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INSTANTANEOUS EFFECT OF MERIDIAN POINT STIMULATION FOR MANAGING SLEEP APNOEA

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CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written nor material which has been accepted for the award of any other degree or diploma, except where due acknowledge has been made in the text.

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ABSTRACT

Background

The compliance and efficacy of current conservative management of sleep apnoea are questionable. Meridian point stimulation is reported to be effective in relieving symptoms of sleep apnoea but the instantaneous effect on sleep apnoea is yet to be determined.

Aims

To identify a critical physiological signal to promptly indicate the occurrence of obstructive sleep apnoea (OSA) and to evaluate the effectiveness of a new approach – instantaneous meridian point stimulation – in managing the symptoms of OSA.

Methods

This research was divided into two stages. Stage 1 involved selecting and evaluating a critical signal for immediate indication of OSA. Ten subjects with OSA underwent nocturnal sleep study and their physiological signals were recorded. Stage 1 involved 3 tests. Test 1 evaluated the promptness of using the pulse oximetry (SpO2) level to indicate OSA by measuring time difference between cessation of airflow and the selected threshold. Test 2 evaluated Receiver operating characteristic (ROC) value using phase relationship between thoracic and abdominal signals to indicate OSA. Phase relationship was evaluated by measuring the magnitude excursion of the peak of the two signals in a breathing cycle during OSA and normal breathing. Test 3 evaluated sensitivity and specificity using the mean absolute amplitude of thoracic

and abdominal effort of the subjects to indicate OSA. OSA was indicated if a reduction in mean absolute amplitude was found at 10 seconds before and from the onset of OSA. Stage 2 evaluated the efficacy of instantaneous meridian point stimulation in managing OSA using a single-blinded research design. Twenty-seven subjects were randomly assigned to three groups, namely LU7 meridian point group, sham point group and no stimulation group. They received two nights of sleep study, with one baseline test and one intervention test. Frequency and duration of sleep apnoea, average SpO_2 levels and average number of arousals were compared between the two nights.

Results

Stage 1: In Test 1 the mean time difference (MTD) between ONAC and the threshold was 22 seconds. In Test 2, ROC value using phase relation of thoracic and abdominal signals to indicate OSA was 0.427. In Test 3, sensitivity and specificity values using the mean absolute amplitude of thoracic and abdominal signals were over 0.8. Stage 2: Frequency and duration of sleep apnoea, and average oxygen desaturation were significantly improved only in the MPSG with a p-value <0.05.

Discussion

Findings in Stage 1 suggested that the mean absolute amplitude of thoracic and abdominal signals was likely to effectively and promptly indicate the occurrence of OSA. Findings in Stage 2 suggested that subjects who received meridian point stimulation exhibited better management of sleep apnoea than the other groups with significant differences in terms of frequency and duration of sleep apnoea, and the average SpO_2 level between the baseline and intervention study, while the number of arousals did not increase dramatically.

Conclusion

In this research, the criteria and efficacy of meridian point stimulation were identified and tested. Study findings suggested very promising results for the application of this new method in managing symptoms of OSA and also showed that the method would be non-invasive, convenient and easy to use.

SUMMARY OF PUBLICATIONS AND AWARDS

1. Ng A. S. L., Chung J.W.Y., Gohel M.D., Yu W.W.M., Fan K.L., Wong T.K.S. (2006) Using pulse oximetry level to indicate the occurrence of sleep apnoea events, Studies in health technology and informatics, 122, p.672-675

2. Ng A. S. L., Chung J.W.Y., Gohel M.D., Yu W.W.M., Fan K.L., Wong T.K.S. (2008) Evaluation of the performance of using mean absolute amplitude analysis of thoracic and abdominal signals for immediate indication of sleep apnoea events, Journal of Clinical Nursing, 17, 17, 2360-2366

3. Ng A. S. L., Chung J.W.Y., Gohel M.D., Yu W.W.M., Fan K.L., Wong T.K.S. (2008) Evaluation of the instantaneous effect of meridian point stimulation on apnoeic attack for patients with sleep apnoea, Journal of Clinical Nursing (Submitted)

4. Gold Medal Award, Inventions: Smart wristband for sleep apnea, International Trade Fair Ideas, Inventions and Novelties (IENA), 2006, Nuremberg, Germany

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Chapter 1 Introduction

1.1 Introduction

This chapter is divided into three parts. The first part provides an overview of the problems of current management methods for patients with sleep apnoea; the second part states the research questions; and the third part outlines the aims and the objectives of the research.

1.2 Background

Sleep apnoea is characterised as repetitive episodes with cessation of breathing during sleep that results in oxygen desaturation and frequent arousals. Patients with sleep apnoea usually experience excessive daytime sleepiness, and loud snoring or breathing pauses that are observed by their bed partners. Symptoms such as nocturnal headache, depression and enuresis may be present in some patients [112].

Sleep apnoea can be classified as obstructive, central and mixed. Obstructive sleep apnoea is most common while central sleep apnoea is least common of the three types of sleep apnoea [158]. The development of obstructive sleep apnoea (OSA) is mainly due to the anatomy of the small upper airway [224]. Central sleep apnoea is characterized by a lack of ventilatory drive to breathe during sleep, resulting in insufficient or absent ventilation and compromised gas exchange [53]. The mechanism of mixed sleep apnoea, however, has not been clearly specified in the previous studies. Mixed sleep apnoea is the combination of obstructive and central sleep apnoea [158]. Pascualy (2000) pointed out that

mixed sleep apnoea occurred due to unusual low level of carbon dioxide in blood after an OSA event. In turn, this carbon dioxide level is low enough to trigger a central sleep apnoea event, thereby producing mixed sleep apnoea [158].

Sleep apnoea, which is usually regarded as a disorder rather than a disease - or a final common pathway of many diseases [112] - has been discussed for nearly half a century [113]. The negative impact of sleep apnoea on the individual is significant as well as on society in general. Clinically, sleep apnoea produces excessive daytime sleepiness [165], which is caused by fragmented sleep. During the onset of a sleep apnoea event, a signal, due to the decrease in oxygen desaturation, is sent from the brain to the upper airway muscles. As a result, micro-arousal is usually found after a sleep apnoea event in order to increase the ventilation effort [5]. Because of the repetitive occurrences of arousal during sleep, people with sleep apnoea are often reported to have cognitive dysfunction and memory loss [165]. This may result in employment difficulties, social disharmony and emotional disturbance [57].

Sleep apnoea has significant costs for society as well as the individual. An American study found that people with undiagnosed sleep apnoea were seven times more likely to have multiple traffic accidents due to poor quality of sleep. Problems related to daytime sleepiness and traffic accidents are also prevalent in Hong Kong. A local study in which 216 bus drivers were interviewed found that 40% of the subjects had experienced daytime sleepiness and 13.4% had fallen asleep while driving [205].

Although previous studies have not specifically examined the mechanism between sleep apnoea and cardiovascular condition, it is believed that intermittent occurrences of sleep apnoea may directly depress cardiac contractility or indirectly reduce cardiac performance by causing pulmonary

vasoconstriction and by increasing pulmonary arterial pressure [185]. Hence, apart from daytime sleepiness, it has been found that sleep apnoea is often associated with acute and substantial cardiovascular stress, hypoxemia, sympathetic activation, acute pulmonary and systematic hypertension, and decreased stroke volume [193]. However, there has not been sufficient testing to determine the exact relationship between cardiovascular disease and sleep apnoea. Nor have previous studies provided an in-depth analysis of cause and effect relationship between these mechanisms. Although the mechanisms underlying the development of cardiovascular disease in sleep apnoea patients are still poorly developed, hypotheses were made which attempted to explain these mechanisms. A previous study hypothesizes several mechanisms of cardiovascular outcome due to sleep apnoea, including sympathetic over-activity which increases cardiac input, selective activation of inflammatory pathways which is caused by intermittent hypoxia, endothelial dysfunction and metabolic dysregulation which increase cardiovascular risk, the latter particularly involving insulin resistance and disorders in lipid metabolism [155]. In fact, it was found that therapy with continuous positive airway pressure (CPAP) has been associated with benefits to cardiovascular morbidity and mortality such as hypertension, coronary artery disease, cardiac arrhythmias and stroke [137]. This suggestion demonstrates that OSA is closely associated with cardiovascular disease.

The negative impact of sleep apnoea on the general population has been far reaching. According to Young *et al*. [236], sleep apnoea affects up to 4% of the world's adult population and it is estimated that as many as 18 million people have symptoms of sleep apnoea in the United States [228]. In Asia, the prevalence of obstructive sleep apnoea in middle-aged men and women is 4.1-7.5% and 2.1-3.2% respectively [117]. A previous Hong Kong study summarised the clinical records of a local hospital and estimated that the prevalence of sleep apnoea in Hong Kong was similar to Caucasian data with a

male predominance of around 84%. The mean age, body mass index (BMI) and apnoea-hypopnea index (AHI) of the hospital's patients were 50, 30.4 and 38 respectively [93]. Another local study estimated that 2% of middle aged workers in Hong Kong suffered from sleep apnoea [117]. Sleep apnoea is more commonly found in elderly than in young people, and is particularly acute among adults in their mid-fifties [20]. The prevalence of sleep apnoea in children is around 2.9% [72]. The most serious problem among sleep apnoea sufferers is that many people go undiagnosed and untreated [71].

It is believed that the objectives of the management methods of sleep apnoea are to alleviate symptoms, improve sleep quality, reduce the frequency of sleep apnoea and hypopnea, and increase the pulse oximetry level [4]. To achieve these objectives, one of the directions of the management method of sleep apnoea is to re-establish breathing immediately without disturbing the quality of sleep in patients. The majority of approaches to managing sleep apnoea symptoms focuses on increasing positive pressure in the airway during obstructive sleep apnoea or directly removing excessive tissues in the airway through surgical modification.

The aim of using the current methods for obstructive sleep apnoea is to enlarge the airway or prevent blockage of the airway during episodes of sleep apnoea. The efficacy of the current methods has been evaluated extensively in previous studies [89, 133, 217]. However, the reported efficacy, degree of complexity, potential for morbidity and adverse effects of the approach varies between studies. One of the main drawbacks is low compliance as patients usually experience discomfort when using a device that involves positive pressure being pumped into their mouth throughout the night. There is further disturbance due to noise from the device [133]. Surgical modifications, meanwhile, may result in postoperative discomfort, nasal regurgitation and voice change [177].

A relatively new approach is to apply electrical pacing to alleviate symptoms of sleep apnoea. Electrical pacing aims to increase the muscular tone of genioglossus and hypoglossal muscles or nerves by stimulating the sub-mental or intra-oral area [78]. The effectiveness of this approach was found to vary between studies [55]. Several studies found that electrical stimulations increase the number of arousale vents [54, 153] without significantly reducing the number of apnoeic episodes [54, 78, 215]. However, other studies found that the frequency of apnoea episodes is reduced [85, 166, 186, 234] while subjects remain asleep during electrical stimulations [141, 166, 186, 188, 234] . The severity of oxygen desaturation of subjects is also reduced [166, 186]. Electrical pacing was found to produce both positive and negative results for different subjects in a trial [188]. A drawbacks of the method is discomfort experienced by the electrodes being invasively implanted inside the intra-oral area of patients [55]. Meanwhile, if surgery is required to implant the electrodes, an experienced medical professional is needed to provide anesthesia and sterile conditions must be met prior to surgery [140]. Hence, electrical pacing has not been widely embraced by medical practitioners.

Another approach is the administering of traditional Chinese medicine (TCM) and acupuncture [256]. Acupuncture has been found to effectively treat sleep apnoea by reducing the frequency and length of sleep apnoea episodes. It has also been found to relieve daytime sleepiness, snoring, dizziness and nocturia, and improve the quality of sleep without any reported adverse effects [269, 276]. In previous studies, acupuncture was given to subjects during a specific period of time followed by an evaluation of the effects. The studies relied on syndrome differentiation in individuals prior to intervention while the long term effects remained unknown. There are in fact limited studies which demonstrate the immediate effects of acupuncture on respiratory problems; however, a study in which acupuncture is applied to relieve cancer related breathlessness found that

70% of patients had a marked symptomatic relief following 10 minutes of acupuncture [66].

As mentioned previously, instantaneous symptom management using electrical stimulation inside the intra-oral area is unlikely to be widely accepted because the location of the stimulation may produce patient discomfort. Hence, stimulations of meridian points would be a more reliable alternative provided the location of stimulation is not sensitive. Existing treatment for sleep apnoea is varied, however, due to the level of patient discomfort and general ineffectiveness of providing adequate solutions, medical practitioners and sleep apnoea sufferers continue to search for alternative treatment.

This study attempts to evaluate whether stimulation of a meridian point can effectively provide symptomatic management by re-establishing breathing and maintaining the quality of sleep during episodes of sleep apnoea. This project includes medical advices from experts in the areas of TCM, and sleep and bio-sensing technology.

Findings from this study could provide an alternative method for healthcare practitioners in effectively managing symptoms of sleep apnoea and provide a reference for sleep apnoea patients regarding the practice of symptom management. To explore the potential cause-and-effect relationship between instantaneous meridian point stimulation and sleep apnoea, the research questions were posed in Section 1.4.

1.3 Scope of Study

The target population of this study was adults with obstructive sleep apnoea (OSA). To evaluate the performance of the critical signal and the efficacy of meridian point stimulation for managing symptoms of OSA, the investigator employed the polysomnography (PSG) device. Detailed descriptions of the sleep study will be described in Chapters 5, 6 and 7.

1.4 Research Questions

To ensure the efficacy of instantaneous meridian point electrical stimulation in managing symptoms of sleep apnoea, it is necessary to identify a critical signal to ensure that the time of intervention is not provided too late after the onset of an episode of sleep apnoea and to avoid prolonged deoxygenation. Because this study attempted to investigate a new intervention method to better manage symptoms of sleep apnoea, an evaluation of the method's efficacy was carried out during the study. Accordingly, the following five research questions were posed.

Question 1: Which physiological signal is able to promptly and accurately indicate the occurrence of sleep apnoea given that the sensor of this signal should not produce much discomfort to the user during use?

Question 2: What is the critical threshold of using this signal to indicate the occurrence of sleep apnoea?

Question 3: Which meridian point is used by TCM doctors to relieve respiratory problems of patients and especially in the immediate management of symptoms of sleep apnoea?

Question 4: Is meridian point stimulation able to manage symptoms of sleep apnoea immediately and improve sleep quality without causing any arousal?

Question 5: In terms of managing effect on sleep apnoea, is there any difference between stimulating a meridian point and a non-meridian point?

1.5 Aim

The aim of this research was to investigate the efficacy of applying a new approach in order to manage symptoms of obstructive sleep apnoea. This approach utilises instantaneous meridian point stimulation in response to the occurrence of a sleep apnoea episode.

1.6 Objectives

Based on the research questions, the following 5 objectives are stated:

1. To identify a critical physiological signal based on the information from the literature.

2. To conduct an experiment to evaluate the performance of the selected critical signal and identify the optimum threshold.

3. To select a meridian point for stimulation. This meridian point should be related to the improvement of the sleep apnoea respiratory condition based on the literature review and the stimulation of this meridian point should not produce any discomfort to sleep apnoea patients.

4. To select criteria for stimulation. The stimulation should not produce any immediate adverse effects, such as skin allergy or pain. The intensity and duration of stimulation are based on criteria of previous studies in which electrical stimulations of meridian point in human subjects was used.

5. To conduct a clinical trial to test the efficacy of meridian point stimulation in managing obstructive sleep apnoea and improving the quality of sleep. Subjects with sleep apnoea should be tested with the intervention by comparing the average number of sleep apnoea episodes and respiratory arousals.

1.7 Organization of the thesis

There are ten chapters in this dissertation. The first chapter provides an overview of the prevalence, negative consequences, current management methods for sleep apnoea, and identifies the knowledge gaps in using the current management methods and TCM to manage sleep apnoea. Research questions are stated based on the knowledge gaps, and the aims and objectives of the research are also discussed in this chapter.

Chapters 2 - 4 review previous literature regarding three important aspects. Chapter 2 focuses on studying sleep apnoea. It includes definitions, mechanisms, prevalence, treatment objectives and treatment methods. This chapter not only provides information about the symptoms of sleep apnoea and identifies the

problems of the current management methods but it also discloses the ideal in relation to management methods for sleep apnoea. Chapter 3 focuses on studying sleep apnoea in light of TCM. The basic theory of TCM and evidence for the existence of meridians are discussed. The syndrome differentiation of sleep apnoea in light of TCM and the meridian point for respiratory problems are also identified in this chapter. In this research, we aimed to test the efficacy of meridian point stimulation in managing symptoms of sleep apnoea. Information in Chapter 4 helped us to select an appropriate meridian point for testing in Chapter 6. It is important to ensure that sleep apnoea is promptly identified in order to have a timely intervention and to be able to manage the symptoms. Hence, this research also aims to identify a critical signal for immediate indication of the occurrence of sleep apnoea. Chapter 4 focuses on studying the physiological signals for monitoring sleep apnoea. Because the current monitoring devices/ sensors for sleep apnoea may still produce discomfort for users during sleep, the existing physiological signals for indicating sleep apnoea were studied and selected for further analysis. The aim was to ensure that the parameters are reliable and the sensors would not cause users any discomfort. Chapter 5 discusses the methodology of the research, the studies and tests that were carried out during the research and also the sequence of the studies and tests.

After studying and selecting the critical signals in Chapter 4, Chapter 6 includes a preliminary study to evaluate the performance of applying the pulse oximetry level, the phase relationship of thoracic and abdominal effort and the mean absolute amplitude of thoracic and abdominal effort to effectively indicate the occurrence of sleep apnoea. Subjects who were diagnosed with obstructive sleep apnoea to participate in a nocturnal sleep study were invited and then studied the reliability of using the selected physiological signals to detect obstructive sleep apnoea. The signals were evaluated in terms of promptness and accuracy. The

results of this session helped us to identify an appropriate indicator and also the threshold at which a timely intervention would be needed.

Although Chapter 5 presents the methodology of the entire research project, Chapter 7 provides details about the methodology, specifically for the clinical trial which evaluates the efficacy of meridian point stimulation for managing symptoms of sleep apnoea. The methodology in this chapter includes the exclusion and inclusion criteria, subject recruitment, the protocol of the experiment and the analytical method.

Chapter 8 states the results of the pilot test with discussion. The pilot test only tested the feasibility of conducting the experiment and was tested only if the dependent variables could be obtained. The pilot test also helped to investigate whether arousals occurred due to the electrical stimulation. Afterwards, a main test was conducted, the results of which are stated in Chapter 9. Finally, the conclusion of this research is stated in Chapter 10.

1.8 Significance

These research findings should assist medical practitioners and researchers in establishing a better alternative for managing obstructive sleep apnoea which is more user-friendly and cost-effective for sleep apnoea sufferers than the current management methods. For example, since patients are not required to wear sensors or actuators on their face or inside their mouth while sleeping, the proposed alternative has obvious appeal.

The findings of this research should also provide a new direction for researchers and medical practitioners in managing symptoms of obstructive sleep apnoea. Traditional management of sleep apnoea mainly focuses on the causes and

location of symptoms, such as the uvulopalatopharyngoplasty surgery, the use of oral appliances and the CPAP machines, the overall aim of which is to treat sleep apnoea by removing excessive tissues in the airway or enlarging the airway passage by using certain tools.

The method used in this research, however, is based on the theory of TCM. Intervention is provided immediately following the onset of sleep apnoea symptoms, which is a departure from the traditional treatment of using meridian point stimulation. TCM is usually given to patients for a specific period of time and there has been no study to report the instant effects of the treatment. Details of sleep apnoea using the meridian point stimulation will be discussed in the Chapter 3, a research area which may stimulate further studies in the future.

Also of importance in this research is that suggestions should be provided for healthcare professionals so that the occurrence of sleep apnoea episode can more promptly be indicated. Subsequent intervention to manage obstructive sleep apnoea can also be provided in a more timely fashion, ideally without interrupting and compromising the quality of sleep.

1.9 Abbreviation

ADL - Average Desaturation Level
AHI - Apnoea-Hypopnea Index
AI - Apnoea Index
ARA - Average Respiratory Arousal
AS - Abdominal Signal
ASR - Apnoea Sleep Ratio
BMI - Body Mass Index
CG - Control Group

CPAP - Continuous Positive Airway Pressure

CSA - Central Sleep Apnoea

CTAS - Combination of Thoracic and Abdominal Signal

ECG - Electrocardiogram

EEG - Electroencephalogram

EOG - Electrooculogram

EMG - Electromyogram

HDNJ - Huang Di Nei Jing

HRV - Heart Rate Variability

MAD - Mean Apnoeic Duration

MTD - Mean Time Difference

MPSG - Meridian Point Stimulation Group

ONAC - Onset of Nasal Airflow Cessation

OSA - Obstructive Sleep Apnoea

PAT - Peripheral Arterial Tone

PDS - Percentage of Deep Sleep

PSG - Polysomnography

RDI - Respiratory Disturbance Index

REM - Rapid Eye Movement

ROC - Receiver Operating Characteristic

SE - Sleep Efficiency

SG - Sham Group

SpO_2 - Pulse oximetry

SWL - Slow Wave Sleep

TCM - Traditional Chinese Medicine

TS - Thoracic Signal

UPPP - Uvulopalatopharyngoplasty

1.10 Summary

This introductory chapter discusses the present situation of sleep apnoea, its prevalence, and the aims, objectives and significance of conducting this research. In the next chapters, there will be an in-depth discussion of the previous studies which focused on the treatment methods for sleep apnoea, meridian point stimulation for respiratory disorders and sleep apnoea, and the physiological signals for sleep apnoea indication.

Chapter 2 Literature Review 1: Obstructive Sleep Apnoea

2.1 Introduction

This chapter is divided into 3 parts. The first part discusses the background information of obstructive sleep apnoea (OSA), including the pathogenesis, definitions and measurement of severity. The second part focuses on the treatment objectives of OSA, which studies the expectations of clinical practitioners and researchers for a desired outcome of treatment for OSA patients. The third part reviews the current solutions of OSA in previous studies.

