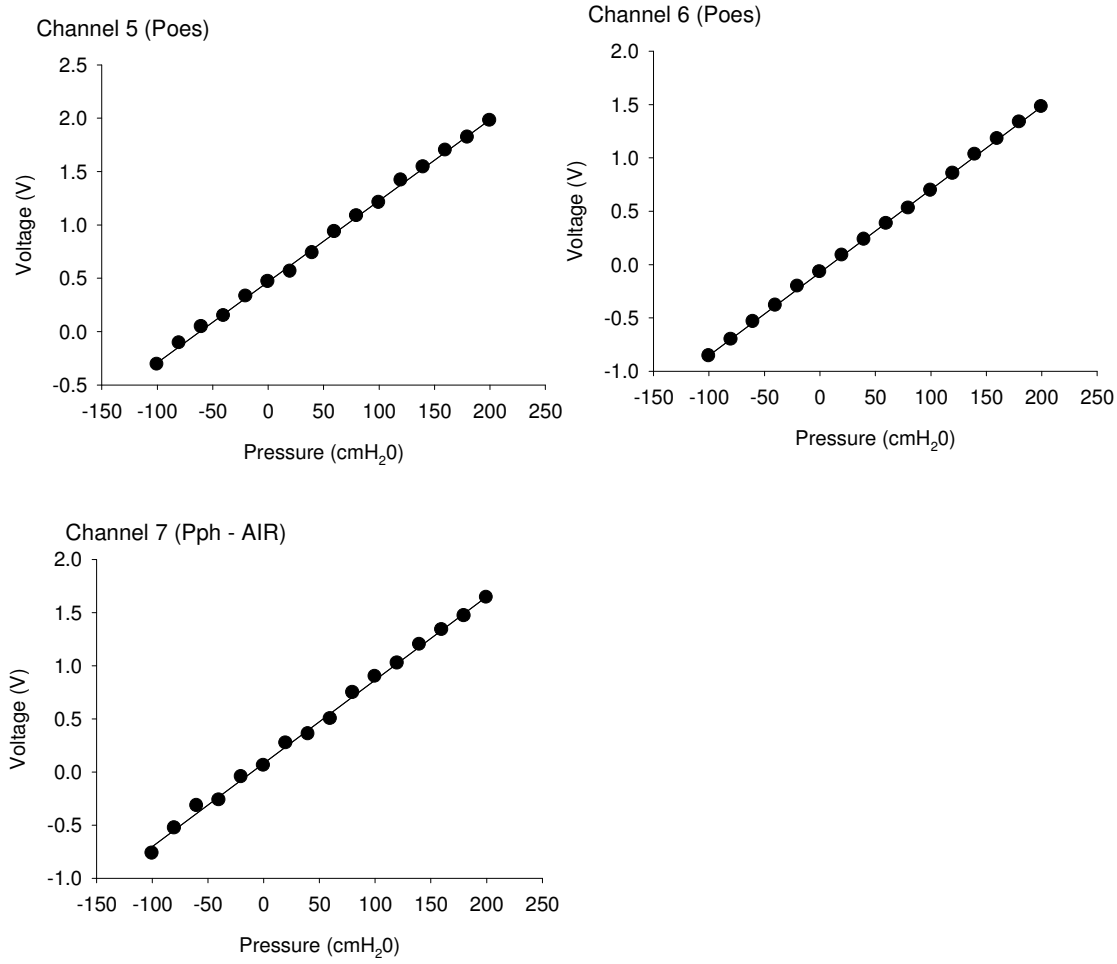


The voltage output of the differential pressure transducer output was linear over the range of nasal and mask pressures reported in this thesis (-40 to 40cmH_20).

APPENDIX TWO

Linearity check of the pressure transducers attached to the flow resistors for the Dentsleeve (Monitoring Kit, Abbott Ireland, Sligo, Republic of Ireland) and custom-made amplifier (Medical Technology and Physics, Sir Charles Gairdner Hospital, Nedlands, WA, Australia). The pharyngeal side hole (Channel 7) was perfused with air at a rate of 0.08ml.min^{-1}. All other side holes were perfused with distilled water at a rate of 0.15ml.min^{-1}. A water manometer was used to deliver known pressures and the voltage output of the transducers recorded and plotted against these pressures.





The voltage output of the differential pressure transducers was linear over the range of pharyngeal, oesophageal, LOS and gastric pressures reported in this thesis (-100 to 200cmH_20).