2.2 Definitions of Sleep Apnoea

Sleep apnoea is defined as the cessation of airflow for at least 10 seconds during sleep [2, 139]. There are 3 types of sleep apnoea: obstructive, central and mixed. Obstructive sleep apnoea is defined as "the decrease in airflow or chest wall movement to amplitude that was smaller than approximately 70% of the baseline amplitude while obstructive hypopnea is same as sleep apnoea but the amplitude was smaller than approximately 50% of the baseline amplitude". Central apnoea is defined as "the absence of airflow, or nearly absent, for 10 seconds or more, and there was no evidence of effort from both abdominal and thoracic channels". Mixed sleep apnoea is an episode which initially appears with central sleep apnoea, but is then followed by obstructive sleep apnoea [226].

The above statement has been used in clinical practice to diagnose different types of sleep apnoea [226]. Other previous research, however, has attempted to use different criteria to define sleep apnoea in their own studies. Flemon *et al.* [67] reviewed 51 articles from 1990 to 2001 which were related to the criteria of defining all types of sleep apnoea.

In a study conducted by Ree *et al.* [173], sleep apnoea is defined as a minimal 50% decrease in amplitude of nasal pressure flow signal. Gugger *et al.* (1995) also used nasal pressure flow to define sleep apnoea. They suggested that a complete cessation of nasal pressure flow, instead of a reduction of 50%, should be found during sleep apnoea [76]. A study by Man (1995) attempted to use nasal temperature flow signal to define sleep apnoea. They mentioned that sleep apnoea is defined as a minimal of 50% decrease in the amplitude of nasal temperature flow [130]. As nasal pressure and temperature flow can be used in diagnosing sleep apnoea, a study attempted to compare the validity of these two parameters to estimate the severity of sleep apnoea. Results of this study suggested that the detection rate of respiratory events measured by nasal pressure sensors is superior to the use of the nasal thermistor [180].

Nasal pressure flow was used as the primary criteria and oxygen desaturation level as the secondary criteria to diagnose sleep apnoea in a study conducted by Bagnato (2000). In this study, sleep apnoea was defined as at least a 50% decrease in nasal airflow in association with more than 3% oxygen desaturation from the baseline level [6]. In most publications, sleep apnoea was also defined as at least a decrease of 4% from the baseline level [2, 139, 148]. Apart from the oxygen desaturation level, chest wall movement was also used as the secondary criteria in a study. Sleep apnoea was defined as the decrease in nasal temperature flow in association with at least 50% decrease in chest wall movement [225]. However, this study did not specify the types of sleep apnoea.

From these previous studies, it can be summarised that more than 50% reduction of nasal pressure flow and temperature flow are usually regarded as the primary criteria, while at least 4% oxygen desaturation and 50% reduction in chest wall effort are usually used as the secondary criteria in defining any type of sleep apnoea.

2.3 Pathogenesis of Obstructive Sleep Apnoea

The cause of OSA is usually due to the narrowing of the pharynx and upper airway during sleep [5]. The pharyngeal dilator muscles are normally able to maintain patency during waking hours. However, muscle activity tends to fall during sleep which allows the collapsing of the upper airway [219].

It is believed that anatomic abnormalities of the pharynx play a role in the pathogenesis of OSA. The pharynx is typically divided into the nasopharynx, the oropharynx (which is divided into the retropalatal and retroglossal regions) and the hypopharynx. A study found that around 75% of subjects have more than one site of obstruction in the airway and the obstruction sites can be found in the nasopharynx, velopharynx, laryngopharynx and hypopharynx [26].

Isono *et al* [94] proposed a concept of "balance of pressures" which pointed out that there are five major determinants of the size or caliber of the upper airway: (1) the baseline pharyngeal area, which is determined by both craniofacial and soft tissue structures (2) the collapsibility of the airway (3) the pressure which the airway (intraluminal pressure, P_L) (4) the pressure acting on the out side surface of the pharynx wall (tissue pressure, P_{tis}) such as compression by the lateral pharyngeal fat pad, a large neck, the effect of gravity on sub-mandibular fat and a large tongue confined to a small oral cavity (5) the pressure exerted by the pharyngeal dilating muscles (P_{musc}). Current evidence suggests that patients

with obstructive sleep apnea (OSA) may have greater pharyngeal critical pressure (Pcrit), which reflects the increase in upper airway collapsibility [73, 94]. In these studies, mandibular advancement, sleep posture, tongue position, neck flexion and enlarged uvulas, may all affect the results of pharyngeal collapsibility [191].

Another study by Sforza [192], however, suggested that pharyngeal collapsibility was influenced neither by neck size nor by body mass index, but affected the collapsibility together with obesity, upper airway structure, and abnormalities in muscle control. Other factors were also examined if they affect the pharyngeal collapsibility. Weight loss [187] and sleep position [162] is associated with decreases in upper airway collapsibility in obstructive sleep apnea rather than sleep stages [162] and gender [179]. Moreover, the decreased in lung volume results in a decrease in the area of the pharynx, an increase in its collapsibility and the loss of caudal traction or tug on the trachea [29, 30, 87].

Obesity occurs in most OSA patients with large necks when compared with both non-apnoeic snorers and weight-matched controls [105]. It was found that neck circumference correlates with several soft-tissue variables measured from lateral cephalometry [49], BMI and apnoea severity [48]. A study suggested that obesity mediates its effects in OSA through fat deposition in the neck [65]. This study also suggested that there is a relationship between craniofacial abnormality and OSA in non-obese patients [65]. Another study suggested that OSA patients who sleep in the supine position may narrow their velopharynx, and increase thickness of their tongues and soft palates, which may result in increasing the severity of OSA [235]. Apart from obesity, it is suggested that craniofacial abnormality, sleeping positions nasal obstruction, jaw malformation, floppy epiglottis and paralysed vocal cord are the predisposing factors which contribute to OSA [5, 219]. These factors are likely to cause the narrowing of the airway and results in OSA.

2.4 Measurement of Severity of Sleep Apnoea

Section 2.2 mentioned the definitions of sleep apnoea, aiming at determining if a sleep apnoea event is present during sleep. On the other hand, the severity of sleep apnoea can be quantified using the apnoea-hypopnea index (AHI) and respiratory disturbance index (RDI) [67]. In some previous studies, AHI and RDI shared the same meaning [10, 168]. In other studies, however, there is difference between these two terms in definition. AHI represents the number of sleep apnoea and hypopnea episodes per hour [103]. Patients with AHI between 5 and 15, 15 and 30 and over 30 are considered as mild, moderate and severe cases respectively [103]. RDI includes apnoea, hypopnea and respiratory event related arousals (RERAs) episodes per hour [164]. In comparison with RDI, AHI is a more common indicator for evaluating the severity of sleep apnoea [164].

2.5 Measurement of Sleep Quality

Sleep quality can be assessed using different tools or methods. The examples are the multiple sleep latency test (MSLT), Epworth Sleepiness Scale (ESS), and evaluation of the occurrence of arousals [138].

Monitoring of sleep structure in terms of the sleep staging of an individual can help to quantify sleep in a sleep study [14]. It is generally believed that sleep should follow a specific pattern with rapid eye movement (REM) sleep and non-rapid eye movement (non-REM) sleep. There are 4 stages in non-REM sleep. Stages 1 and 2 are regarded as light sleep while stages 3 and 4 are regarded as deep sleep or slow wave sleep (SWS). Chokroverty (2003) mentioned that theoretically and normally, non-REM sleep occupies 80% while REM sleep occupies 20% of total sleep time [43]. Of the 80% of non-REM sleep, 60% are light sleep and 20% are deep sleep [43]. The above estimations, however, are only used as a reference and the validation of this statement needs further testing. Limited studies were found to link different sleep stages directly with sleep quality. However, a study suggested that deprivation of SWS may worsen sleep quality than deprivation of REM sleep [172].

MSLT and ESS have been used to assess daytime sleepiness of an individual. MSLT measures the time that a subject takes to fall asleep in a designed environment. Meanwhile, sleep status was monitored using the electroencephalograph (EEG). Although MSLT has been regarded as a standard measure of sleepiness [36], a study suggested that MSLT has poor performance in discriminating daytime sleepiness from narcolepsy as compared with ESS [145]. ESS is another tool that evaluates the severity of daytime sleepiness. ESS is a questionnaire which aims to ask the likeliness of a subject to fall asleep during daily activities. A study, however, found that ESS has a statistically significant association with self-rated problem sleepiness [41]. This study also

suggested that ESS is not associated with the results of the MSLT test as well as AHI [41]. Although the ESS score improved in some studies after using treatment for sleep apnoea, it is still believed that individual subjective rating of daytime sleepiness may be affected by misinterpretation and bias [167].

Measurement of micro-arousal event can be used as another method to reflect the degree of sleep fragmentation. According to Ree *et al.* (1995), sleep disturbance can be estimated from the occurrence of sleep apnoea which ends with evidence of arousal on the electroencephalogram (EEG) [173]. Thus, measuring microarousals has been widely used as the standard technique for providing an index of sleep fragmentation, rather than daytime sleepiness. Rechtschaffen and Kales defined an arousal event as an increased frequency in EEG for at least 10 seconds [172]. The American Acadamy of Sleep Medicine (AASM), however, recommends that a micro-arousal event should be scored when there is an increase in EEG frequency for at least 3 seconds [23]. Arousal can be expressed in number per hour of sleep which is called the "arousal index". An arousal index up to 10 can be considered as normal [43]. Apart from sleep fragmentation, previous studies also attempted to evaluate the ability of using the number of arousal to predict the severity of daytime sleepiness. These studies, however, found that the arousal index is not significantly correlated with the score of ESS [167, 203]. Although there have been limited criteria that assesses the performance of using microarousal to evaluate daytime sleepiness or sleep deprivation of individuals, a study found that treatment of the sleep disruption owing to OSA can be achieved by minimising the occurrence of arousal-promoting stimuli [109]. From this study, it is possible that the degree of sleep disruption can be linked by the occurrence of micro-arousals.

2.6 Treatment Objectives of Sleep Apnoea

To evaluate the efficacy of treatment or management methods, it is very essential to refer to the treatment objectives for sleep apnoea and attempt to achieve these goals. It is found that there are 3 studies which state the treatment objectives for sleep apnoea.

In a study presented by the American Sleep Disorders Association which aims to provide guidelines for clinical research in evaluating the efficacy of treatment for sleep related breathing disorder in adults suggested that the treatment objectives for sleep disordered breathing are to improve vitality, moods and fatigue, and to improve the sleepiness and the neuro-cognitive function of the patients [2].

Hudgel *et al.* (2007) suggested several treatment objectives which specifically focused on sleep apnoea, rather than sleep disordered breathing. In this study, the treatment objectives were to relieve the clinical signs and symptoms of OSA, normalize AHI and oxyhaemoglobin saturation, reduce morbidity and mortality, improve quality of life and minimize side effects [89].

A study conducted by Hui *et al.* (2000) also mentioned specifically, the treatment objectives for sleep apnoea. In this study, they focused on introducing different types of treatment and specified the treatment objectives of sleep apnoea for relief of disabling daytime sleepiness and improvement of quality of life [90].

Based on the above information, it can be summarized that the treatment objectives of sleep apnoea can be divided into three aspects. The first aspect is the relief of symptoms of sleep apnoea. The main symptoms for sleep apnoea in these studies are the duration of OSA and oxyhaemoglobin saturation. The second aspect is the improvement in sleep quality or daytime sleepiness. The third aspect is the improvement in quality of life.

2.7 Classification of Treatment Methods

More than 500 papers related to treatment or management for sleep apnoea is found in the Medline database from 1966 to 2006. From these previous studies, it is found that the interventions for sleep apnoea patients can be divided into treatment and management, and also into conservative and medical methods.

The difference between treatment and management is that treatment can remove symptoms in the long run whereas management can only remove the symptoms when the user is using a particular method. In other words, it means that even one night without management can reverse almost all the loss in symptoms [112].

The conservative method refers to any method which encourages the patients to change their behaviours or habits whereas the medical method relies on using tools, devices or surgeries to completely remove or manage the symptoms.

2.7.1 Conservative method

Weight control

Weight control can be regarded as the earliest and a conservative method for treating sleep apnoea [113]. Initially, it was assumed that the predisposing factor of OSA is obesity because about two thirds of OSA patients were obese [182]. This issue was further proved by a study which concluded that there is a linkage between weight loss and upper airway collapsibility in OSA patients [187]. It was found that the relationship between weight loss and severe sleep apnoea is non-linear [28]. Although the relationship is non-linear, another study still suggested that the number of apnoea can be reduced by 50% with a 10% loss in weight [89]. A weight control program was carried out for 32 sleep apnoea patients and it was found that there is a significant response in reducing OSA at 6 months. The weight of these patients, however, returned to pre-treatment level after two years [102]. Due to the difficulty in achieving and maintaining weight, other forms of therapy may be required [90].

As diet therapy is relatively ineffective in treating obesity in the long term, Bariatric surgery was suggested as another form of treatment for weight reduction. Procedures of Bariatric surgery include Gastric Banding (GB), Vertical Banded Gastroplasty (VBG), Roux-en-Y Gastric Bypass (RGB), Biliopancreatic Diversion or Duodenal Switch (BPD/DS), and Long-Limb Roux-en-Y Gastric Bypass (LLRYGB). Bariatric surgery has demonstrated marked improvement in obstructive sleep apnoea/hypopnea syndrome by reducing weight according to the previous studies [25, 38, 159, 198]. Among these studies, Bariatric surgery reduced Respiratory Disturbance Index (RDI) by 55-70% and increased the minimum oxygen desaturation by almost 30%. Regarding the sleep quality, non-REM deep sleep stages (N3) increased from by 20% and the REM sleep increased by 10%.

Safety is a primary concern and there were no conclusive statements with respect to operative mortality and 30-day morbidity in a meta-analysis of Bariatric surgery [32]. However, this study pointed out that the purely restrictive procedures (GB and VBG) may be associated with vomiting in the postoperative period and the lodging of a good particle within the band or wing. The RYGBP may be associated with the dumping syndrome, iron deficiency anemia, the life-long need for oral or intramuscular vitamin B 12 supplementation and dilation of the bypassed distal stomach in the event of a small bowel or Roux limb obstruction [33]. Gastric dilation can lead to rupture and possibly death. The marked mal-absorption procedures (BPD/DS and LLRYGBP) can be associated with severe vitamin, mineral, nutrient malnutrition and may induce diarrhea, though mild and malodorous flatus [84, 132, 134, 189].

Avoidance of alcohol and sedatives

Another conservative method is the avoidance of alcohol or other sedatives, such as benzodiazepines, narcotics or barbiturates. It is because alcohol and sedatives suppress the upper airway muscle activities [182]. A study was conducted which involved five sleep apnoea patients and found that the duration and the frequency of apnoea episodes, and the severity of hypoxemia increase with high dosages of alcohol [95]. Although alcohol may increase the severity of sleep apnoea, there are no previous studies which can prove that sleep apnoea is treatable by merely avoiding the consumption of alcohol.

Change of sleeping position

Change of sleeping position is also a conservative method which encourages sleep apnoea patients to sleep in a lateral position. It is because the collapsibility of the upper airway, in terms of critical closing pressure (Pcrit) in patients with OSA during sleep is lower in the lateral than supine position [200]. A study was carried out to compare the efficacy of positional therapy with nasal CPAP using a prospective, randomised, single blind, crossover study design. Findings suggested that there is no difference between the two treatments in terms of sleep architecture, daytime sleepiness, psychometric test performance, mood and quality of life [99]. It was concluded that position therapy is effective in the short term, whereas the practicality and efficacy in the long term have not been tested [182]. Also, position therapy is recommended for patients with mild OSA and as an adjunctive measure while receiving other medical interventions, such as nasal CPAP and oral appliance [182].

2.7.2 Medical Method

Tracheostomy

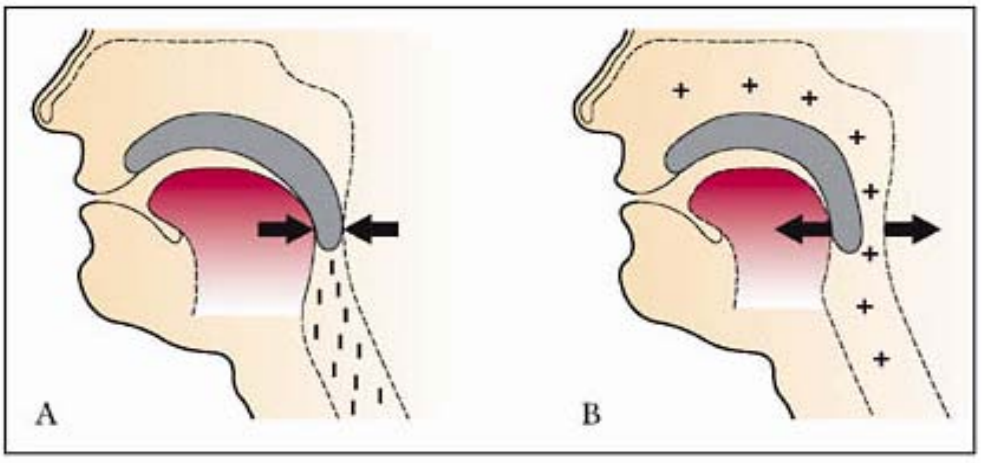
Tracheostomy, which was first introduced in 1961, has been regarded as the earliest treatment for severe obstructive sleep apnoea patients [114]. It is invasive and regarded as a highly effective form of therapy. It is a form of medical intervention that creates a percutaneous opening and inserts a rigid or a semi-rigid tube into the trachea. The patient can breathe through the tube when the external end is unplugged [206]. As it is highly effective, patients were reported to be completely relieved of symptoms and returned to normal activities after receiving this surgery in the long run [112]. The major drawbacks, however, are poor acceptance by patients due to cosmetic reasons [175] and the potential

formation of tracheal granuloma or stomal stenosis [45]. Also, few patients would select a treatment requiring a permanent prosthesis in the neck [150]. Later, in 1981, many patients preferred to use the nasal CPAP, which is regarded as effective as tracheostomy for relieving symptoms of sleep apnoea [77] .

Continuous positive airway pressure (CPAP)

The continuous positive airway pressure (CPAP) device is currently the most common and effective method for relieving symptoms of obstructive sleep apnoea [90, 112] because of its proven safety, efficacy and reversibility [182]. The CPAP device aims to prevent the collapse of the upper airway by applying positive pressure during inhalation to increase the volume of inhaled air and decrease the labour in breathing [100].

Figure 1 *The airway (A) without CPAP and (B) with CPAP [100]*

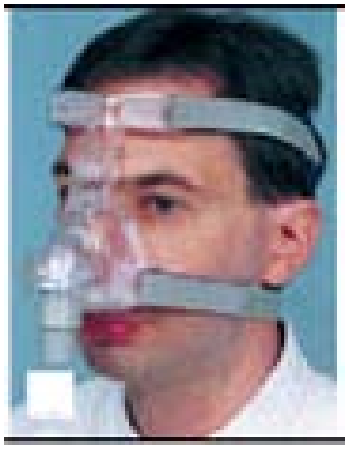


In Figure 1, the left picture is the obstructed airway. The right picture shows an unobstructed airway because the airway patency is maintained by positive pressure. Patients have to wear a mask during sleeping.

Usually, patients require admittance into a hospital for additional sleep studies to determine the level of CPAP during different sleep stages [112]. There were at least 5 randomized controlled trials which have proven that there are significant improvements in symptoms and daytime functioning of the subjects [90]. A trial found that the mean AHI is reduced from 28 to 3.4 during the use of CPAP in a group of 32 patients with moderate OSA [61]. Another trial found that there are significant improvements in terms of objective sleepiness (sleep onset latency test), subjective daytime sleepiness (Epworth daytime sleepiness score), and symptom scores (assessment of snoring, nocturnal choking, morning headache, nocturnal awakenings, daytime napping, evening napping, sleepiness whilst driving) [60]. Mild OSA patients with AHI between 5 and 15 were also helped by the CPAP treatment in terms of symptoms, mental flexibility and mood [59].

Some CPAP devices are designed with a well fitted mask while some can be operated quietly. Additional functions of CPAP devices, such as humidification, heated humidification and auto-adjustable unit for controlling the overall mean pressure during the night, may improve the compliance, but the overall cost may also increase [112]. A study, however, found that the long term compliance rates of CPAP devices are still only 60% to 70% [75, 214]. Patients have to wear a mask on their face, so they generally feel uncomfortable and are inconvenienced [122]. Figure 2 illustrates a person wearing the CPAP mask.

Figure 2 Person with CPAP mask



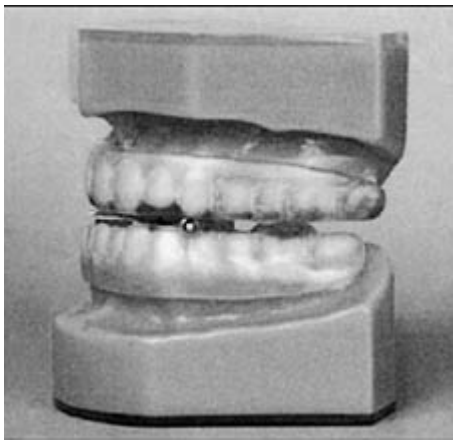
Marquez *et al.* (1998) found that around 61% of participants complained after using the CPAP device because of nose dryness, congestion, and rhinorrhea [133]. Forty-six percent of participants complained that their sleep was disturbed due to noises from the CPAP devices and six percent of participants gave up the treatment because of side effects [133]. Some patients developed a severe panic reaction when they were on the nasal CPAP circuit [112].

Tracheostomy and the CPAP can be applied to sleep apnoea patients if no specific sites of obstruction in the upper airway is found [112]. Another approach for considering a suitable method for sleep apnoea patients is to identify the cause. In some circumstances, apnoea is caused by a specific condition or disease, and if it is possible, this disease should be treated. Examples of such diseases are acromegaly, sarcoidosis, carcinoid syndrome, hypothyroidsm, goiter and lymphoma [112]. Another suggestion is to find the site of the obstruction along the airway. In this case, surgeries may be applied to cure these problems. The possible sites of obstruction are the nasal area due to anatomical abnormalities or inflammation, and enlarged tonsil or adenoids [89]. Face skeletal abnormality can also be a factor and surgery might be useful in improving the symptoms of snoring and sleep apnoea [124].