APPENDIX THREE

Response rates for each channel on the Dentsleeve catheter (Dentsleeve Pty Ltd., SA, Australia). Each side catheter side hole was occluded and the rate of pressure increase (rise time) recorded for each channel. Data presented are the mean (SD) of three trials.

Channel	Flow rate ($ml.min^{-1}$)	Rise time ($cmH_20.s^{-1}$)
1 (water)	0.15	80 (8)
2 (water)	0.15	100 (4)
3 (sleeve)(water)	0.15	103 (6)
4 (water)	0.15	89 (10)
5 (water)	0.15	116 (4)
6 (water)	0.15	92 (12)
7 (air)	0.08	106 (1)

According to previous studies, pressure rise rates to accurately measure peak pressures along the oesophagus need to be between 50-100$mmHg.s^{-1}$ (68.5-137$cmH_20.s^{-1}$)[567,568]. *The rise rate for sideholes and sleeve fall within this range and therefore are appropriate for accurately recording oesophageal and lower oesophageal sphincter pressures.*

APPENDIX FOUR

Linearity check of the RepHlux Tracer™ (Alpine Biomed, Fountain Valley, CA).

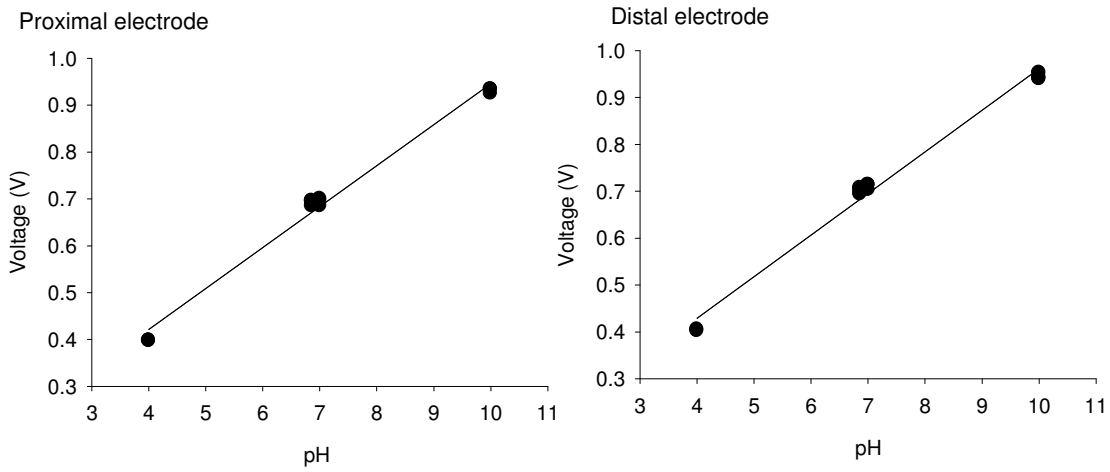
pH calibration and temperature correction

pH buffer solutions have a known value generally quoted at 25 ºC. Because pH measurements in all studies in this thesis were conducted at normal human body temperature (approximately 37ºC) the pH Extension module in Chart 5 (ADInstruments, Castle Hill, New South Wales, Australia) was used to correct for the effect of temperature. This software uses the Nernst equation (below) to make the necessary temperature corrections to the pH being monitored.

Nernst equation:

$E = E_o - (RT/nF)pY$. Where:

- E is the observed potential (in volts);
- E_o is the potential (volts) when pY = 0;
- R is the gas constant, $8.314 K^{-1} mol^{-1}$;
- T is the temperature in Kelvin;
- F is the Faraday constant, 96487 C mol^{-1};
- N is the number of electrons transferred at the electrode (the charge of the ion);
- $pY = -\log_{10}[Y]$; and
- [Y] is the activity of the ionic species 'Y'. For low concentrations ([Y]<0.1mol L^{-1}) the activity will be approximately equal to the concentration of Y.



The voltage output of the RepHlux Tracer™ was linear over the range of pHs reported in this thesis.

APPENDIX FIVE

Gastro-oesophageal reflux questionnaire[5,526] distributed to all patients undergoing diagnostic polysomnography at the Respiratory Sleep Disorders Clinic, Sir Charles Gairdner Hospital.

Appendix 5 could not be included in this digital thesis for copyright reasons.

Please refer to the print copy of the thesis, held in the University Library.

APPENDIX SIX

Gastro-oesophageal reflux questionnaire distributed to all patients undergoing repeat polysomnography for optimization of their CPAP therapy.