Oral appliance

Patients who cannot tolerate the CPAP may use an oral appliance or in other terms, mandibular advancement. An oral appliance is another non-invasive measure for snoring and obstructive sleep apnoea (OSA). An oral appliance is mainly used to hold the mouth and tongue in place to prevent the blockage of the airway. Oral appliances were effective in relieving apnoea in 20% to 75% of patients with OSA in a study [142] and it is well tolerated by sleep apnoea patients with less serious side effects than the CPAP device. It is usually effective in treating mild to moderate cases [90]. A study reported that the oral appliance can improve snoring in 80% to 100 % of patients and eliminated snoring in 15% to 64% of patients [64]. The oral appliance, however, may cause occlusal change and temporal mandibular joint discomfort. Figure 3 shows the oral appliance.

Figure 3 Oral appliance [100]



Drug

Drug therapy plays a limited role in treating sleep disordered breathing and usually applies to a small amount of patients. It is used only if CPAP or the oral appliance is ineffective or not available [112]. Protriptyline and fluoxetine are used if a patient has obesity and mild to moderate obstructive apnoea without hypercapnia. The aim of using protriptyline and fluoxetine are to suppress rapid eye movement sleep and thus, reduce apnoea in some cases. The side effect is an increase in sleeping difficulties [80]. Another study found that the side effects of taking protriptyline are dry mouth, impotence, constipation, and urinary hesitancy [31]. Another form of drug therapy is to use nasal steroids and decongestants. The aim of applying steroids is to help patients with nasal congestion widen the upper airway. The effectiveness of these methods, however, is only limited to a short period of time [112]. Other medications, such as progesterone, theophylline, and acetazolamide are not recommended as a good method for sleep apnoea patients [184].

Surgery

Due to the complications of tracheostomy, such as stoma or airway infections, granuloma formation and difficulty in speech, uvulopalatopharyngoplasty (UPPP) is regarded as an alternative surgery which aims to remove the excessive tissues in the airway, such as uvula and pharyngeal arches or the soft palate. UPPP was introduced in 1981 which was also the same year that the nasal CPAP emerged. A review on medical treatments for sleep apnoea mentioned that around 40% to 50% of patients have the number of apnoea events reduced by about half after UPPP surgery [112]. A meta-analysis showed that there is a 41% chance of achieving an AHI lower than 20 after UPPP surgery [197]. Another study

concluded that UPPP does not modify long-term mortality [81] and will not improve apnoea due to nasal obstruction [112].

Laser assisted uvulopalatopharyngoplasty (LAUP) is another form of surgery which was introduced by Kamami in 1990. The aim of this surgery is to progressively shorten or tighten the uvula and palate through a series of carbon dioxide laser incisions and vaporizations [175]. Kamami noticed that 40% of patients were cured with improvement in RDI from 41.5 to 16.9. Another study found that there is a 48% success rate, 21% of patients experiencing a worsening of their disease, 15% without significant changes, and 36% had a postoperative RDI greater than 20, after the LAUP [217]. Another study mentioned that the indication of LAUP is for snoring alone rather than OSA [90]. A more in-depth study is essential to investigate the long-term efficacy of LAUP for sleep apnoea patients.

Maxillo-mandibular advancement is another form of surgery which is recommended for patients with craniofacial abnormalities. This method aims to enlarge the retrolingual and retropalatal airway using a rigid plate fixation and bilateral sagittal split mandibular osteomy with bicortical screw fixation [175]. A report showed that this method successfully managed 90% of the patients [86]. The cost of this surgery may be high due to the complexity of the procedure and the associated orthodontic therapy [174]. Complications of this method were anaesthesia of the lower lip in most patients, tooth injury and wound infection after the surgery [182].

Due to the limited efficacy of UPPP and LAUP in some patients, other forms of surgery have been developed and designed to remove excessive lingual tissue and increase the calibre of the retrolingual oropharynx. Examples are glossoplasty, laser midline glossectomy, radiofrequency tissue ablation, lingualplasty and tongue base suspension [182]. These surgeries may be able to

treat mild to moderate sleep apnoea. A study conducted a randomised control trial which aimed to compare the efficacy of temperature controlled radio frequency tissue ablation (TCRFTA) of the tongue and soft palate with sham placebo surgery and nasal CPAP of 90 mild to moderate OSA patients. It was concluded that TCRFTA improves reaction time, disease specific quality of life and subjective sleepiness whilst CPAP improved quality of life and sleepiness. Overall, TCRFTA and nasal CPAP produced comparable improvements in quality of life with mild to moderate obstructive sleep apnoea [231]. The complication of this surgery was tongue base abscess. The possible reason was the use of perioperative rinse, antibiotics, and steroids during surgery [231]. Surgery, however, is still not widely accepted by patients because of invasiveness and the formation of postoperative trauma.

Electrical stimulation

A relatively new approach for managing sleep apnoea is the application of electrical pacing. Electrical stimulation has been used for restoring breathing in patients with high quadriplegia causing respiratory paralysis and patients with central alveolar hypoventilation [46]. Electrical pacing is placed on the phrenic nerves. It was found that many patients have strong positive results after receiving the stimulation. Current applications of electrical pacing for sleep apnoea aim at increasing the muscle tones of the genioglossus and hypoglossal muscles or nerves by attaching electrodes in the sub-mental or intra-oral area [78].

Electrode pacing can be divided into three approaches. They are surface electrodes, muscular electrodes (on the surface of muscles and intramuscular), and nerve electrodes [138]. The methods of using electrical pacing for managing sleep apnoea was initially introduced in 1981 by a group of Japanese researchers.

Their study involved six subjects and it was found that electrical pacing decreases the incidence of apnoea episodes and promotes a deeper sleep, but without induced arousals, and changing blood pressure and heart rate [141]. This study stimulated subsequent studies. These studies mainly focused on electrical stimulation for managing symptoms of sleep apnoea or provided muscle training.

Among these studies, electrical stimulations were usually applied either upon the general submental or intraoral area [54, 78, 215], or specifically, the lingual musculature [50], hypoglossal nerve [186], soft palate [188] and genioglossus [152, 234] of subjects. The effectiveness of using electrical stimulation varied in different studies [55]. Several studies mentioned that electrical stimulations increased the number of arousal events [54, 153] while without significantly reducing the number of apnoeic episodes [54, 78, 215]. Other studies, however, mentioned that the frequency of apnoea episodes reduced significantly [85, 166, 186, 234] while subjects remained asleep during electrical stimulations [141, 166, 186, 188, 234] and the severities of oxygen desaturation of subjects were reduced [166, 186]. This method also produced both positive and negative results on different subjects in a trial [188].

Although the efficacies in terms of number of apnoea episodes and the arousal index of electrical pacing vary among these studies, it was found that the effect of electrical nerve stimulation is better than muscle stimulation as neural stimulation required much less energy and stimulation on the genioglossus is preferred [140]. Also, it is suggested that electrical pacing is more effective on patients with obstructive sleep apnoea rather than central sleep apnoea as the respiratory drive ceases in the central apnoea completely and breathing does not occur even if the upper airway is open [140].

Drawbacks of using electrical stimulation are that the stimulation may produce discomfort to the users as electrodes are invasively implanted inside the intra-oral area of patients [55] and also the intra-oral area is sensitive to stimulations. If surgery is required to implant the electrodes into the oral area, an experienced medical professional should provide anesthesia and sterile techniques prior to the surgery [140].

Another concern is whether the stimulation can be applied continuously without causing muscle fatigue overnight or in a closed loop form. A study mentioned that the stimulation level used in the current literature is much lower than the maximum recruitment level of the muscles. Therefore, patients will not experience discomfort during waking hours and so, continuous stimulation can be applied for mild OSA patients by merely decreasing the upper airway compliance. This study, however, mentioned that it is still favorable to apply closed loop stimulation than continuous stimulation because intensive stimulation can cause the fatigueable fibers to become fatigue resistant in the long term [140]. If closed loop stimulation is used, a prompt and reliable physiological signal will play an essential role in the stimulation as this signal will help in deciding the time of stimulation by continuously monitoring the respiratory condition of the patient.

In light of this issue, it is very critical to select a physiological signal which can promptly indicate the occurrence of sleep apnoea and ensure that the sensor will not cause any discomfort to the patients during sleep.

Sections 2.7.1 and 2.7.2 discussed the methods for sleep apnoea patients in view of western medicine. As mentioned in section 2.7, these methods can be divided into conservative and medical, and into treatment and management. Table 1 summarises the methods into these 4 categories.

Table 1 *Summary of sleep apnoea interventions in four approaches*

	Treatment	Measure
Conservative	● Weight Control	● Position training ● Avoidance of alcohol and seductives
Medical	● Tracheostomy ● Surgeries (UPPP, LAUP)	● CPAP device ● Oral appliance ● Electrical stimulation

Regardless if treatment or the measure is conservative or medical, they have been studied previously, but none of these methods are able to completely remove or manage symptoms of sleep apnoea with satisfactory compliance.

2.8 Summary

This chapter presents the definitions, mechanism and treatment objectives of obstructive sleep apnoea. We also discussed the problems of current management methods for OSA patients. In the next chapter, reviews regarding the application of OSA in light of traditional Chinese medicine (TCM) and the methods for managing OSA using the TCM approach will be discussed.

Chapter 3 Literature Review 2:
Obstructive Sleep Apnoea in Traditional Chinese Medicine

3.1 Introduction

This chapter discusses obstructive sleep apnoea (OSA) using the theories of traditional Chinese medicine (TCM) and the application of TCM in managing OSA. This chapter consists of three parts. The first part introduces the theories of TCM which includes the concept of "Qi", meridian theory and forms of meridian point stimulation. The second part focuses on syndrome differentiation of OSA in TCM. The third part studies and selects a meridian point which is believed to be effective in relieving symptoms of OSA immediately by using electrical stimulation. Thus, the efficacy of applying electrical stimulation on this meridian point for managing symptoms of OSA is evaluated in Chapter 8.

3.2 Theories of Traditional Chinese Medicine

Theories of TCM have over 3000 years of development [251]. TCM emphasizes on "wholism", "syndrome differentiation" and the regulation of "Qi". Wholism refers to the integrity and unity of the entire body. It also refers to the inter-relationship between nature of the body and the external natural surroundings [274]. Change in nature may directly or indirectly influence the body, causing physiological and pathological reactions [97, 232]. In TCM, these physiological and pathological reactions can be recognized and diagnosed using "treatment determination based on syndrome differentiation" [274]. It is a method that not only focuses on the syndromes, but also decides an appropriate

therapeutic measure according to the diagnosis. In TCM, syndrome differentiation involves the identification of syndromes (辨證), symptoms (症狀) and diseases (辨病) [274]. The main difference of the diagnostic method between TCM and western medicine is that syndromes are identified using four examination methods only in TCM. They are inspection, auscultation-olfaction, interrogation and palpation (望聞問切) [121]. After determination of the syndromes, treatment options are mainly decided with four approaches: "treat deficiency conditions by supplementation" (虛則補之), "treat excess conditions by purgation or reduction" (實則瀉之), "treat heat conditions with cold or cooling method" (熱則寒之) and "treat cold conditions with warming or heating method" (寒則熱之) [259].

In TCM, human health depends on the motivation of energy within the body, which is known as "Qi" (氣). Hypothetically, "Qi" should be maintained in a way that it should not exceed a certain limit and move in a smooth and balanced way through a series of meridians in the form of twelve channels underneath the skin [259]. Stagnation, excessive or deficiency of "Qi" may become pathological factors in causing diseases [259]. Thus, stimulation of various meridian points can correct the flow of "Qi" in order to optimize health [19].

The theory of the meridian (經絡學說) is an important part of TCM. Meridians are distributed along different hypothetical pathways in the body called "Jing" (經) and "Luo" (絡). These pathways allow the circulation of "Qi" and blood flow within the human body [35]. "Jing" means a hypothetical path which includes 12 regular meridians, 8 extra meridians and 12 divergent meridians. "Luo" means a hypothetical net which includes 15 collaterals, minute collaterals and superficial collaterals [259]. The theory of meridian is an important component in TCM which combines physiology, pathology, diagnostic theories and treatment principles, together with the theory of "Yin Yang" (陰陽) and the five elements and the theory of "Zang Fu" (臟腑). It constitutes a theoretical

basis of Chinese medicine [259]. Meridian point stimulation can be used as health care, self-care technique for promoting health balance, curing or preventing diseases and disorders by stimulating the specific meridian points in order to stimulate the meridian flow and function of internal organs. In TCM, there are 14 meridians and 361 meridian points. Each meridian or meridian point connects a specific organ aimed at circulating "Qi" and blood [19].

3.3 Existence of meridian

It is of interest to verify whether meridian and meridian points exist in reality, or if they are only a hypothetical assumption. A trial was conducted in 1977, in which the subjects were asked if they have any sensations along a pathway underneath the skin surface after receiving electrical stimulations. The results found that around 1.3% of subjects have sensations of soreness (酸), numbness (麻), distension (脹) and tingling (痛) along the large intestine meridian by applying stimulation on the "Jing" meridian point (井穴) [255]. This phenomenon is the so called "propagation sensation along the channel" or PSC (循經感傳). This phenomenon, however, was only found in around 10% to 20% of the population [260].

Another phenomenon, namely the "Latent propagation sensation along the channel", or LPSC (隱性循經感傳) was introduced in the previous literature which is expected to be found in 58% to 100% of the population [260]. LPSC refers to any sensation induced by electrical stimulation as well as mechanical stimulation (such as tapping) [260]. The word "latent" is used because unless through tapping, no prominent sensation of propagation can be felt. It was suggested that the phenomenon of LPSC is basically coincident with the traditional theory of the meridian in TCM [260]. An extensive study was conducted in 1981 in which tapping stimulations were applied at the Jing points

which belongs to the large intestine or stomach channel. Specific propagational numb feelings were reported by the subjects along these two channels [244]. Another study summarised the findings of 200 patients in acupuncture clinics and concluded that around 68.5% of patients are found to have positive LPSC [237]. Subsequent studies or trials on LPSC have been conducted. In 1990, a trial was carried out and it was found that there are changes in the physiological properties (including sound and electrical impulse) propagating along the large intestine channel during the application of needling or other stimuli on the Jing meridian point (井穴) [222]. This large intestine channel was coincident with the traditional intestine channel as suggested in TCM.

Apart from the sensations reported by the subjects, it is found that impedance is lower at the meridian point of the large intestine channel than that at the control point, but electrical currents on the meridian point are higher than that at the control point [222].

A trial was conducted on animals which aimed to compare electromyological changes between the meridian points of the pericardium and lung meridians of cats after they received electrical stimulation on their left inferior cardiac nerve [241]. In TCM, the pericardium meridian governs the heart. Indications of the pericardium meridian are heart problems and emotional agitation. The results of this experiment showed that the electromyological change of the pericardium meridian increases distinctly after the stimulation of the left inferior cardiac nerve. The electromyological of the lung meridian does not show any significant changes after the stimulation of the left inferior cardiac nerve [241]. Thus, it is believed that there is a specific relationship between a meridian and a specific organ as suggested in TCM.

The phenomenon of PSC or LPSC attempts to provide evidence in relation to the existence of meridians. The path of PSC or LPSC is coincident with the classical theory of meridian. In light of this issue, previous studies suggested that stimulation of the meridian points can provide a therapeutic effect against different pathological conditions [255, 265].

3.4 Property of meridian

Although limited studies were found which focused on studying the property of the meridian, related issues were found in academic books which are related to meridian theory and acupuncture [255, 259, 260]. It can be summarised that the speed of propagation along the meridian is around 0.1 meter per second. The velocity of propagation also varies in different locations. It is suggested that propagation along the forearm or lower leg is faster than the upper arm or upper leg. The width of the meridian is around 0.5 to 3 cm. According to "Huang Di Nei Jing" (黃帝內經), the direction of propagation can be divided into uni-direction or bi-direction, depending on the location of stimulation. Usually propagation is transferred in a bi-direction if the stimulation is released in the middle of the meridian [259]. Propagation can also be affected by mechanical pressure and change of temperature (such as putting ice cubes) over the skin surface [259].

3.5 Forms of meridian point stimulation

There are four types of meridian point stimulation in general. They are acupuncture, acupressure, moxibustion and electrical stimulation. Acupuncture is an invasive therapy which treats pain or disease by inserting a needle at specific points through the skin. A systematic review on acupuncture summarised that it is effective in treating emesis, nausea and relieving pain in previous trials [104]. Although acupuncture is commonly used among TCM practitioners, itching in the punctured region is reported [19, 143]. Also, acupuncture requires a high degree of precaution as well as sterilization [19, 143].

Owing to the invasive nature of acupuncture, other non-invasive forms of meridian point stimulation have been suggested as alternatives. They are acupressure, moxibustion and transcutaneous electrical/nerve stimulations (TENS). These forms of stimulation manipulate a meridian point without applying needles. Acupressure is regarded as a natural therapy which simply uses pressure to achieve a therapeutic effect. Acupressure is usually recommended for relief of pain or fatigue [272]. A review which is related to acupressure summarised that acupressure is effective in treating nausea, primary dysmenorrhoea, depression, sleep disorder, anxiety, and respiratory problems [262]. The efficacy of using acupressure depends on the amount, types, directions, frequencies, area and durations of pressure [272]. A study suggested that acupressure would provide the greatest therapeutic effect when this practise is done by humans, who are living organisms with internal energy (in TCM, it is "Qi") [264]. Thus, acupressure can be referred as a practice of transmitting "Qi" between two living organisms while mechanical devices only provide a mechnical pressure without any transmission of "Qi".

Moxibustion is the burning of moxa or another substance over the skin. It was proven as an effective therapy for enhancing the immune system, blood circulation and treating inflammation [240]. Moxibustion is the stimulation of meridian points using heat [272]. It is suggested that moxa should not touch the skin for an extended time in order to avoid burning [143].

High frequency and low intensity of electrical stimulation have been attempted to replace acupuncture for effectively treating different diseases or disorders, such as pain, depression, anxiety, spinally induced muscle spasms, strokes, gastrointestinal disorders and drug addictions in previous clinical trials [18, 160, 210, 223]. Electrical currents can be applied either invasively or non-invasively, depending on the use of tools. The invasive method is called electroacupuncture, which stimulates the meridian point by an electrical needle. The non-invasive method is called transcutaneous electrical stimulation, or TENS, which stimulates the meridian point through a surface electrode. A trial studied the antinociceptive effects by TENS and electroacupuncture on rats and concluded that the electrical stimulation provided by surface electrodes is as effective as electroacupuncture [220]. Also, non-invasive electrical stimulation does not damage the skin and thus allows the users to continue every day if necessary [143].

The specifications of electrical stimulation vary among different trials. Although electrical stimulations are used for treating different diseases or disorders, it can still be summarised that the common specifications in clinical practices are bi-phasic pulse waves [27, 229, 230] and burst pulse chain [128, 131]. The pulse shape is usually in a square or rectangular form [27, 229, 230, 242, 243]. Also, the pulse frequency within each burst is 100 Hz [128, 131, 208, 242, 243, 261, 270] and the pulse width is 0.2 ms [131, 229, 242, 243, 261]. The burst rate and width are 2 burst per second [128, 131] and 70 millisecond [128, 131] respectively. Another important issue is the intensity. In fact, the intensity used

in a previous study ranged from 0 to 20 mA, but usually between 10 and 11 mA is commonly preferred in clinical trials [101, 229, 230, 242, 243, 261]. From these studies, the highest intensity for not causing arousal is 50 Hz with 40 microseconds pulse duration. TENS can be used for 6-8 hours during sleep and 6 nights weekly [18].

TENS is not suggested for any users with a pacemaker, unstable cardiac diseases, active tuberculosis, an area with active haemorrhage, distal to an area of thrombophlebitis, during pregnancy, uncontrolled seizures, and cognitive impairments [18]. TENS should also be used cautiously in obese patients because of the difficulty in conduction through the skin and adipose tissues which results in increasing electrical currents and burns [18]. It is also important to ensure the electrical stimulation should not be too strong on skin with diminished or absent sensation or fragile skin [18].

Electrical stimulation of the intra-oral area, which was mentioned in the previous session, aims to manage the symptoms of OSA by stimulating the pathological site. This research, however, applies electrical stimulation on the meridian point which aims to regulate the flow of "Qi" and thus manage the symptoms of OSA instantly. Although the location of stimulation is completely different, the ultimate goal of both methods is to instantly relieve the symptoms of OSA. Differentiation of sleep apnoea in TCM is completely different from differentiation in theory of western medicine.

3.6 Obstructive Sleep Apnoea in Traditional Chinese Medicine

3.6.1 Causes of obstructive sleep apnoea in TCM

Although sleep apnoea has been discussed for more than 30 years, academic papers in relation to OSA with respect to TCM were found starting from 1991 [266]. Based on the suggestions in the previous studies, causes of OSA in light of TCM in Chinese are summarized below:

(1) Due to formation of phlegm and blood stasis in the airway, when the lung is not able to generate body fluid and the spleen is not able to digest the fluid, the throat is blocked with phlegm. The phlegm may also become blood stasis afterwards and block the airway which results in obstructive sleep apnoea. *(睡眠呼吸暫停綜合症的病理因由以痰濕和瘀血為主。即肺不能布津，脾不能運化，腎不能蒸化水液，以津液氣化失司而形成痰濕，並阻於喉間，痰濕日久，又可形成血瘀，以致痰瘀互結而成疾)* [266]

(2) There are several reasons. First, the accumulation and stagnation of phlegm in the upper airway causes the retention of "Qi" and causes dysfunction of the lungs. This phenomenon particularly occurs at night during sleep. Thus, snoring episodes and breathing pauses are usually found. Secondly, other pathogenic factors, such as the exposure of wind and heat may cause the deficiency of "Qi and result in obstructive sleep apnoea because of the blockage of phlegm in the airway. Thirdly, smoking may also cause excessive fluid and blood stasis in the airway, and causes the dysfunction of the lung and results in snoring and breathing pauses during sleep. Fourth, emotional disorder would be another factor which causes the deficiency of spleen and stagnation of "Qi" activity, and also causes the blockage of lung "Qi" and the airway. Fifth, the stagnation of the liver "Qi" and the deficiency of the spleen

cause e xcessive bod y f luid a nd phl egm. T hereafter, s noring o ccurs because o f t he pa rtial b lockage of t he ai rway by t he phlegm. L astly, long-term di sease causes t he de ficiency of l ung and spleen function, which l imits t he c ontrol of "Qi" and c auses t he f ormation of phl egm. Snoring r esults be cause of t he i ntermingling of phlegm a nd "Qi" i n t he airway. *(痰濕上阻於氣道，壅滯不暢，痰氣交阻，肺失宣降，入夜尤甚，出現鼾聲如雷及呼吸暫停等症狀。或因外邪犯肺，感受風熱之邪而傷津耗氣，灼津成痰，阻于咽喉，或嗜烟成性，燥傷津液，氣滯血瘀痰凝，肺失宣降而作鼾，甚則呼吸暫停。或因情志失調，憂思氣結，肝失調達，氣機疏泄失常，肺氣閉阻。或肝郁犯脾，津液失布，痰蘊咽喉而眠時鼾鳴。或因久病勞欲，久病肺弱脾虛，氣失所主，津液失布而成痰，痰氣交阻而致鼾)* [267]

(3) This is due to the blockage of phlegm in the airway which is caused by the deficiency of the spleen function and masking of orifices. *(脾虛濕困，痰瘀阻 竅)* [254]

(4) Due to excessive phlegm in the body, excessive phlegm stagnates in the spleen a nd t he s tomach a nd m ay affect t he r egulation of Q i a nd m ay mask of the orifices. Obstructive sleep apnoea is resulted. *(痰濕壅盛，內滯脾胃，氣機運行失常，痰氣交阻 ，蒙蔽清竅所致)* [268]

(5) Due to excessive phlegm which stagnates in the spleen and the stomach and t hus a ffects t he regulation of Q i. Finally, phl egm a nd "Qi" a re intermingled in the airway and results in obstructive sleep apnoea. *(痰濕壅盛，經絡閉阻所致)* [276]

Based on t he di scussions i n t he literature, c auses of s leep a pnoea c an be summarized as (1) the d eficiency of t he s pleen "Qi", (2) bl ockage of "Q i" b y phlegm and (3) masking of orifices.

3.6.2 Treatment objectives of obstructive sleep apnoea in TCM

In Chinese, treatment objectives of obstructive sleep apnoea with respect to TCM are:

(1) To remove the excessive phlegm by reinforcing the spleen, clearing the throat and nose, or invigorating "Qi". *(以健脾化濕祛痰壅盛，或利咽通鼻以治其標，或培補元氣以治其本)* [258]

(2) To reinforce the function of spleen and stomach and improve the regulation of "Qi and blood. *(以健運脾胃，益氣活血為主)* [269]

(3) To remove excessive phlegm, open the orifices and reinforce the spleen and the lung. *(以化痰祛瘀開竅，兼健脾理肺為主)* [254]

(4) To eliminate the pathogenic factors, open the orifices and activate the brain functions *(以祛邪為法，兼開竅醒神的為主)* [268]

(5) To remove excessive fluid, improve the transportation of the fluid, dredge the meridians, remove excessive phlegm, clear the throat and nose, and activate the brain functions. *(以健運化濕，疏通經絡，祛痰，利咽，通鼻竅而醒腦為主)* [276]

To conclude, treatment objectives focus on (1) regulating the lung, (2) reinforcing the spleen, (3) invigorating the kidneys and (4) promoting blood circulation.

3.6.3 Treatments of obstructive sleep apnoea using meridian point stimulation

The common treatment options for sleep apnoea in TCM are administrating Chinese medicine and acupuncture [256], or integrating western medicine with TCM. Options of integration include behavioral training, oral appliances and acupuncture. A study found that treatment with the combination of an oral appliance and acupuncture were able to effectively manage symptoms of sleep apnoea [247].

From 1991 to 2007, eight academic papers which were related to sleep apnoea and TCM, or meridian point stimulation and sleep apnoea, were found. A study emphasized on symptom differentiation of obstructive sleep apnoea and seven studies were related to clinical trials using acupuncture for managing sleep apnoea.

The first study was a pre-post trial which applied acupuncture [273]. In this study, seven meridian points (DU20, EX-HN1, KI3, PC6, RN17, RN23 and ST40) were chosen. After 30 days of treatment, subjects were reported to have 67.8% reduction in terms of the frequency of obstructive sleep apnoea. Validity of this study is questionable as only one subject was involved.

The second study involved a group of subjects and the sample size was 18. In this study, an oral appliance, Chinese medicine and acupuncture were applied at the same time to the subjects. The Chinese medicines were biond magnolia flower (辛夷花), hout tuynia cordata thunb (魚腥草), ling zhi (靈芝), chuanxiong (川芎) and platycodon grandiflorus (桔梗). The selected meridian points were KI3, KI6, LI4, LI11, LR3, PC6, RN4, RN6, RN12, RN17, SP4, SP6, SP9, SP11, SP15, ST24, ST34, ST36, ST40 and ST44. After 20 days of

treatment, subjects were reported to have 62.7% reduction in terms of the apnoea index (AI) [247].

The third study was a pre-post trial which also involved a group of subjects with a sample size of 16 [276]. Acupuncture was given on the DU20, DU26, LI4, RN4, SP6, ST25, ST36 and ST40 meridian points of the subjects. After 30 days of treatment, four patients were reported as normal and ten patients had reduction in terms of the severity of obstructive sleep apnoea. The treatment, however, had no therapeutic effect on two patients.

The fourth study was also a pre-post trial which involved a group of subjects [268]. The sample size in this study was eight. Acupuncture was applied on the motor and sensory area of the brain. The treatment period was 30 days. Results found that the frequency of sleep apnoea in five patients is reduced by 50%. This study, however, did not specify the type of sleep apnoea in the patients.

The fifth study was a pre-post trial which was conducted in a group of subjects [269]. The sample size was 24. Acupuncture was applied on Anmian, EX-HN1, HT7, KI6, ST36 and SP6 meridian points. After 10 days of treatment, it was found that the average AHI of subjects is reduced by approximately 33%.

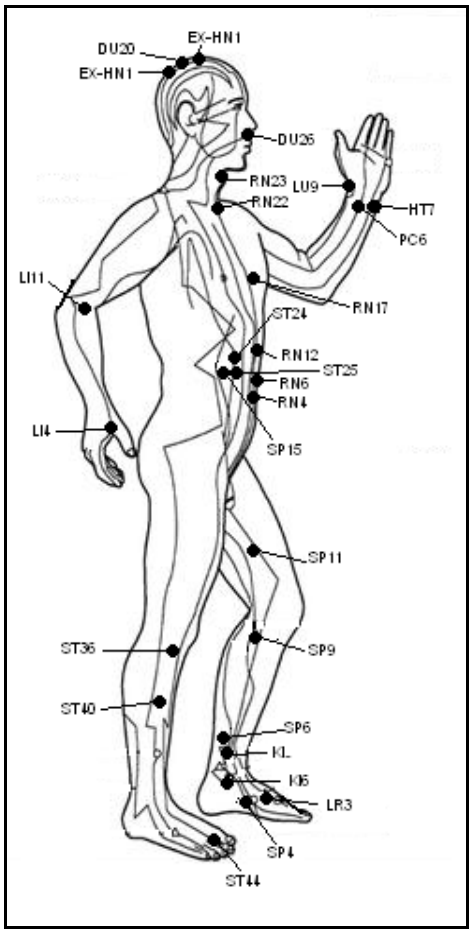
The sixth study was conducted with aims to evaluate the therapeutic effect of subjects after taking Chinese medicine [254]. One hundred and twenty subjects were recruited and they were randomly assigned into treatment and control groups. Subjects in the control group received one form of any treatment, including behavioural control, ACEI medicine, CPAP device, drugs for cardiovascular diseases, injection of Chinese medicine fufang danshen (複方丹參) and acupuncture. Subjects in the treatment group received treatments that were the same as the control group plus the administration of Chinese medicine, including citrus maxima (橘紅), fu ling (茯苓), almond (杏仁) and sinalbin (白

芥子). Effects were assessed after 30 days and 90 days. It was found that AHI in the treatment groups is reduced from 36 to 18 after 30 days, and from 36 to 3 after 90 days. AHI in the control group is reduced from 37 to 24 after 30 days, and from 37 to 30 after 90 days. The authors suggest that the integration of Chinese medicine and traditional therapy is more effective than only using the traditional therapy to manage symptoms of OSA. Obviously, this study did not focus on evaluating the efficacy of acupuncture on OSA. Although acupuncture was provided to patients in this study, the efficacy of acupuncture was unclear as this study only mentions the overall results of the control group in terms of AHI, rather than the efficacy of each therapy.

A recent study focuses on the differentiation of sleep apnoea with respect to TCM. Although this study did not conduct a clinical trial to test the efficacy of stimulating the meridian point for managing OSA, suggestions in terms of the reasons of sleep apnoea and the meridian point were provided based on syndrome differentiation of OSA. They suggested that stimulation on LU9, ST40 and RN22 are able to relief symptoms of OSA.

Referring to the above studies, it can be summarized that a pre-post one group clinical design is commonly used to assess the therapeutic effects of acupuncture on OSA. Also, the “ren” (任脈), “du” (督脈), heart, kidney, large intestine, liver, lung, pericardium, spleen and stomach meridians were usually used to treat obstructive sleep apnoea. Figure 4 illustrates the location of the selected meridian points for sleep apnoea patients according to these clinical trials.

Figure 4 *Summary of the meridian points for treating sleep apnoea in the previous clinical trials*



In the above studies, the "ren", spleen and stomach meridians were commonly used to treat OSA. No adverse effect was reported in these studies. Referring to the results in these clinical trials, symptoms in terms of the frequency and duration of sleep apnoea improved in patients after receiving acupuncture. Daytime sleepiness, snoring, dizziness, nocturia and sleep quality also improved [269, 276]. Although acupuncture produced positive therapeutic effects on sleep apnoea patients and without any reported adverse effects as mentioned in the previous studies, electrical stimulation is still preferred over acupuncture in this research because electrical stimulation is non-invasive and just as effective as acupuncture for relief of symptoms.

3.6.4 Selection of the meridian point for management of OSA

The previous studies have selected different meridian points for treating sleep apnoea as mentioned in section 3.6.3. The treatment objective in these studies, however, aims to cure the root of the disease such as to improve the deficiency of spleen Qi, rather than managing the symptoms immediately. In light of this issue, this section selects a meridian point which is believed to have a potential managing effect on symptoms of OSA. The selection of this meridian point is divided into 4 steps.

Step 1: Selecting the meridian in the upper limb

The selection of the meridian point in this research depends on its indication and location. Stimulation of this meridian point should provide an optimum therapeutic effect to the patients and preferably, the location of stimulation should be convenient and easy for identification. To enhance the user-friendliness of applying meridian point stimulation for managing OSA, it is preferable to select the meridian point in the arm so that the user can adjust the device easily during sleeping. On the other hand, stimulation should be released on the skin surface continuously without causing any discomfort to the user. Thus, electrical stimulation on the intra-oral area, head, neck or chest should be avoided. It is preferable to select the meridian point in the upper limb and provide electrical stimulation in this study. There are six meridians along the upper limb: the lung meridian of the hand; Taiyin (手太陰肺經), pericardium meridian of the hand; Jueyin (手厥陰心包經), heart meridian of the hand; Shaoyin (手少陰心經), large intestine meridian of the hand; Yangming (手陽明大腸經), triple energizer meridian of the hand; Shaoyang (手少陽三焦經) and small intestine meridian of the hand; Taiyang (手太陽小腸經).

Step 2: Studying the indication of the meridian

The second step in selecting an appropriate meridian point is referring to the indications of different meridians based on the theories of TCM. Table 2 summarises the indications of the 6 meridians which are found in the upper limb. The indications are referred as Huang Di Nei Jing, 黃帝內經 (HDNJ), which is the earliest and important source of acupuncture theory [83] [251].

Table 2 Summary of indications of the six meridians in the upper limb

Meridian	Indications
Lung Meridian	● Respiratory disease ● Diseases of the five senses ● Any diseases along the course of the meridian
Large Intestine Meridian	● Upper airway disease ● Diseases of the five senses ● Any diseases along the course of the meridian
Heart Meridian	● Cardiovascular disease ● Neurological disease ● Any diseases along the course of the meridian
Small Intestine Meridian	● Diseases of the five senses ● Febrile disease ● Mental disease ● Any diseases along the course of the meridian
Pericardium Meridian	● Cardiovascular disease ● Neurological disease ● Fullness sensation in the chest ● Gastric pain ● Vomiting ● Spasm of the elbow and arm ● Feverish sensation in the palm ● Any diseases along the course of the meridian
Triple Energizer Meridian	● Diseases of the five senses ● Febrile disease ● Any diseases along the course of the meridian

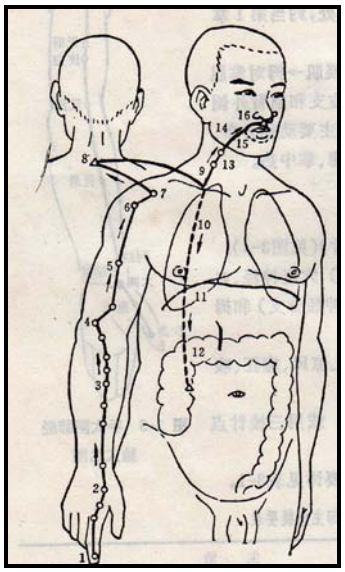
With reference to the indications of these 6 meridians, the lung meridian and large intestine meridian can be selected to manage symptoms of OSA as the indications of these 2 meridians are respiratory or upper airway disease while the other meridians are only used for treating diseases of the five senses, neurological diseases and diseases related to the origin organ of the meridian.

Step 3: Studying the route of the meridian

As the lung and large intestine meridians were selected based on the indications, the next step is to study the route of these 2 meridians. The route of a meridian is a channel which allows the transmission of "Qi" [259]. In TCM, stimulation on a meridian point, which connects to the pathological site (病變部位), may produce an instantaneous managing effect because "Qi" can reach the disease directly and instantaneously (氣至病所) by the stimulation [265]. Hence, this research focuses on a new approach, which is to provide a direct and instant managing effect on the symptoms. In other words, a meridian point chosen in this research is not only based on the indication, but also refers to the pathway of the meridian.

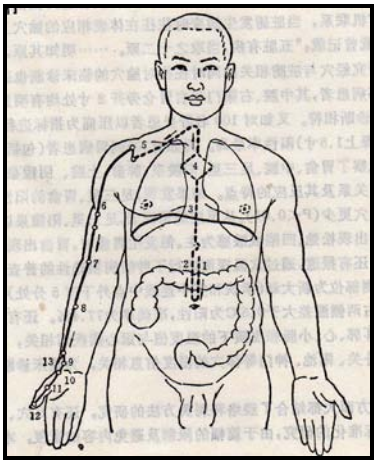
According to TCM, the large intestine and lung meridians pass through the airway to the eyes, nose and chest respectively. The route of the large intestine meridian passes through the airway. The large intestine meridian originates from the tip of the index finger then goes along the lateral side of the forearm and the anterior side of the upper arm, and via the highest point of the shoulder [259]. At the shoulder points, the large intestine meridian divides into two branches. One branch goes downward towards the lungs, diaphragm and large intestine. Another branch goes upwards towards the neck and cheek, enters the lower teeth and gums, and then curves around the upper lip and crosses to the opposite side of the nose [259]. Figure 5 shows the route of the large intestine meridian.

Figure 5 The large intestine meridian [259]



The route of the lung meridian also passes through the airway. The lung meridian originates in the middle portion of the body and goes downwards to the large intestine and then turns upwards via the diaphragm to connect with the lungs. There are two branches. One starts inside the chest, in the lungs, surfaces in front of the shoulder, down the upper arm, elbow, forearm, and wrist to the end of the thumb. Another goes from the lung, via the throat and the armpit to the tip of the thumb [259]. The lung meridian controls all the respiratory passages [143]. Figure 6 shows the route of the lung meridian.

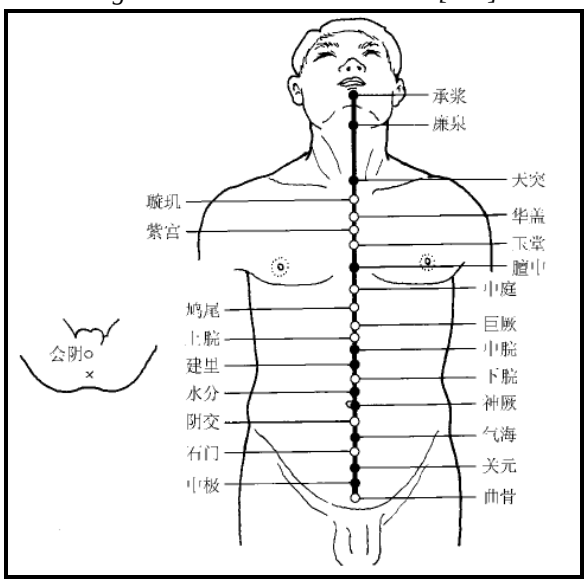
Figure 6 The lung meridian [259]



Step 4: Studying the connection of the meridians

With reference to HDNJ, the lung meridian connects to the large intestine and ren meridians [251]. The connection point between the large intestine and lung meridians, and the connection point between the ren and lung meridians is the Lieque (列缺, LU7) meridian point. According to the theory of the "eight confluence points" (八脈交會穴) which was developed by Dou Hanqing (竇漢卿) in the Yuan Dynasty (元代) [277], the eight confluence points refer to any meridian points which connect the twelve main meridians (十二經絡) and the eight extra meridians (奇經八脈). Lieque (LU7) is one of the "eight confluence points" which connects to the lung meridian and the "ren" meridian. Figure 7 shows the route of the "ren" meridian.

Figure 7 The "ren" meridian [249]



The “ren” meridian passes through the upper energizer and aims to regulate “Qi” and blood of the heart and lungs. Stimulations of this meridian can help patients for relief of coughing, asthma, chest pain, vomit and clear sputum [263]. Tanzhong (CV17), Tiantu (CV22) and Lianquan (CV23) meridian points, which belong to the “ren” meridian, are used to treat airway diseases [263]. Stimulation on the “ren” meridian by acupuncture and cupping therapy (拔罐) was also used in treating asthma in a previous trial [248].

To provide a systematic review about the potential contributing factors of the six meridians on sleep apnoea, Table 3 summarises the indications, route and connecting meridian of the six meridians:

Table 3 Summary of contributing factors of the six meridians for sleep apnoea

Contributing Factor		Lung Meridian	Large Intestine Meridian
1	Via the upper limb	√	√
2	Meridian via the airway	-	√
3	Branch via the airway	√	-
4	Treats respiratory disease	√	√
5	Treats throat disease	√	√
6	Connects to	➢ Large intestine meridian ➢ Ren meridian	➢ Lung meridian

Step 5: Selecting the meridian

Of these two meridians, the lung meridian may provide a better therapeutic effect for respiratory disease by applying the instantaneous meridian point stimulation as compared with the other meridians. It is because the lung meridian connects to the large intestine and "ren" meridians. According to TCM, stimulations of the "ren" meridian can help in treating abdomen, chest, neck, tongue, throat and head diseases [143, 259] and indication of the large intestine and lung meridians is respiratory disease. These three meridians also pass through the airway.

Step 6: Selecting the meridian point

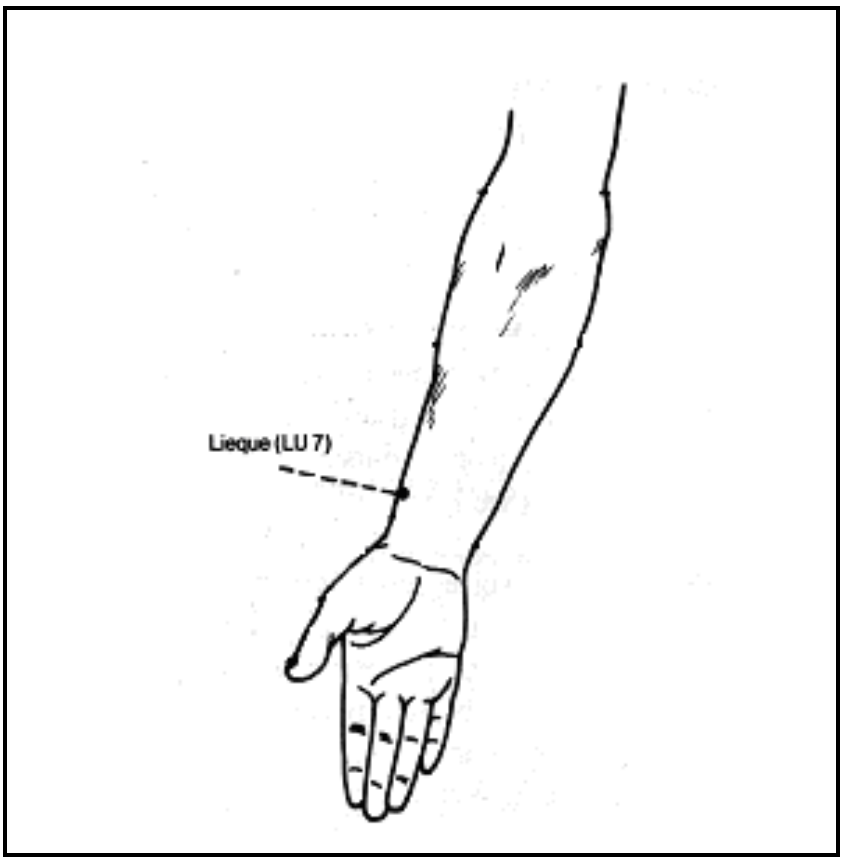
The lung meridian is proposed to provide a direct therapeutic effect on sleep apnoea as this meridian connects the airway and also controls the respiratory system according to its indications. The Lieque (LU7) meridian point is selected for providing instantaneous intervention to manage symptoms of sleep apnoea because of the following reasons:

Indications of the Lieque point is airway problems (lung disease, chest disease, coughing, asthma and sore throat) [251, 259]. As compared with other meridian points along the lung meridian, the LU7 connects to the "ren" and large intestine meridians [251]. This may help in maximizing the the rapeutic effects on managing symptoms of sleep apnoea by applying instantaneous meridian point stimulation

3.6.5 Identification of the location of the Lieque meridian point

The Lieque (LU7) meridian point is located on the anterior forearm of a 3 finger width above the wrist. Moreover, it is located on the medial (ulnar) edge of the radial artery and on pul se V (right, endocrines; left, organs of sense). Several meridian points can be found adjacent to the LU7 point. LU7 is located at a 5 finger width under the kongzui (LU6) meridian point, a little above the Jingqu (LU8) meridian point, and separated by the large palmar tendon from Neiguan (PC6) [143, 259]. Figure 8 illustrates the location of the Lieque (LU7) meridian point.