Questions 5-22 and 29-33 were derived from the Gastro-oesophageal *reflux questionnaire (Appendix five).* ***Note:*** *the wording of these questions was altered slightly to ask about symptoms experienced 'since using CPAP'.*

Questions 1-4 are additional questions regarding patients diagnosis and treatment of Obstructive Sleep Apnoea.

Questions 23-28 are additional questions regarding common side effects experienced with CPAP treatment.

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APPENDIX SEVEN

Busselton survey used for general population data in Chapter Three.

The gastro-oesophageal *reflux symptom questions from Locke et al*[5,526] *are found in Section 9 of the Busselton Health Survey.*

The questions derived from the Berlin Questionnaire[527] *for assessment of risk of Obstructive Sleep Apnoea are found in Section 8 of the Busselton Health Survey.*

The Berlin questionnaire is divided into three sections. Section 1 contains questions regarding an individuals' presence of snoring, snoring intensity and whether their snoring bothers others. Also included are questions regarding witnessed apnoeas during sleep. Section 2 asks how often individuals feel tired or fatigued after sleep, how often they feel tired, fatigued during wake time, and whether they ever fall asleep driving a car. Section 3, respondents are asked if they have hypertension. A section is considered positive if there are two affirmative answers in either section 1 or 2, or one affirmative response in section 3. Individuals who have positive scores in two of the three sections are considered to be at high risk for OSA.

Appendix 7 could not be included in this digital thesis for copyright reasons.

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APPENDIX EIGHT

Publications arising from this thesis

1. **Shepherd KL**, DC Chambers, E Gabbay, DR Hillman, PR Eastwood. Obstructive Sleep Apnoea and Nocturnal Gastro-oesophageal Reflux are Common in Lung Transplant Patients. *Respirology* (accepted 19-May-2008). This paper represents Chapter Seven of this thesis.

2. **Shepherd KL**, Holloway RH, Hillman DR, Eastwood PR. The Impact of Continuous Positive Airway Pressure on the Lower Esophageal Sphincter. *American Journal of Physiology (Gastrointestinal and Liver Physiology)* 292(5): G1200-1205, 2007. This paper represents Chapter Five of this thesis.

Manuscripts in preparation

1. **Shepherd KL**, James AL, Musk AW, Hillman DR, Eastwood PR. The Prevalence of Nocturnal Gastro-oesophageal Reflux is increased in Obstructive Sleep Apnea. Submitted to *Sleep* 9/09/2008.

2. **Shepherd KL**, Hillman DH, Holloway R, Eastwood P. Characteristics of Nocturnal Gastro-oesophageal Reflux Events in Obstructive Sleep Apnea. For submission to the *Journal of Applied Physiology*.

3. **Shepherd KL**, James AL, Musk AW, Hillman DR, Eastwood PR. Obstructive Sleep Apnea is a significant risk factor for Nocturnal Gastro-oesophageal Reflux Symptoms in the General Population and Obstructive Sleep Apnea patients. For submission to *Chest*.

Other relevant publications

1. Eastwood PR, Katagiri S, **Shepherd KL**, Hillman DR. Modulation of upper and lower esophageal sphincter tone during sleep. *Sleep Medicine* 8(2): 135-143, 2007.

   Editorial: Orr WC. Esophageal function during sleep: another danger in the night. Sleep Medicine 8(2): 105-106, 2007.

2. **Shepherd KL,** Jensen CM, Maddison KJ, Hillman DR, Eastwood PR. Relationship between upper airway and inspiratory pump muscle force in obstructive sleep apnea. *Chest* 130(6): 1757-1764, 2006.

3. Maddison KJ, **Shepherd KL**, Hillman DR, Eastwood PR. Function of the Lower Esophageal Sphincter during and after high-intensity exercise. *Medicine and Science in Sport and Exercise* 37(10): 1728-1733, 2005.

APPENDIX NINE

International Conference Presentations

1. **Shepherd K**, Chambers D, Gabbay E, Hillman D, Eastwood P. Nocturnal gastro-oesophageal reflux and sleep-disordered breathing after lung transplant. 5th Congress of the World Federation of Sleep Research and Sleep Medicine Societies, Cairns, Qld. Sleep and Biological Rhythms 2007 5(supp 1): A179. *POSTER PRESENTATION.*
2. **Shepherd K**, Hillman D, Eastwood P. Occurrence of gastro-oesophageal reflux symptoms in a sleep clinic population. 5th Congress of the World Federation of Sleep Research and Sleep Medicine Societies, Cairns, Qld. Sleep and Biological Rhythms 2007 5(supp 1): A109. *POSTER PRESENTATION.*