Figure 8 Location of the Lieque (LU7) meridian point



3.6.6 Indication of the Lieque meridian point

Indications of the LU7 meridian point is the improvement of the condition of the "respiratory passages including influenza, throat opposite, tonsils, larynx, cough, trachea; bronchioles; abundant mucus; fever from lungs; pulmonary congestion (contracted breath, less energy for breathing), rusty and red sputum" [143].

A review summarised studies with concern to the clinical trial using the LU7 point between 1996 and 2006, and concluded that the LU7 point is used to effectively treat respiratory diseases, head and neck pain, reproductive-organ disease and urinary disease in previous clinical trials [275]. Hence, it is promising to apply the LU7 point for treating respiratory diseases.

3.7 Summary

This chapter discusses the core concept of TCM, including the regulation of "Qi" and also depicts evidence that meridians exist. Stimulation on a meridian point is likely to produce a direct therapeutic benefit on curing diseases and enhancing health conditions of individuals. The causes of OSA in light of TCM based on previous literature were summarised and a meridian point was selected which is used by TCM doctors to relieve symptoms of respiratory diseases. The lists of the indications of such meridian points based on the literature were also discussed. The optimum stimulation intensity that is used in previous studies is depicted. The meridian point chosen in this chapter will be tested with the application of electrical stimulation on patients with OSA in terms of managing effects. The results will be stated in Chapter 8.

Chapter 4 Literature Review 3: Physiological Signals for Indication of Sleep Apnoea

4.1 Introduction

In this chapter, the physiological signals that were also used in previous studies for the diagnosis of obstructive sleep apnoea (OSA) were studied. The performances of these physiological signals in terms of sensitivity and specificity, and also the drawbacks of using the signals to diagnose OSA are summarised in this chapter. Based on the information in this chapter, a critical signal was selected and evaluated with its performance to indicate the occurrence of OSA in terms of promptness and accuracy. This will be discussed in the chapter 6.

4.2 Significance of Physiological Signal Detection

In order to effectively manage symptoms of sleep apnoea, intervention must be applied as soon as possible. As sleep apnoea can occur at anytime during sleep, it is preferable to be able to predict episodes. To date, however, there has been limited research on being able to predict when a sleep apnoea event actually occurs during an overnight sleep study. One study was attempted to apply the artificial neural network to predict OSA [110], however, it only focused on using clinical scores, such as daytime sleepiness and body mass index (BMI), to predict whether the subject could potentially develop OSA.

To investigate the possibility of using a signal to predict the occurrence of a sleep apnoea event would require extensive research on human physiology, with no point of reference, given the absence of prior studies. An alternative approach would be to monitor the physiological changes of patients during sleep apnoea events and to identify a critical signal that could effectively and promptly indicate the occurrence of sleep apnoea. Ideally, this would be done using a sensor which would not interfere with patient comfort.

4.3 Physiological Signal for Polysomnography (PSG) Study

Selecting a critical parameter requires a study of signals that have been commonly used for diagnosing sleep apnoea. Firstly, it must be determined which signals or tools are currently used by medical professionals to identify sleep apnoea. In hospitals or sleep laboratories, a polysomnography (PSG) device has generally been used [226]. PSG is a graphs howing multi-physiological signals. Subjects must wear numerous sensors in order to monitor and record their physiological changes during sleep. Signals include electroencephalogram (EEG), electrocardiogram (ECG), electromyogram (EMG), electro-occulogram (EOG), nasal and temperature flow, thoracic and abdominal movement, snoring, pulse oximetry level and sleeping position.

Portier *et al.* [169] have noted that using the PSG for sleep apnoea monitoring is "labour intensive and expensive". For sleep assessment, patients usually need to spend a night in a sleep laboratory or hospital and must wear numerous sensors and electrodes that are attached to their face, neck and limbs. Adhesive sensors cause discomfort to users.

Portier *et al.* [169] have thus proposed the need for setting up a practical, less expensive and less time consuming approach to monitoring sleep apnoea, preferably under home or unattended conditions. A portable PSG device is an alternative to screening sleep apnoea but patients must still wear numerous sensors [157]. The need for a study requiring less physiological signals to diagnose sleep apnoea is evident.

Because of the lengthy waiting period for a sleep study in hospital, a possible solution is to simplify the process of monitoring and allow home-based sleep apnoea monitoring.

The American Sleep Disorders Association (ASDA) has categorized the monitoring method of sleep apnoea into 4 types [63]. Type 1, the standard PSG, which is currently used in hospitals and sleep laboratories, monitors around 10 types of physiological signals of subjects. Type 2, a comprehensive portable PSG, is used at home and in the monitoring of around 10 types of signals. Type 3, modified portable sleep apnoea, is tested by the monitoring of 3 or 4 types of physiological signals of subjects at home. Type 4 monitors only one type of physiological signal of subjects. It is acceptable by the ASDA to use only one type of signal to diagnose sleep apnoea, however, it is not recommended.

In this study, the primary concern was whether the application of a single parameter was reliable in indicating OSA. The portable monitoring task force of the American Academy of Sleep Medicine (AASM) suggested that portable monitoring of sleep apnoea must record airflow, respiratory effort and blood oxygenation at a minimum [42]. However, the above monitoring approaches were suggested for medical professionals to estimate the total number of sleep apnoea events for one night. The results were used to diagnose whether the individual suffered from sleep apnoea or not, rather than immediate indication of the occurrence of a sleep apnoea event. There have been studies which have

attempted to provide a reference point for using only one type of physiological signal to diagnose sleep apnoea. The following paragraphs reveal previous work in which only one physiological signal was applied to monitor sleep apnoea.

4.3.1 Electroencephalogram (EEG)

An electroencephalogram (EEG) is mainly used to assess the sleep quality of an individual. An electroencephalogram (EEG) is associated with different sleep stages. Rechtschaffen and Kales (1968) developed a classic scoring system, which classifies different sleep stages based on the frequency and amplitude of the EEG [172]. The use of an EEG to identify the sleep stages of an individual during a sleep study brings into questions whether EEG signals are linked to the respiratory status of users and whether it would promptly indicate the occurrence of OSA.

One way to explore this area is to determine whether there is a relationship between brain activity and sleep apnoea. Central sleep apnoea stems from the brain's failure to control breathing as mentioned in the literature [129]. For OSA, respiratory arousal usually occurs during upper airway obstruction, which is provoked by stimuli from the medullar centre [109]. Because of the repetitive occurrences of micro-arousals, an EEG is a good indicator of the degree of sleep fragmentation [167]. Micro-arousal is characterised as an abrupt shift in the EEG frequency, which lasts from 3 -10 seconds and does not result in complete awakening [4]. As micro-arousal is usually found at the end of a sleep apnoea event [4], it is very promising to evaluate the severity of sleep apnoea in individuals by only using EEG signals as an indicator of the number of arousals during a sleep study.

Limited studies, however, have been found to apply EEG signals alone in screening suspected cases of sleep apnoea. Although it is very promising to apply EEG signals to evaluate the severity of sleep apnoea, the ability of using this signal to promptly indicate the occurrence of sleep apnoea is uncertain. This is due to the fact that the arousal was found at the end, rather than at the beginning of a sleep apnoea event.

4.3.2 Electrocardiogram (ECG)

An electrocardiogram (ECG) has been mainly used to monitor the regularity of heartbeat during a sleep study. Apart from monitoring whether there are any abnormal ECG signals during a sleep study, researchers have also studied the phenomenon of arrhythmias during and after sleep apnoea episodes [24, 246]. Most importantly in this session is whether heart rate can be used as a prompt and critical indicator by interpreting the regularity of heart rate in order to monitor sleep apnoea.

Bradycardia has been reported as characteristic of sleep apnoea in recent decades [24]. Patients with sleep apnoea tend to have a lower heart rate during sleep apnoea and a higher heart rate following breaths after cessation of breathing [24]. Zwillich *et al.* (1982) pointed out that increased vagal efferent activity during sleep apnoea appeared to cause bradycardia. They also reported that the degree of bradycardia increased with an increase in the duration of sleep apnoea in almost all sleep apnoea events [246]. Findings of another study also suggested that nocturnal episodes of bradyarrhythmia was directly related to the severity of sleep apnoea [211]. This study also suggested that obesity and REM sleep increased the chances of having bradycardia in subjects because obesity and REM sleep increased the risk of having sleep apnoea events. The study of

Zwillich *et al.* however, suggested that the degree of bradycardia did not vary with the type of sleep apnoea [246].

Because of the phenomenon of bradycardia in sleep apnoea, more and more studies have focused on studying the rhythmic change of heart rate. Heart rate variability (HRV), which reflects the activity of the autonomic system, has been studied in recent years to screen suspected cases of sleep apnoea [79, 146, 171, 176]. Theoretically, the cessation of breathing activates autonomic components in the respiratory center of the medulla. Impulses are then sent to the heart to compensate for the lack of oxygen and low blood pressure [70]. A study was conducted to measure the spectral components of ECG signals in short 2-minute time windows with sleep apnoea and the results were compared with healthy control subjects. It was concluded that an elevated sympathetic tone was found during disordered breathing, which is a reference to HRV signals [51]. Another study also concluded that sympathetic activation increased during the course of sleep apnoea as the sympathetic activity of sleep apnoea patients during wakefulness, sleep and with CPAP [147] was measured. Previous studies have proven that the performance of using time domain HRV for screening sleep apnoea is satisfactory [161, 176].

It was found, however, in previous studies on HRV and the screening of sleep apnoea, that usually a considerable sample size of ECG data was needed in order to identify each sleep apnoea event. The time length of ECG signals for each analysis ranged from 30 seconds to 5 minutes and the analysis was performed after instead of during a sleep study [70, 176, 239]. The optimum time length of ECG signals required to perform HRV analysis was further investigated by Chazal *et al.* (2004) [39]. In this study, different time lengths of ECG signals were captured for classification of sleep apnoea and normal breathing. The shortest time length was 15 seconds and the longest was 90 seconds. Findings suggested that the classifier using HRV analysis in their study was able to

correctly identify sleep apnoea events in both short and long time lengths. However, there was a reduction in terms of accuracy for both short and long time lengths of data. The reason for a reduction in accuracy in short epochs was an insufficient number of QRS complexes in order to derive statistically meaningful estimations of the autonomic activity or breathing changes related to sleep apnoea [39]. In summary, the study suggested that the optimum time scale for HRV analysis was around 60 seconds.

4.3.3 Nasal and oral flow

Inspiratory effort can be determined by using oesophageal pressure (Pes) to estimate pleural pressure [62]. However, because the method is invasive and uncomfortable, thus having an adverse effect on sleep [181], oesophageal pressure has not been routinely monitored by most sleep centres.

A simple and less invasive alternative to Pes monitoring is to use nasal and oral flow signals [62]. Signals of nasal and oral flow are usually measured in terms of pressure and temperature. A pressure flow sensor is a nasal cannula, which is a plastic hollow tube. A temperature flow sensor, meanwhile, is merely a small piece of wire. According to the American Academy of Sleep Medicine Task Force (AASMTF), nasal and oral flow is recommended as an indicator in monitoring sleep apnoea events during a sleep study [2]. A study also recommended that a nasal airflow sensor produced accurate results in calculating AHI without monitoring oesophageal pressure [108].

Nasal and temperature airflow has an excellent agreement with a pneumotachography but a drawback has been false positive identification of sleep apnoea and hypopnea due to nasal congestion as well as mouth breathing [82]. Users may still experience discomfort from the sensor, however, as the tip

of the nasal flow sensor occludes the nasal passage [127]. A study has also pointed out that patients have sometimes complained about nasal irritation from the placement of the nasal cannula [3].

It would appear that a nasal and oral flow signal produces accurate results in so far as it directly reflects the respiratory condition of the orifices, however, it is still not preferable for continuous monitoring during sleep because the sensor may be dislocated due to frequent body movement and subjects may experience discomfort when using it.

4.3.4 Snoring

Snoring is the primary symptom of OSA. Snoring occurs when there is partial blockage of the airway, causing a vibration of the throat or other airway muscles [123]. Habitual snorers may not always suffer from sleep apnoea. However, snoring is regarded as a key indicator when determining if subjects are more likely to suffer from sleep apnoea. A study developed an algorithm using snoring signals to identify pure breathing, snoring and OSA [209]. The study showed that the sensitivity of OSA detection was 86-100% while the specificity was around 50-80%.

One study actually suggested that the snoring pattern in OSA patients may be different from habitual snorers [163]. Snoring in OSA is characterised as relatively more powerful with a high frequency and occurring at the end of an apnoeic event while habitual snoring is characterised as the repetitive occurrence of snoring with a cyclic change in frequency [163]. This phenomenon was also suggested in another study [120].

Although a snoring sensor is light-weight and it is apparently easy for practitioners to interpret snoring signals, two things have to be taken into consideration before choosing snoring as a critical parameter in this research. Firstly, there is no clear cut stance on "loud snoring" in OSA based on previous studies and the severity of sleep disorder breathing interpreted by snoring varies among individuals [209]. Secondly, snoring may not be a prompt indicator of OSA because snoring occurs after the cessation of breathing, that is, well before the subject resumes breathing. Thus, using snoring as a critical indicator means intervention may not be provided in this case in a timely matter.

4.3.5 Body position and movement

In a sleep study, the aim of monitoring body position is to identify if there is a relationship between the frequency of sleep apnoea events and the sleeping position in order to provide relevant medical advice to patients [69]. Body positions have been shown to influence the upper airway collapsibility and thus may increase or decrease the chance of having OSA events [69]. Patients who sleep in supine positions may increase the gravitational pull on their uvulas and other airway muscles. This may result in a further decrease in the airway size and thus impede air flow during respiration. A study found that the severity of sleep apnoea in patients lessoned by avoiding the supine position during sleep [13]. As body position is monitored to evaluate if there is a risk factor of causing OSA in a particular patient, limited studies have been found on using body position as an immediate indicator of the occurrence of OSA.

Apart from monitoring body position during sleep, the frequency of body movement is also linked to OSA. One study attempted to investigate whether there was a relationship between OSA and periodic limb movement (PLM). The study suggested that PLM was associated with the severity of OSA [8], in which

case an increase in the frequency of OSA would also mean an increase in the frequency of PLM. Based on this study, it seems that PLM can be used as an indicator to predict the severity of OSA. However, it also suggests that PLM occurred in association with micro-arousal at the termination of OSA [8]. Therefore, PLM occurs at the end of a sleep apnoea event. It was found, however, that body movement is not only linked to sleep apnoea or arousal but may also occur in healthy individuals during spontaneous arousal [207] or occur anytime during sleep for posture change. In view of the above considerations, body movement may not be a reliable indicator of OSA.

4.3.6 Blood pressure and pulse arterial tone (PAT)

Blood pressure usually falls when an individual is sleeping and rises with arousal [144]. OSA patients tend to have higher blood pressure than normal individuals [52]. Patients with OSA may experience increased mean systolic blood pressure and blood pressure variability as repetitive arousals increase blood pressure variability [47]. As mean blood pressure increases in OSA patients, the question is whether the occurrence of sleep apnoea can be detected by measuring the change in blood pressure during sleep. It is critical to identify if blood pressure changes concurrently with the occurrence of OSA.

The intra-arterial blood pressure monitoring is invasive and with inherent risk [92]. Hence, a currently non-invasive monitoring method for monitoring finger arterial pressure is proposed which provides a fast, effective and continuous method for screening sleep apnoea. This non-invasive method monitors the pulse arterial tone (PAT). PAT reflects the changes in blood flow in the peripheral arteries [151]. Bar *et al.* (2003) pointed out that the changes in blood flow in the peripheral arteries reflects sympathetic nervous system activity, and the autonomic system regulates many physiological conditions such as respiration

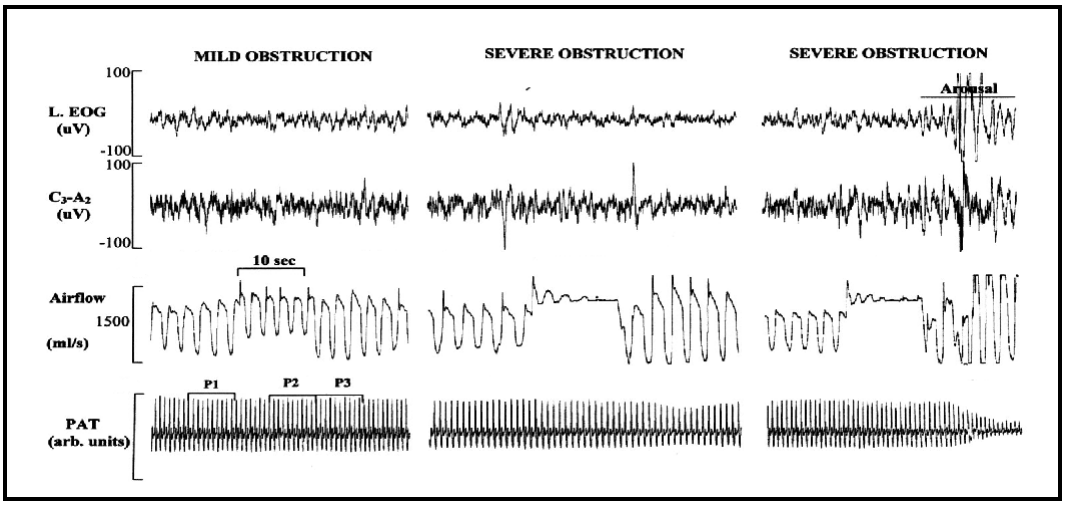
and arousals [7]. Bar *et al.* carried out a study on 69 subjects with suspected OSA and 33 healthy subjects to examine the efficacy of using PAT signals to screen sleep apnoea. The study demonstrated that there was a high-correlation between the results of PAT and the apnoea-hypopnea index (AHI), which was measured by a polysomnography. The study also found that the receiver operating curve (ROC) value was between 0.82 and 0.87 [7] and seemed to indicate that PAT signals were reliable in detecting the occurrence of OSA.

The promptness of using this signal to indicate OSA is key in this research. Although the accuracy of PAT in screening suspected cases of OSA was found to be high in previous studies, Imadojemu *et al.* (2002) suggested that apnoea-induced vasoconstriction usually occurred during post apnoea [91].

Another study was also carried out to evaluate the influence of OSA and arousal on the PAT signal [151]. Figure 9 shows the polysomnography tracings of EOG, EEG (C3-A2), airflow and PAT signals, which were captured simultaneously in this study. The left tracing is an event with mild obstruction. The middle tracing is an event with severe obstruction. The right tracing is an event with severe obstruction and arousal. EOG and EEG signals in the right tracing show arousal during post apnoea with abrupt changes in the amplitude of the two signals. With reference to the nasal flow (airflow) and the PAT signals of the 3 tracings, PAT signals did not change significantly during a mild obstruction event but the amplitude was decreased during a severe obstruction event. The duration of OSA in these 3 tracings was around 10 seconds. In the middle tracing, it was found that the amplitude of PAT slightly decreased after an apnoea event. In the right tracing, the amplitude of the PAT signal decreased dramatically in association with arousal. The decrease in amplitude of the PAT signals was found after the subject had restored breathing, usually 5 to 8 seconds post apnoea. From these tracings, it seems that PAT signals may not be able to indicate mild cases of OSA and may not even be able to indicate all OSA events as promptly as nasal airflow

signals.

Figure 9 *Tracings of the EOG signal, EEG (C3-A2) signal, airflow signal and PAT signal [151]*



4.3.7 Thoracic and abdominal efforts

Thoracic and abdominal movement can be used to differentiate between obstructive sleep apnoea (OSA), central sleep apnoea and mixed sleep apnoea. This is because thoracic and abdominal effort is absent during central sleep apnoea and both are present during OSA [195]. Although central sleep apnoea can be identified through thoracic and abdominal effort, limited studies have been carried out on whether there are any changes in these two signals despite the continued presence of effort during OSA. Hence, it remains uncertain as to whether thoracic and abdominal signals can be applied as the only indicator in promptly diagnosing OSA.

In previous studies, it was suggested that the phase relationship between thoracic and abdominal signals could be used to detect the occurrence of OSA. A patent document claimed that it was possible to use the phase angles of thoracic and abdominal signals to diagnose sleep apnoea [115]. The inventors claimed that a sleep apnoea event could be detected by measuring the variability of the difference in phase angles between thoracic and abdominal effort. The variability of phase angle was measured and compared with the baseline phase angle (a pre-calibrated value) in every ten seconds. According to the patent document, this method was suggested as a critical indicator to detect OSA and can be used as an indicator to trigger a therapy apparatus such as a CPAP device.

Other studies have also pointed out that OSA is usually associated with paradoxical thoracic and abdominal movement [201, 212]. This refers to a situation in which the thoracic and abdominal cavities move opposite each other due to the obstruction of the upper airway. Varady *et al.* [212] conducted a study to evaluate the performance of using phase difference analysis of thoracic and abdominal signals to distinguish the type of sleep apnoea from normal breathing and the results were satisfactory.

Apart from the phase relationship, it is uncertain whether the amplitude of thoracic and abdominal signals changes corresponding to the occurrence of OSA. With reference to the definition of the types of sleep apnoea, patients with central apnoea have no thoracic and abdominal movement during sleep apnoea events [195]. In a study, OSA was defined as approximately a 30% reduction in airflow or thoraco-abdominal excursion in association with a 4% decrease of oxygen desaturation [149]. The aim of this study was to describe the characteristics of OSA rather than evaluate the performance of using the amplitude analysis for indicating OSA. To further confirm the phenomenon of a change in the amplitude of thoracic and abdominal signals before and during OSA, polysomnography tracings of nasal airflow, and thoracic and abdominal

effort were recorded simultaneously in a study [148]. These tracings are shown in Figure 10. The duration of Figure 10 was 3 minutes and the duration of OSA events were around 24 to 32 seconds.

Figure 10 *Polysomnography tracings of nasal airflow, and thoracic and abdominal effort during obstructive sleep apnoea [148]*

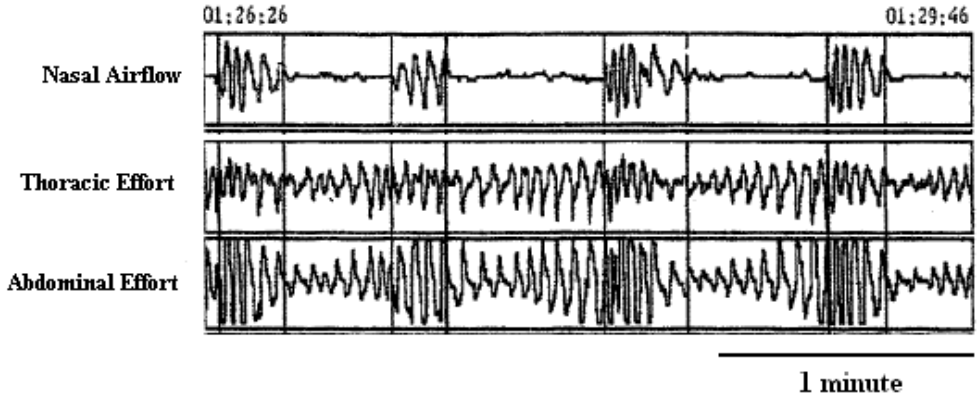


Figure 10 shows that the amplitude of thoracic and abdominal effort decreased concurrently with the decrease of nasal airflow signals with around 25% in effort. Hence, it seems promising that the change in the amplitude of the signals to indicate OSA was as prompt as nasal airflow signals.

A previous study, however, attempted to apply the concept of the phase relationship of the two signals in indicating OSA in a smart garment. Loriga *et al*. [126] conducted a study to introduce the potential application of using the smart textile materials to measure thoracic and abdominal effort. By using the smart textile material, the phase differences and the amplitudes of thoracic and abdominal signals as indicators of the occurrence of sleep apnoea can be measured. This sensor only uses a piece of soft and breathable textile cloth to increase the comfort of users. However, the study did not evaluate the

performance of using the smart garment as an immediate indicator of OSA events.

It would appear that the majority of previous studies have only explained the potential application of using thoracic and abdominal signals to differentiate OSA from normal breathing and limited tests to evaluate the performance of these signals. Meanwhile, the promptness of applying these signals to indicate OSA events remains uncertain.

4.3.8 Pulse oximetry level

Pulse oximetry (SpO_2) level has been used to provide screening for OSA [106, 148, 169, 221, 224, 227, 238]. Because of the expense and a long queuing time for sleep studies in hospital or sleep laboratories, previous studies have attempted to use home based pulse oximeter monitoring to diagnose suspected OSA [224]. The use of a pulse oximeter in measuring the level of arterial oxygen saturation was previously believed to be cost effective and user-friendly [12, 148]. A pulse oximeter senses the differences between oxyhaemoglobin and deoxyhaemoglobin in the absorption spectra [227, 238]. Based on research studies in the past 11 years, the sensitivity and specificity of using the pulse oximeter for screening sleep apnoea was found to vary from 31 to 98% and from 41 to 100% respectively [148]. Although this constituted a wide range in terms of sensitivity and specificity, it was believed that the SpO_2 level was likely to produce satisfactory screening power for sleep apnoea.

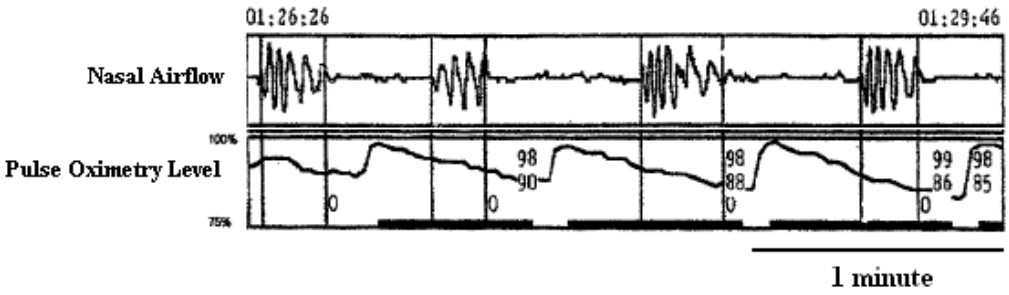
The majority of previous studies generally focused on evaluating the performance of using the SpO_2 signal to estimate the number of sleep apnoea events and compared the results with nocturnal polysomnography in order to determine the severity of diseases of individuals [227]. Although the results were

satisfactory, no study was found to use the SpO_2 level to provide immediate indication of OSA. Hence, the time that the SpO_2 level would normally be used in response to an apnoeic event remains uncertain.

It is also very important to interpret the threshold of the SpO_2 level for indication of sleep apnoea. In fact, threshold value is critical in assessing the performance of a signal as it affects the sensitivity and specificity values in a diagnostic test. According to a review about the SpO_2 level, there is no universally accepted definition of oxygen desaturation in sleep-disordered breathing [148]. However, in most publications, oxygen desaturation is defined as a decrease of $\geq$4% from the baseline level [2, 139, 148] even though the reason for using 4% from the baseline as the threshold value is not specified. Based on this definition, it would seem that the identification of a baseline level is also critical given that the baseline value is used to directly compare against the threshold value. In fact, the baseline SpO_2 level during normal breathing may not always be 100%. A previous study found that the mean SpO_2 level was 96.5% ($\pm$ 1.5%) during sleep in 350 healthy individuals and that it decreased slightly with increasing age [148]. Notably, however, body movements, vasoconstriction, and hypertension may affect the reading of the SpO_2 signal [148] and should be carefully considered when performing the test using the SpO_2 level.

Figure 11 illustrated the polysomnography (PSG) tracings of the nasal airflow signals and the pulse oximetry level (SpO_2), which were recorded simultaneously in a study [148]. OSA occurred when the nasal airflow signals were flat and oxygen desaturation was found with an underline score in the tracing of the pulse oximetry level. The duration of OSA events in Figure 11 was around 24 to 32 seconds. Although the SpO_2 was not able to indicate OSA as promptly as nasal airflow signals, it would appear that the SpO_2 level reflected the occurrence of OSA before the termination of the OSA event.

Figure 11 *Polysomnography tracings of nasal airflow signal and pulse oximetry level during obstructive sleep apnoea [148]*



Hence, a study of whether the SpO_2 level would be able to indicate OSA before the termination of OSA remains paramount. Seemingly, the application of the SpO_2 level was only to provide screening for suspected sleep apnoea. An analysis of this signal was performed after the sleep study to estimate the frequency of sleep apnoea, instead of immediate indication of an apnoeic event. It also remains uncertain about whether the use of the SpO_2 level would be able to immediately reflect the occurrence of OSA.

4.3.9 Other parameters

There are some parameters that were used in the screening of suspected sleep apnoea. One study used video recording to evaluate the possibility of a subject having OSA. This study predicted the likelihood of subjects having OSA using a scoring system based on noisy breathing, movement, walking episodes, chest retractions and mouth breathing based on the investigator's clinical assessment [199]. Although the sensitivity in this approach was around 90%, an experienced medical professional was involved. Another approach evaluated daytime sleepiness as an indicator of a subject having OSA [98]. These approaches

tended to evaluate the possibility of subjects having OSA, rather than the immediate indication of a sleep apnoea event.

4.3.10 Selection of physiological signals for immediate indication of OSA

The selection of a physiological signal to indicate OSA is very important in this research in order to ensure that intervention is provided once it is needed. Ideally, patients should feel comfortable when using sensors during sleep. Nasal and oral flow signals can be used as a single parameter that is able to directly and immediately reflect the respiratory status of users. Because the sensors have to be placed underneath the nose, patients may feel uncomfortable and irritated when using them. Hence, the possibility of using alternative signals to replace the nasal and oral flow sensor according to the literature must be explored. This chapter details the use of different signals including EEG, ECG, HRV, snoring, body position and movement, peripheral arterial tone (PAT), pulse oximetry level, and thoracic and abdominal effort to estimate the severity of OSA.

It was found that previous studies were primarily carried out to evaluate the performance of selected signals in screening OSA in order to simplify the process of diagnosis, reduce the queuing time for a sleep study in hospital, and also to reduce the cost and need for the facilities usually involved in conducting a sleep study. Hence, the measurable outcome of all these studies is being able to use these signals to predict the frequency of OSA in one night and to be able to correlate the results with the standard PSG, rather than evaluating accuracy and promptness of the signal in the indication of an apnoeic event.

It was found that EEG, snoring, body movement and PAT signals usually responded to OSA during a post-apnoeic event and were usually associated with arousal. Hence, the signals may not be able to promptly indicate the occurrence of OSA and thus allow intervention in time. HRV also required a considerable sample size for analysis in each apnoeic event. Although it seems that HRV was able to accurately screen the suspected cases of OSA, the performance of screening individual apnoeic events is questionable because <60 seconds of an ECG data set for HRV analysis was not recommended [39].

Of these signals, the pulse oximetry level has been widely used in previous studies to provide screening of suspected sleep apnoea with satisfactory sensitivity. Although the pulse oximeter has been commonly used in sleep laboratories and at home to provide screening of suspected OSA, diagnosis has been made only after the sleep study. Limited studies were found which had tested the ability of this signal to promptly indicate the occurrence of sleep apnoea.

As mentioned earlier, some previous studies suggested that it is promising to use thoracic and abdominal signals for instant indication of sleep apnoea. There are two approaches to measuring the severity of OSA using these two signals. One is to measure the phase relationship between the two signals during OSA and one is the change in the amplitude of the two signals from normal breathing to OSA. The first approach was evaluated in a study conducted by Varady *et al.* (2003) with rather satisfactory results in detecting OSA from a central case [212]. The second approach has not been evaluated in previous studies by conducting any clinical trial but this phenomenon was suggested in the previous studies [149]. The critical threshold at which OSA can promptly be distinguished from normal breathing remains unknown.

The pulse oximeter and thoracic and abdomen belt are the sensors which are expected to be comfortable to use during sleep. If these signals can effectively and promptly monitor sleep apnoea, it can be assumed that the monitoring of respiration would be widely accepted by patients because the pulse oximeter and thoracic and abdominal effort sensors are light-weight and portable. Thoracic and abdominal effort sensors can be made from soft and flexible textile cloth, and would be more appealing to users in detecting OSA than traditional PSG or nasal airflow sensors.

4.4 Summary

This chapter reviewed the physiological signals that have been used for monitoring sleep apnoea in previous studies. In the Chapter 6, the pulse oximetry signal, and thoracic and abdominal signals were studied by evaluating the performance of using these signals to promptly indicate obstructive sleep apnoea. In addition, the critical threshold is identified.

Chapter 5

Theoretical Framework

In this chapter, a theoretical framework is presented which illustrates a structure of interrelated concepts and theories based on the literature review, resulting in the constitution of the research focus for this study. The theoretical framework is shown in Figure 12.

A theoretical framework was shown in the followings:

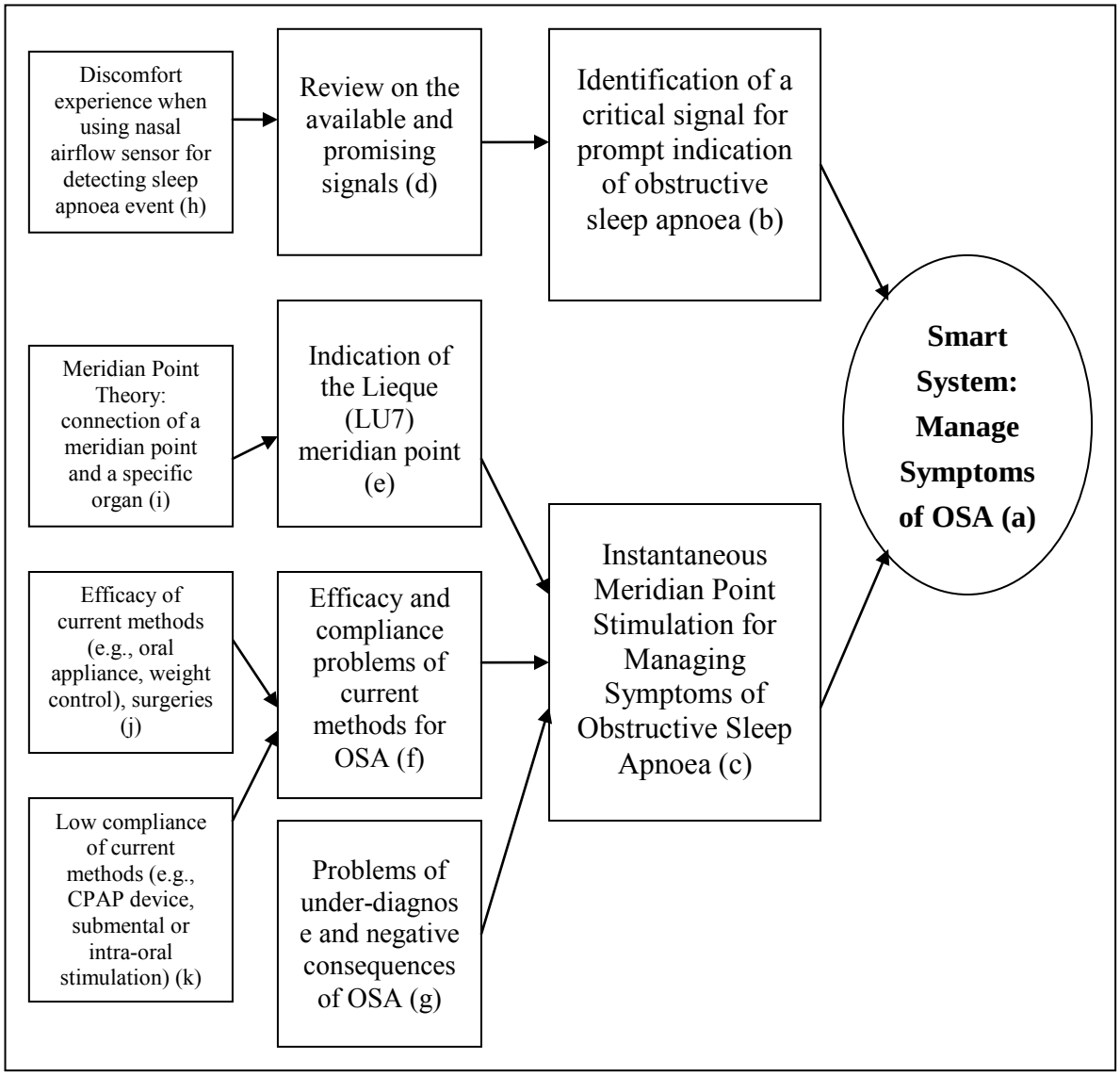


Figure 12 The conceptual; framework of this research

In the theoretical framework, the items (h-k) in the left column are the problems related to OSA. Items d - g illustrates the concepts or theories that have been studied or applied previously in the related research area according to the problems (h-k). After reviewing the previous theories or concepts, two fundamental research objectives (b-c) were set and will serve as a theoretical base in this research. Ultimately, a research target was set (a). To summarize, this theoretical framework mainly shows (1) the area of the applied theories that were used in this study and (2) the cause and effect relationship among different items.

Chapter 6
Methodology

6.1 Introduction

The previous chapters review the literature on definitions, mechanism and syndrome differentiation of obstructive sleep apnoea (OSA) in relation to traditional Chinese medicine, meridian point and the physiological signals that are used to indicate OSA. This chapter introduces the research design and the studies that were carried out in this research.

6.2 Research Design

As mentioned in Chapter 1, the objectives of this research were to identify a critical signal and the threshold as well as assess the efficacy of applying instantaneous meridian point stimulation in response to the occurrence of an apnoea episode. To achieve these two objectives, this research was divided into two studies.

The first study focused on the identification of a critical physiological signal for immediate indication of OSA. According to the literature review in Chapter 4, the pulse oximetry (SpO_2) level, the phase relationship of thoracic and abdominal signals and the mean absolute amplitude appeared very promising in being able to monitor and immediately indicate the occurrence of an OSA event. However, to date there have been limited studies carried out on the performance of using these signals in a group of OSA patients. Hence, the first research task was to conduct sleep studies on a group of OSA patients, record their physiological signals and analyse the performance of using these signals to

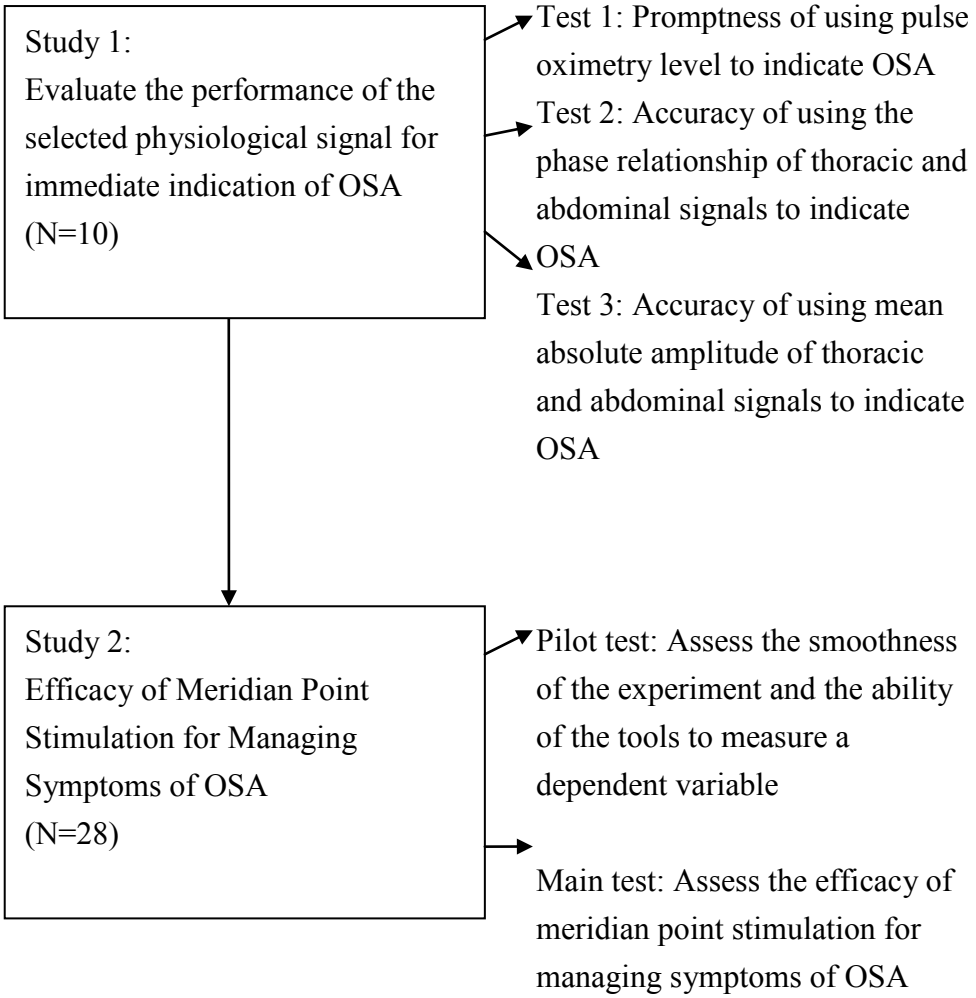
immediately indicate the occurrence of OSA. Ten subjects with OSA were recruited for the study, during which there were 3 tests. The first test assessed the performance of the SpO_2 level by evaluating how promptly the signal could indicate the occurrence of an OSA event in a given threshold. The second test evaluated the performance of using the phase relationship to indicate the occurrence of OSA in terms of sensitivity and specificity. The third test assessed the performance of using the mean absolute amplitude of thoracic and abdominal signals to indicate the occurrence of OSA in terms of the ROC value and identify the thresholds of these signals in optimum sensitivity and specificity. Details about the methods of this study are described in the next chapter.

The second study aimed to evaluate the efficacy of applying the instantaneous meridian point stimulation to managing symptoms of OSA. Twenty-eight subjects with OSA were recruited for this study and were divided into meridian point stimulation group, sham group and control group. This study included a pilot and a main test. Details of the procedures in this experiment are described in Chapter 8. This study used a single-blinded control trial design. Subjects did not know which interventions they were receiving during the study. In this study, a nasal airflow signal was used as a critical indicator to trigger intervention when apnoea occurred. The aim was to test the efficacy of meridian point stimulation, given that the intervention was triggered accurately with minimum error in the experiment. Hence, in this study the indicator was neither signals of SpO2 nor thoracic and abdominal efforts. The outcome measures and results of this study are discussed in Chapters 9 and 10.

6.3 Study Flow

Two studies were conducted in this research, the flow of which is shown in Figure 13.

Figure 13 Study Flow



Chapter 7

Identification of a Critical Signal for Instantaneous Indication of Sleep Apnoea: A Preliminary Study

7.1 Introduction

In this chapter, a study was conducted to perform three tests to investigate the efficacy of the pulse oximetry signal, and thoracic and abdominal signals in terms of promptness and accuracy to indicate the occurrence of sleep apnoea.

7.2 Aims

The aim of this study was to evaluate the performance of using the pulse oximetry signal, and thoracic and abdominal signals to indicate sleep apnoea. Performance was evaluated in terms of (1) promptness and (2) accuracy.

7.3 Objectives

The objectives of this study were to conduct a sleep study and record signals of nasal airflow, pulse oximetry level, the thoracic and abdominal effort of subjects with OSA and analyse the performance of these signals for immediate indication of OSA. The performance of these signals was to be evaluated using two methods. The first method would evaluate the promptness of the selected physiological signal for indication of sleep apnoea using the threshold that was identified in the literature, and the second would evaluate the accuracy of the signals given that the threshold was unknown. If the signal was able to provide prompt and effective indication, the ideal threshold would then be selected.