National (Australian) Conference Presentations

1. **Shepherd K**, Chambers D, Gabbay E, Hillman D, Eastwood P. Nocturnal gastro-oesophageal reflux and sleep-disordered breathing after lung transplant. Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Auckland, NZ, 2007. Respirology 2007; Volume 12 (suppl 1): A59. *POSTER PRESENTATION.*
2. **Shepherd K**, Hillman D, Eastwood P. Occurrence of gastro-oesophageal reflux symptoms in a sleep clinic population. Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Auckland, NZ, 2007. Respirology 2007; Volume 12 (suppl 1): A74. *POSTER PRESENTATION.*
3. **Shepherd K**, Holloway R, Hillman D, Eastwood P. The effect of continuous positive airway pressure on lower oesophageal sphincter function. Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Canberra ACT. Respirology 2006; 11(Suppl 2): A17. *ORAL PRESENTATION.*
4. **Shepherd KL**, Jensen CM, Maddison KJ, Hillman DR, Eastwood PR. Relationship between upper airway and inspiratory pump muscle force in obstructive sleep apnoea. Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Sydney NSW. Respirology 2004; 9(Suppl 2): A69. *POSTER PRESENTATION.*

5. **Shepherd K**, Holloway R, Hillman D, Eastwood P. The effect of continuous positive airway pressure on lower oesophageal sphincter function. Upper Airway Symposium, Rottnest, WA, 2007. *INVITED ORAL PRESENTATION.*

Local (West Australian) Conference Presentations

1. **Shepherd K**, Hillman D, Eastwood P. Occurrence of gastro-oesophageal reflux symptoms in a sleep clinic population. Australian Society for Medical Research (WA Branch) Research Week, 2007. *ORAL PRESENTATION.*
2. **Shepherd K**, Hillman D, Eastwood P. Occurrence of gastro-oesophageal reflux symptoms in a sleep clinic population. Sir Charles Gairdner Hospital Young Investigator Awards, 2007. *ORAL PRESENTATION.*
3. **Shepherd K**, Chamber D, Gabbay E, Hillman D, Eastwood P, 2007. 'Nocturnal gastro-oesophageal reflux and sleep-disorder breathing after lung transplant', Annual Scientific Meeting of The Thoracic Society of Australia and New Zealand (WA Branch), Perth Australia. *ORAL PRESENTATION.*
4. **Shepherd K**, Holloway R, Hillman D, Eastwood P, 2006. 'Relationship between continuous positive airway pressure and lower oesophageal sphincter function' Australian Society for Medical Research, Research Week Symposium, Perth Australia. *ORAL PRESENTATION.*
5. **Shepherd K**, Holloway R, Hillman D, Eastwood P. The effect of continuous positive airway pressure on lower oesophageal sphincter function. Thoracic Society of Australia and New Zealand (WA Branch) Annual Scientific Meeting, Mandurah, WA. *ORAL PRESENTATION.*
6. **Shepherd KL**, Jensen CM, Maddison KJ, Hillman DR, Eastwood PR. Relationship between upper airway and inspiratory pump muscle force in obstructive sleep apnoea. Sir Charles Gairdner Hospital Young Investigator Awards, 2004. *ORAL PRESENTATION.*
7. **Shepherd KL**, Jensen CM, Maddison KJ, Hillman DR, Eastwood PR. Relationship between upper airway and inspiratory pump muscle force in obstructive sleep apnoea. Thoracic Society of Australia and New Zealand (WA Branch) Annual Scientific Meeting, Mandurah, WA, 2004. *ORAL PRESENTATION.*

APPENDIX TEN

Awards to Kelly Shepherd

2008 Completion Scholarship, University of Western Australia *(commenced June 1).*

2007 Finalist, Young Investigator Award, Sir Charles Gairdner Hospital.

2007 Trainee Travel Grant, 5th Congress of the World Federation of Sleep Research and Sleep Medicine Societies, Cairns, Queensland, Australia.

2007 Travel Grant, Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Auckland, New Zealand.

2006 Travel Grant, Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Canberra, Australia.

2005 Finalist, Hospital Young Investigator Award, Sir Charles Gairdner.

2005 Glaxo Smith Kline Young Investigator Award, Thoracic Society of Australia and New Zealand (WA Branch) Annual Scientific Meeting, Mandurah.

2004 Travel Grant, Thoracic Society of Australia and New Zealand Annual Scientific Meeting, Sydney, Australia.