7.4 Methods

7.4.1 Subjects

Subjects with obstructive sleep apnoea (OSA) and who were aged from 18 to 65 years were recruited to undergo a PSG study. Subjects were recruited through convenient sampling or poster advertisement at the Hong Kong Polytechnic University. Exclusion criteria included mental illness, chronic or cardiovascular diseases, severe skin disease, pregnancy and subjects having undergone uvulopalatopharyngoplasty (UPPP) surgery.

Prior to the sleep study, all subjects were required to attend an introductory session in the sleep laboratory. During this session, information of aims, procedures, safety precautions and the potential risk of the test were explained to the subjects. Written informed consent for the study was then obtained from the subjects. The consent was approved by the Human Subjects Ethical Sub-committee of the Hong Kong Polytechnic University.

7.4.2 Procedures

After the introductory session, all subjects were invited to undergo a nocturnal polysomnography (PSG) study at the sleep laboratory at the Hong Kong Polytechnic University. Subjects had to wear the PSG sensors during sleep using the Siesta portable PSG system. The PSG device was used to monitor and record the physiological signals of subjects during sleep. The physiological data of subjects were recorded regarding nasal airflow, nasal and oral temperature flow, electroencephalograph (EEG), electrocardiograph (ECG), electromyogram (EMG), electrooculogram (EOG), thoracic effort, abdominal effort, pulse oximetry (SpO_2) level, limb movement, sound and sleeping position. The pulse

oximeter sensor was attached to the middle finger of the subject's left hand. Subjects were told to avoid using the CPAP device or other treatment for OSA during the sleep study, to refrain from drinking alcohol or tea one day prior to the study to avoid insomnia and to try to stay relax during the sleep studies. The minimum recording duration of a sleep study was six hours and the sleeping time was between 22:00 and 08:00.

The subjects were required to put on thoracic and abdominal belts during sleep. These two belts could not to be too tight or too loose in order to ensure good signal reception. The thoracic and abdominal belts were made from piezoelectric materials. The model of the thoracic band was Compumedic NR-3700-0103 and the abdominal belt was Compumedic NR-3700-0102. Prior to the PSG recording, the researcher was required to check the synchronization of the thoracic and abdominal signals while subjects were awake and also to check if the sensors were well connected. The frequencies of nasal flow, and thoracic and abdominal signals were 64Hz. All of these signals were recorded in terms of voltage.

After completing the sleep studies, the researcher identified OSA events in each sleep study. The definition of OSA was the cessation of breathing for at least 10 seconds during sleep in association with 4% of oxygen desaturation [2, 139]. A systematic sampling method was used to select the respiratory events for analysis. The systematic sampling method consisted of samples being random initially, and thereafter at regular intervals. This method ensures that all samples have an equal chance of being selected. Afterwards, analyses were conducted to evaluate the performance of the pulse oximetry level and thoracic and abdominal signals for immediate indication of sleep apnoea. The outcome measures of these signals are described below.

7.4.3 Physiological indicator 1: Pulse oximetry level

Sleep apnoea is associated with the occurrence of oxygen desaturation based on its definition [2, 139]. Hence, this study attempted to investigate whether the pulse oximetry (SpO_2) level could be a prompt indicator of the occurrence of obstructive sleep apnoea (OSA). In this test, it is assumed that the promptness of using the SpO_2 level to indicate OSA could be interpreted by measuring the time difference between the onset of the cessation of breathing and the time when the pulse oximetry level met its threshold.

The threshold in this study was defined as 4% of oxygen desaturation from the baseline level. This threshold was selected based on the definition of sleep apnoea which suggested that there was cessation of breathing for 10 seconds in association with 4% oxygen desaturation from the baseline level [2, 139]. In other words, supposing that the baseline level of the SpO_2 level was 98%, a sleep apnoea event would be identified when the SpO_2 level dropped from 98% to 94%. The baseline level was obtained while subjects were still awake 10 seconds prior to sleep. The average value of these 10 seconds was taken. Because in a real situation the definitions of threshold as well as the cessation of airflow would be more complex, the criteria for definition of included and excluded events in this test are described below.

In order to clearly and accurately demonstrate the time difference between the onset of nasal airflow (ONAC) and the threshold, this session presented the examples of showing the onset of nasal airflow cessation (ONAC) and the threshold. Two examples of identifying ONAC and the threshold in a sleep apnoea event are illustrated in Figures 14 and 15.

Figure 14 Illustrations of ONAC and the Threshold

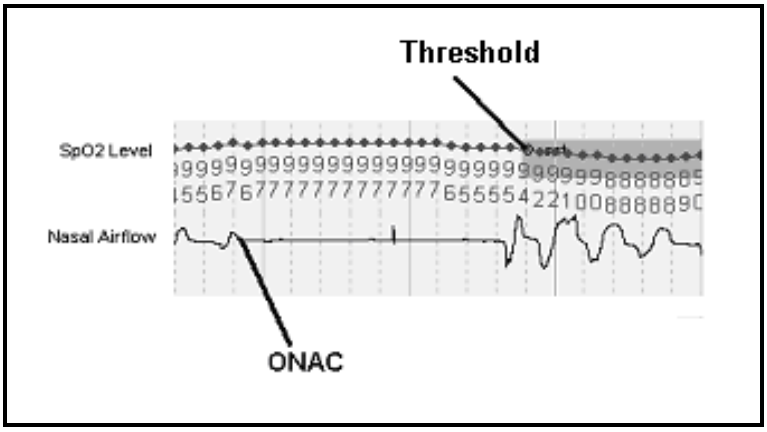
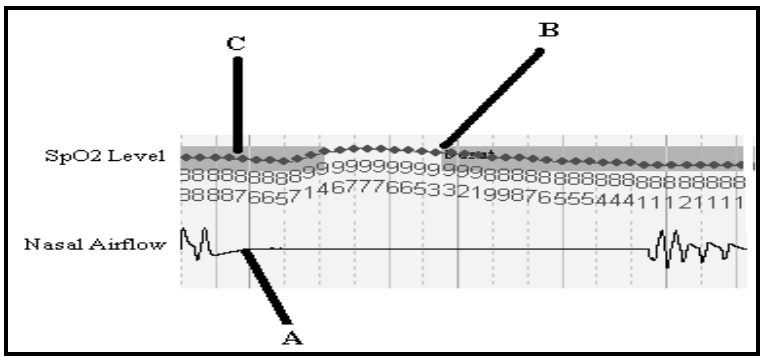


Figure 14 illustrates an example of ONAC and the threshold. The Y-axis is the pulse oximetry signal (SpO_2) and nasal airflow signal. The X-axis is the time frame. In Figure 14 the time frame is 36 seconds. The baseline level of the pulse oximetry level of this subject was 98%. In this case, ONAC was identified at the time when the cessation of nasal airflow began while the threshold was defined as the time when the pulse oximetry level met the threshold which was 94% of oxygen de saturation level. Time difference was measured between these two points. In this case the time difference between ONAC and the threshold was 20 seconds.

In some circumstances, it is found that the SpO_2 level remained at a low level (less than 85%) during ONAC due to the effect of deoxygenation caused by the previous sleep apnoea event. This situation occurred especially some time after a sleep apnoea event. The SpO_2 level gradually increased afterwards and it decreased again during the sleep apnoea event. Figure 15 illustrates an example of this phenomenon. The Y-axis shows the data of the output signals and the X-axis shows the time. The time frame is 33 seconds.

Figure 15 Illustration of the threshold (B) in this event



In Figure 15, "A" refers to ONAC as it was the time when the onset of cessation of breathing occurred. "B" refers to the threshold of the sleep apnoea event. "C" refers to the oxygen desaturation due to the previous sleep apnoea event. In this example, "B" is regarded as the threshold instead of "C" even though an oxygen desaturation event appeared during "A". The oxygen desaturation event that occurred during "A" was due to the last sleep apnoea event, and "B" was the first oxygen desaturation event after ONAC. Hence, "B" was regarded as the threshold in this sleep apnoea event. In this case, the time difference between ONAC and the threshold was 12 seconds.

It was found that patients with severe sleep apnoea may experience repetitive occurrences of OSA events, which cause cyclical drops in the SpO_2 level. Figure 16 illustrates an example of this situation. The time frame was 150 seconds.

Figure 16 *Continuous desaturation of blood oximetry level due to repetitive occurrences of sleep apnoea events*

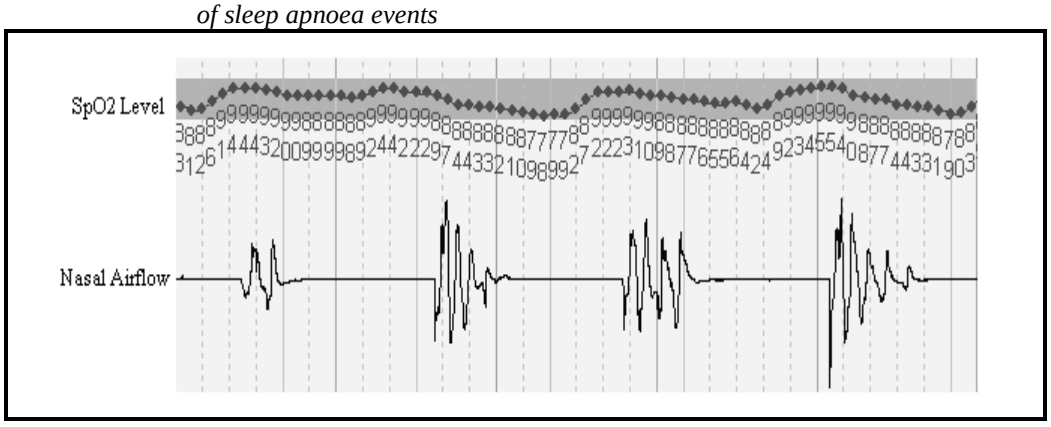


Figure 16 illustrates 5 consecutive OSA events. Sleep apnoea occurred when the nasal airflow signal was flat. The duration of each sleep apnoea event was approximately 25 seconds. Because of repetitive occurrences of sleep apnoea events, the SpO_2 level remained at a low level. Consequently, the threshold could not be met and it was difficult to identify OOD. In this case, these events were excluded because the SpO_2 level was far below the threshold during this period of time. Meanwhile, events were excluded while subjects were awake or during a signal's noise. As a preliminary study, it is attempted to involve 10 subjects and select 50 OSA events related to each subject.

The measurement of time difference between ONAC and the threshold was taken by using a time scale in the PSG program, which was intended to measure the time frame of any selected event. The time difference of each OSA event was measured and the values of all subjects were averaged using Excel software. In addition, the performance of the SpO_2 level in individual subjects was also evaluated. The time unit in this test was seconds. Events with signal artifacts and continuous episodes of sleep apnoea were excluded.

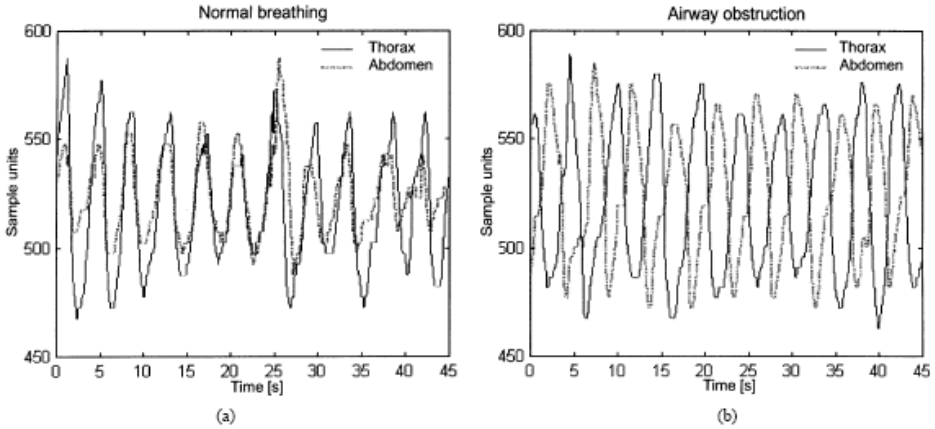
7.4.4 Physiological indicator 2: Phase relationship of thoracic and abdominal signal

It was suggested that two methods to identify sleep apnoea using thoracic and abdominal signals could be used to indicate the occurrence of sleep apnoea according to the literature [149, 212].

The first method could measure the phase relationship of thoracic and abdominal signals - it was hypothesized that OSA could be immediately indicated by analysing the phase relationship of the thoracic and abdominal effort – and the second method could be used in the subsequent test.

Using a previous study which tested the phase relationship of thoracic and abdominal signals during OSA as a reference [212], the detection of OSA using the phase relationship of the two signals was based on the fact that the thoracic and abdominal respiratory movements happened simultaneously during normal breathing. The detection of the phase relationship of the two signals was detected by using the time domain phase relationship as the phase difference between the thoracic and abdominal signals. The phase difference between the two signals should be approximately zero during normal breathing and the magnitude of excursions should be in the common phase. It was found that the phase differences of the thoracic and abdominal movements began to increase when the airway was obstructed. Patterns of in-phase and counter-phase, as suggested in this study, are shown in Figure 17.

Figure 17 *Patterns of (a) in-phase during normal breathing and (6) counter-phase during airway obstruction of the thoracic and abdominal signals [212]*



The left diagram shows the in-phase relationship of the two signals during normal breathing in which thoracic and abdominal effort are in the same phase. The right diagram shows the counter-phase relationship of the two signals during airway obstruction. Events with the presence of a signal artifact due to body movement and awakening were excluded from this test.

Hence, counter-phase phenomenon was regarded as "true positive (TP)" while in-phase phenomenon was regarded as "false positive (FP)" during OSA. Conversely, counter-phase phenomenon was regarded as "false negative (FN)" while in-phase phenomenon was regarded as "true negative [194]" during normal breathing.

The criteria of defining in-phase and counter-phase of the two signals were set in this test. Referring to a study of Varady *et al.* (2003), which specified that the in-phase pattern of thoracic and abdominal effort was defined when the deviation of the peak of the two signals was less than 12.5% (1/8) in a given breathing cycle. In fact, it was assumed in the study that the length of breathing cycle of

the two signals was identical. The counter-phase pattern of thoracic and abdominal effort was defined by the deviation of the peak of the two signals being more than 12.5% in a given breathing cycle of the two signals. This study the deviation is simplified from 12.5% to 10% to reduce complication during the measurement of the threshold.

Fifty respiratory events - 25 OSA events and 25 normal breathing events for each subject - were captured for analysis. The conditions of in-phase and counter-phase of thoracic and abdominal effort of the 10 subjects were evaluated manually using the time-scale function in the PSG program.

The steps for measuring the phase relationship were: (1) identify and randomly select OSA events and normal breathing events by referring to the nasal airflow signal; (2) locate the peak of thoracic and abdominal signals in the first breathing cycle of a sleep apnoea or normal breathing event; (3) measure the deviation of the peaks of thoracic and abdominal signals and classify the events into positive or negative based on the phase relationship of the 2 signals (in this test, it was assumed that the length of the breathing cycle of thoracic and abdominal signals was identical; hence, this study only measured the length of the breathing cycle of the thoracic signal and evaluated the threshold, that is, 10% from the peak in a cycle based on the thoracic signal); (4) input the results of the phase relationship (positive or negative) in the test variable column and input the apnoea state in the state variable column in the SPSS software; and (5) calculate sensitivity and specificity value and derive a ROC curve using SPSS software.
In this test, for reference we also aimed to capture the PSG tracings of the thoracic and abdominal effort during OSA and normal breathing.

7.4.5 Physiological indicator 3: Mean absolute amplitude of thoracic and abdominal signal

The second method in using thoracic and abdominal signals for immediate indication of the occurrence of OSA involved a comparison of the amplitude of the two signals before and during OSA. Previously, it was suggested that the thoracic effort decreased during sleep apnoea in both OSA and central sleep apnoea [67]. Hence, it has been generally accepted that there is no thoracic and abdominal effort during central sleep apnoea. However, there has been no study to prove that the amplitude of thoracic and abdominal signals would also be able to indicate OSA. This test attempted to identify the critical threshold of using this method.

This test measured the relative difference in respiratory effort during OSA and normal breathing. Thus, it is interesting to know whether the respiratory effort during OSA remained the same as in normal breathing or in fact it was different from normal breathing and if so, to what degree had the effort changed? This test attempted to select the change in mean absolute amplitude of (1) thoracic, (2) abdominal and (3) a combination of thoracic and abdominal signals for analysis.

Fifty respiratory events of each subject were captured - 25 events were of OSA (positive) and 25 events were of normal breathing (negative) for further ROC analysis. "Positive event" was defined as the presence of nasal airflow for ten seconds, followed by a cessation of nasal airflow in the subsequent ten seconds. "Negative event" was defined as the presence of nasal airflow for at least 20 seconds without any oxygen desaturation.

The first step of the analysis was to identify OSA events based on the nasal airflow signal after the sleep study. The second step was to obtain the average absolute value of the amplitude with 10 seconds prior to the onset of sleep apnoea and 10 seconds well after the onset of sleep apnoea in each OSA event.

For a normal breathing event this study calculated the mean absolute amplitude of the whole event with 20 seconds duration. Afterwards, this study also calculated the change in percentage in terms of mean absolute amplitude from the first 10 seconds to the subsequent 10 seconds in each event. In other words, the duration of each event for analysis was 20 seconds. Subsequently, one value which was the percentage change of mean absolute amplitude from the first 10 seconds to the subsequent 10 seconds of each event was calculated. This value was input in the test variable column and the apnoea state was input in the state variable column. Finally, an ROC analysis was conducted to obtain the ROC values (or area under the curve) and derive the ROC curves.

The data set of thoracic and abdominal signals of each event was extracted in terms of voltage and calculated using Microsoft Excel software. Receiver operating characteristic (ROC) analysis was performed to calculate the ROC values of the three types of signal. If these signals were likely to accurately indicate when sleep apnoea had occurred, a corresponding threshold was identified. Using the SPSS software, an ROC curve analysis was conducted with a 95% confidence interval of area under the ROC curve. The performance of using this signal for individual subjects was analysed. As a continuous dataset was used to perform an analysis, the threshold value using these 3 types of signal were identified.

7.5 Results

7.5.1 Subjects' information

Ten male subjects with obstructive sleep apnoea (OSA) participated in this study. All of these subjects were severe OSA patients with an age and BMI ranging from 37 to 61, and 21 to 32 respectively. Table 4 shows the age, body mass index (BMI) and apnoea index (AI) of the subjects.

Table 4 Subjects' Information

	Mean / SD
Age (years):	47.10 / 9.643
Body Mass Index (kg/m^2):	27.02 / 3.27
Apnoea Index:	46.69 / 14.78

7.5.2 Performance of pulse oximetry signal

In this test, fifty OSA events were captured from each subject for analysis. The mean time difference between the onset of cessation of nasal airflow (ONAC) and the threshold of each subject was measured and is shown in Figure 18.

Figure 18 *Mean Time Differences (MTD) between ONAC and the threshold, and standard deviation for the ten subjects in error bar chart*

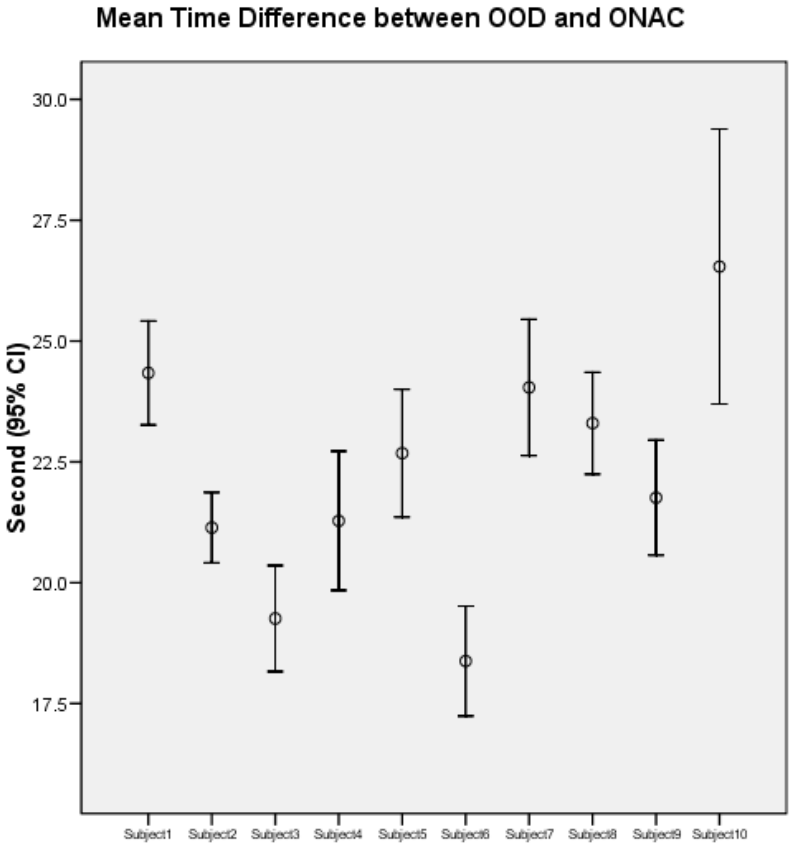


Figure 18 shows the average time difference with the standard deviation of each subject using an error bar chart. The mean time difference between ONAC and the threshold ranged from 18.5 to 26.5 seconds among the subjects. The overall mean time difference between ONAC and the threshold of these 10 subjects was 22.27 seconds. Among all of the OSA events of these subjects, the OSA event with the longest time difference between ONAC and the threshold was 56 seconds and the event with the shortest time difference was 10 seconds.

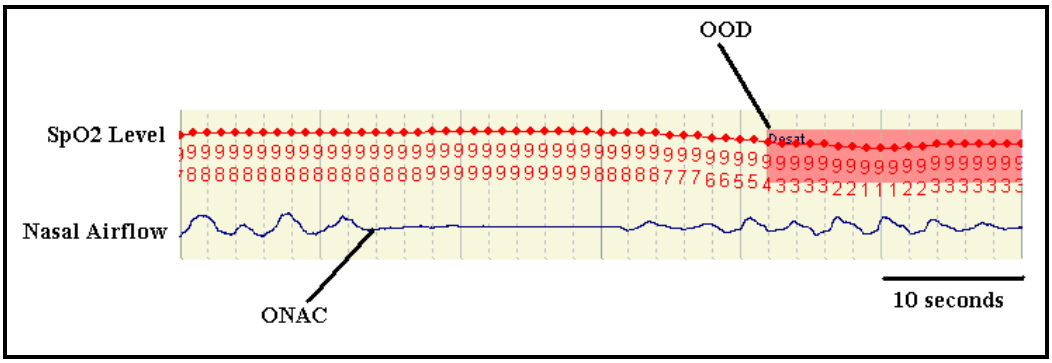
Table 5 shows the Apnoea-Hypopnea Index (AHI), Mean Apnoea Duration (MAD) and Mean Time Difference (MTD) between ONAC and the threshold of each subject in terms of seconds.

Table 5 *Apnoea-Hypopnea Index (AHI) and Mean Apnoea Duration (MAD) and Mean Time Difference (MTD) between ONAC and the threshold of the ten subjects*

Subject	1	2	3	4	5	6	7	8	9	10
AHI	37.5	72.6	65.4	27.7	56.4	38.3	43.7	83.5	59.4	42.6
MAD (second)	23.8	28.9	21.4	42.4	32	21.4	32.4	20.2	22.4	31
MTD (second)	24.3	21.1	19.3	21.3	22.7	18.4	24.0	23.3	21.8	26.5

Under some circumstances, the time difference between ONAC and the threshold could be lengthened in an apnoeic event, if it was preceded by a long duration of an OSA event. Hence, this study attempted to verify if the mean time difference between ONAC and the threshold would be shortened, as long as there was no OSA as well as oxygen desaturation at 1 minute prior to the present OSA event. Figure 19 shows an example of this scenario.

Figure 19 *Illustration of a sleep apnoea event without oxygen desaturation during and 1 minute before ONAC*



Discussion

SpO_2 level has been commonly used to provide additional information for diagnosing sleep apnoea [12, 148]. Medical practitioners define sleep apnoea as the cessation of breathing for at least ten seconds in association with 4% oxygen desaturation [2]. The pulse oximeter is also very useful as a single parameter to provide a home-based overnight screening of users with suspected sleep apnoea [224]. However, limited studies were found to have evaluated the performance of using the SpO_2 level as an immediate indicator of sleep apnoea. Hence, the SpO_2 signals before and during OSA was calculated and studied if there was a time delay if we used this signal to indicate the occurrence of OSA.

Ten male subjects diagnosed with OSA participated in this study. Fifty events of OSA were randomly selected from a sleep study and from each subject for analysis. Time difference between the onset of nasal airflow cessation (ONAC) and the threshold was measured for each event as this study assumed that time difference between ONAC and the threshold would be critical in reflecting the performance - in terms of promptness - of using the pulse oximetry level to detect whether OSA has occurred. The shorter the time difference, the faster the

signal to indicate OSA using a predefined threshold.

In this study, it is found that the overall mean time difference (MTD) between ONAC and the threshold of the ten subjects was around 22 seconds. To interpret whether 22 seconds of time delay is effective in indicating sleep apnoea, this study made a simple assumption. According to the definition of sleep apnoea [2, 139], the minimum duration of a sleep apnoea event is 10 seconds. Assuming that sleep apnoea is identified at 22 seconds after the true occurrence of sleep apnoea, there is around a 12 second delay to trigger the intervention.

Apart from estimating the overall mean time difference between ONAC and the threshold to measure the promptness of using the SpO_2 signal for indicating OSA, this study also measured the mean time difference between ONAC and the threshold among individual subjects. The performance of the SpO_2 signal in each subject is shown in Figure 18. It is found that the shortest mean time difference was approximately 18 seconds. It would appear that the SpO_2 signal was still unable to indicate the occurrence of OSA as quickly as the nasal airflow signal.

During the process of scoring the mean time difference, generally it is observed that the time difference was particularly long after a lengthy sleep apnoea episode, especially for events longer than 30 seconds. This phenomenon was commonly found in patients with a lengthy sleep apnoea episode and especially during REM sleep. The reason for a long time difference may be due to the fact that the SpO_2 level decreased sharply after a lengthy episode which then required a longer time to return to its original level. When the second episode of sleep apnoea occurred, the SpO_2 signal may still have been at a very low level. In which case, if the second event of sleep apnoea appeared before the SpO_2 level recovered to the baseline level, inevitably there would have been a long time delay of desaturation after the cessation of breathing. Hence, it is assumed

that Apnoea-Hypopnea Index (AHI) and the duration of sleep apnoea directly affected the performance of the SpO_2 signal. In Table 5, it would appear that AHI was not a factor in affecting the time difference because the time difference was not the lowest in subject 6 and it was not the highest in subject 10. However, it appears that the average duration of sleep apnoea may affect time difference because subject 6 had the shortest average duration of sleep apnoea while subject 10 had the longest average duration of sleep apnoea. The reason is that AHI only reflects the frequency of sleep apnoea during a sleep study. Patients with a high frequency of the occurrence of sleep apnoea may have a shorter duration of sleep apnoea. Hence, AHI did not directly cause the delay in indicating sleep apnoea.

As the time difference between ONAC and the threshold can be affected by oxygen desaturation due to previous OSA events, a PSG tracing of an OSA event without OSA previously and oxygen desaturation during ONAC was captured. This is shown in Figure 19. It is found that the time difference between ONAC and the threshold was 28 seconds.

Another factor that may have affected the performance of the SpO_2 signal in this study is the selection of the baseline level in this study, which is also key and which may affect test findings in general. The indication of sleep apnoea using the SpO_2 level is likely to have many false alarms if the setting of the baseline level is too high. Frequent occurrence of false alarms should be avoided as they trigger unnecessary interventions for subjects, which cause sleep disturbance.

However, intervention may not be able to trigger during sleep apnoea if the setting of the baseline level is too low. Despite the suggestion by most publications that oxygen desaturation during sleep apnoea is defined as a decrease of $\geq$4% from the baseline level [2, 139, 148], these studies do not specify the reason for using 4% as the threshold value to classify sleep apnoea. Also, the aim of referring to the baseline SpO_2 level in previous studies or

practices was mainly to diagnose suspected cases of sleep apnoea, rather than the immediate identification for triggering intervention.

To effectively define the threshold, a convenient method is the use of the maximum SpO_2 level (i.e. 100%) as the baseline, despite discussions in the literature that the baseline SpO_2 for healthy subjects during sleep is 96.5% [74]. In this study, however, the baseline level of the subjects was mostly 97-98% when subjects remained asleep with normal breathing for more than one minute. Hence, 96.5% may not be a suitable baseline level. Another suggestion for the threshold is to find out the highest SpO_2 level during the sleep study or the average SpO_2 level during normal breathing in a sleep study. In this study, the baseline level was selected while the subjects were awake. The subjects were asked to lie down in the supine position for 20 seconds and to stay awake during this time. It is believed that the first few seconds of the recording may be affected by the movement of the subject and the initialized setting of the sensor. Hence, the reading of the SpO_2 level was taken from the fifth to the fifteenth second of the recording, and to obtain the average of these 10 seconds in this test. It is believed that this method is able to reflect the pulse oximetry level of an individual, rather than as a whole, and under normal breathing conditions in a sleeping posture.

In this test, it is suggested that the pulse oximetry signal was not likely to promptly indicate the occurrence of sleep apnoea for several reasons. Firstly, the performance of this signal was directly affected by the duration of the previous sleep apnoea event. The longer duration of the previous sleep apnoea event meant a longer time for the SpO_2 level to recover to its baseline level. As a result, the time difference between the ONAC and the threshold of the present sleep apnoea event may have been lengthened. Secondly, a long time difference between ONAC and the threshold was also found even if there was no apnoea event in the preceding time. This phenomenon is shown in Figure 19. The time

difference was around 28 seconds given that there was no sleep apnoea event in five seconds before sleep apnoea and the baseline level was 98%. In this case, the performance of the pulse oximetry level was still very poor. Thirdly, the SpO_2 level was unable to indicate sleep apnoea promptly during a period with continuous episodes of sleep apnoea because the level remained at a very low level and the SpO_2 level was unable to meet the baseline level. Consequently, these events were excluded in this test. As this study involved only one mild case, it is invalid to select this parameter as a prompt indicator for sleep apnoea based on the above reasons - it may not be effective in identifying sleep apnoea generally and may not be feasible for providing timely intervention for patients especially with a long duration of sleep apnoea.

The findings of this research suggested that a time delay was likely when the pulse oximeter was used to immediately indicate the occurrence of sleep apnoea, especially among patients with severe sleep apnoea.

The results from this test suggested that there was a time delay from the "onset of 4% of oxygen desaturation from the baseline level" after the "cessation of nasal airflow". The duration of the delay was usually around twenty seconds. Oxygen desaturation events were usually found during sleep apnoea events or even after the termination of sleep apnoea. Although the SpO_2 level is an effective, convenient and comfortable tool for screening suspected sleep apnoea patients, the results of this study do not suggest that it provides immediate indications of the occurrence of sleep apnoea, especially in patients with severe sleep apnoea. Hence, the possibility of using thoracic and abdominal effort as the only parameter to indicate the occurrence of sleep apnoea and eliminate any discomfort experienced by patients will be examined.

7.5.3 Performance of the phase relationship of thoracic and abdominal signals

In this test, 25 OSA events and 25 normal breathing events of 10 subjects were captured for analysis. Using the phase relationship of the thoracic and abdominal signal as an indicator, it is found that 104 OSA events were correctly identified out of 250 OSA events and 135 normal breathing events were identified out of 250 normal breathing events. Table 6 shows the ROC value, sensitivity and specificity of this test.

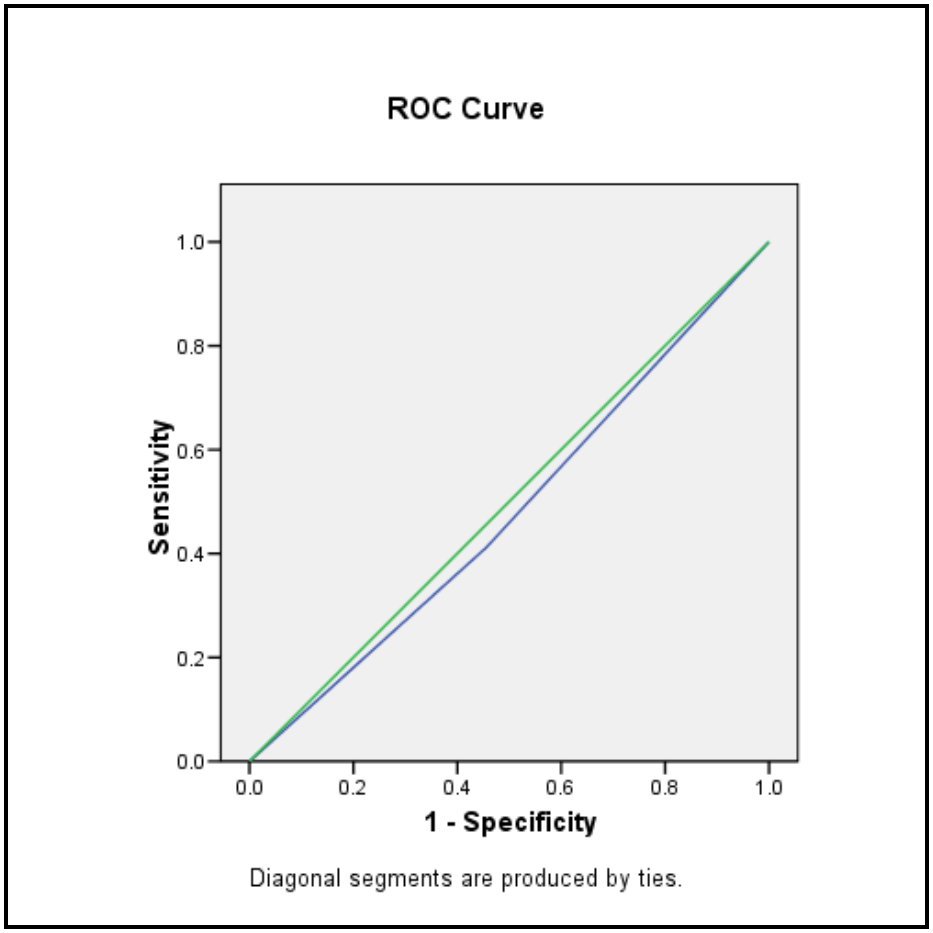
Table 6 *Area under ROC curve, sensitivity, specificity and significance (with 95% confidence interval) of the in-phase and counter phase analysis of the thoracic and the abdominal signals*

ROC Value	0.427
Sensitivity	0.474
Specificity	0.480
Significance (p-value)	0.395

This study also attempted to evaluate the performance of the phase relationship of thoracic and abdominal signals on individual subjects. Performances were evaluated based on the area of 95% confidence interval. It is found that only one subject had an ROC value over 0.8; two subjects had an ROC value between 0.6-0.79; and 7 subjects had an ROC values less than 0.6.

The ROC curve was also derived based on the results of 250 OSA events and 250 normal breathing events of 10 subjects. This is shown in Figure 20. The blue line is the ROC curve using the phase relationship of thoracic and abdominal signals to diagnose OSA and the green line is the reference line.

Figure 20 *ROC curve (the blue line) of the phase relationship analysis of thoracic and abdominal signals*



This test captured the PSG tracings with the in-phase and counter-phase patterns of thoracic and abdominal signals during the OSA and normal breathing of subjects for illustration. Figures 21 and 22 show the phase relationship of the two signals during OSA. Figures 23 and 24 show the phase relationship of the two signals during normal breathing in between OSA events. Figures 25 and 26 show the phase relationship of the two signals during normal breathing.

Figure 21 Illustration of counter-phase pattern of the thoracic and abdominal effort in PSG tracing during obstructive sleep apnoea of a subject

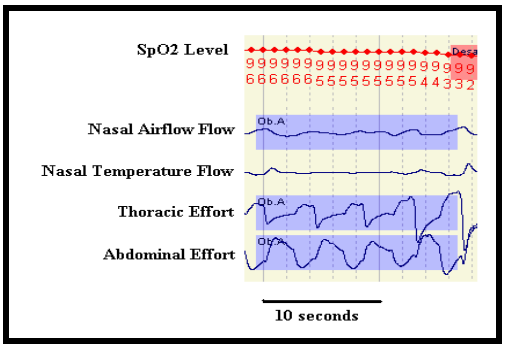


Figure 22 Illustration of in-phase pattern of the thoracic and abdominal effort in PSG tracing during obstructive sleep apnoea of a subject

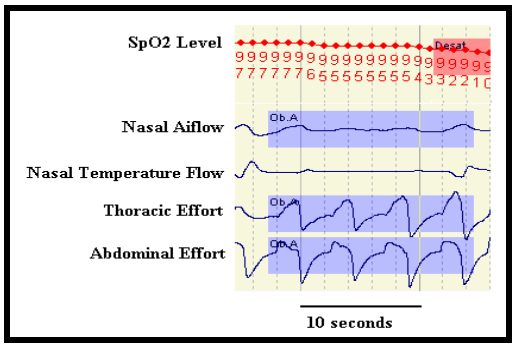


Figure 23 Illustration of counter-phase pattern of the thoracic and abdominal effort in PSG tracing during the normal breathing event of a subject. The normal breathing event was found in between two obstructive sleep apnoea events

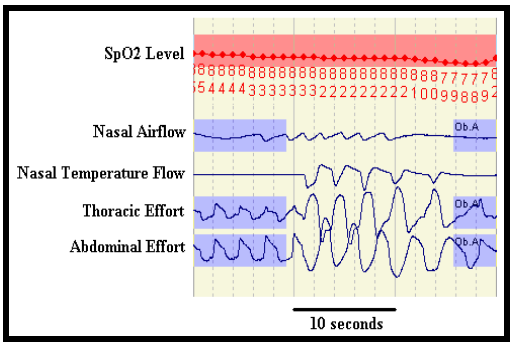


Figure 24 Illustration of in-phase pattern of the thoracic and abdominal effort in PSG tracing during the normal breathing event of a subject. The normal breathing event was found in between two obstructive sleep apnoea events

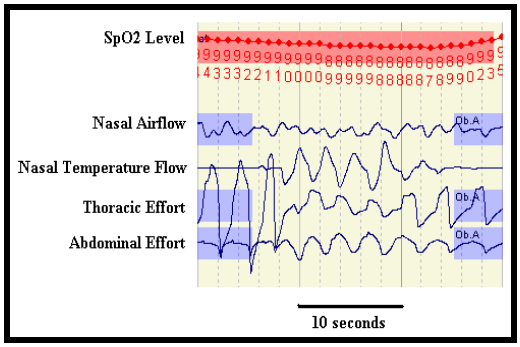


Figure 25 Illustration of counter-phase pattern of the thoracic and abdominal effort in PSG tracing during normal breathing of a subject

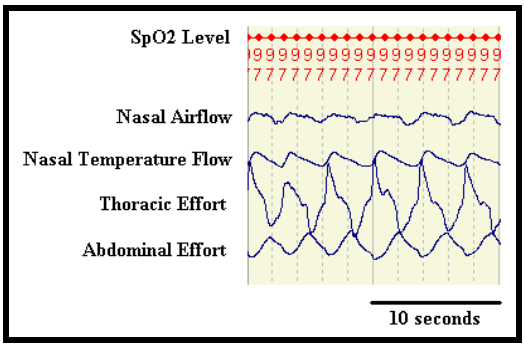
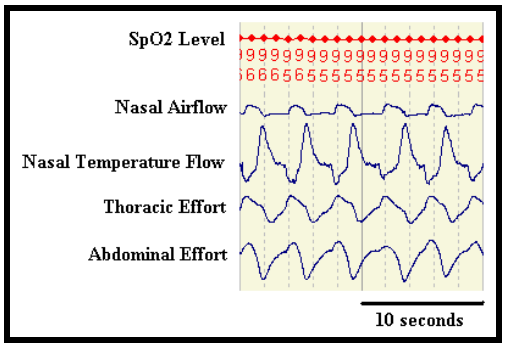


Figure 26 Illustration of in-phase pattern of the thoracic and abdominal effort in PSG tracing during the normal breathing of a subject



Discussion

This study aims to examine whether thoracic and abdominal signals followed a specific phase pattern during OSA and normal breathing as suggested in the literature. The pattern is that the phase differences of thoracic and abdominal movements begin to increase if the airway is obstructed. In other words, the counter-phase phenomenon of thoracic and abdominal effort can be found when the airway is completely obstructed, and inversely an in-phase pattern is found during normal breathing.

In this test, a cut-off point was unable to be determined because the diagnosis of the occurrence of OSA using the phase relationship was discrete data (either presence or absence). Hence, only the ROC value (or area under the curve, AUC), and sensitivity and specificity were calculated.

In this test, both sensitivity and specificity with 95% CI were lower than 0.5, an arguably poor performance when indicating the occurrence of OSA [216]. The results of the ROC value also estimated that the probability of correctly indicating the occurrence of OSA using the phase relationship with a 95% confidence interval was nearly 50%. Among individuals, the phase relationship of thoracic and abdominal signals had good performance in indicating OSA in one subject with an ROC value higher than 0.8. However, the test performance was still very poor in the majority of subjects.

An ROC curve was derived, which is shown in Figure 20. It would appear that the ROC curve of using the phase relationship of thoracic and abdominal signals is not a very reliable indicator as the curve is closed to the diagonal line at 45° to the horizontal. The area under the ROC curve shows the probability that the test correctly classifies the two patients (one positive and one negative) in the random pair. The sensitivity, specificity and ROC value of this test was only

around 0.5 means which means that the overall performance of this signal in terms of its accuracy to discriminate both positive and negative cases of OSA events is poor.

This study also captured tracings from the PSG device with demonstrations of an in-phase and counter-phase pattern of thoracic and abdominal signals during OSA and normal breathing in one subject. The tracings are shown in Figures 21 to 26. In Figures 21 and 22, all signals within an OSA event are highlighted in purple. It was found that both in-phase and counter-phase relationships of thoracic and abdominal signals could be found during OSA in one subject. There were 2 situations regarding normal breathing in OSA patients. One situation was that normal breathing was found during a certain period of time. This situation may have occurred when the subject slept in a lateral position, which may have improved the collapsibility of the airway [69]. In this case, the phase pattern of thoracic and abdominal effort remained constant during this period of time.

Another situation was that normal breathing was found in between 2 OSA events. In this case, the phase pattern of thoracic and abdominal effort may have changed rapidly from OSA to normal breathing. Hence, this study captured the signal in both cases, the tracings of which are shown in Figures 23 and 26. In Figures 23 and 24, the duration of normal breathing is short (less than 20 seconds). Both the in-phase and counter-phase relationship of the two signals were also found in one subject. Figures 25 and 26 were captured with the duration of normal breathing, which was longer than 5 minutes. Again, both in-phase and counter-phase patterns were found in a subject. Hence, regardless of whether the length of normal breathing was short or long, in-phase and counter-phase patterns could be found if only in one subject during a sleep study.

Although it seems that phase relationship was not likely to differentiate OSA and normal breathing events in this study, phase differences were tested in a study carried out by Varady *et al.* [212]. The results from the study of Varady *et al.* using the phase difference were promising in reflecting the breathing status of OSA patients. The findings of the study were completely different from this study. The differences in terms of method between their study and this test were that, firstly, the signal frequency of filtering in their study was 3.25Hz while the frequency in this study was 64Hz. Secondly, the noise of the signals in the study of Varady *et al.* were filtered out using the piecewise linear approximation to facilitate efficient and simple estimation of the phase angle in order to save computing cost; whereas this study did not apply the piecewise linear approximation. The method, however, of identifying the phase relationship was similar. Both studies also compared the distance of the corresponding local maximum and minimum positions of two signals. The magnitude of excursions was more than 10% of a breathing cycle in both cases. The study of Varady *et al.* involved only 6 subjects, with 4 OSA patients, one healthy subject and one subject with central sleep apnoea. This study, meanwhile, included 10 subjects with OSA. As the study of Varady *et al.* also involved a central sleep apnoea case and a healthy subject, findings in the study to distinguish OSA and normal breathing events using the phase relationship of thoracic and abdominal signals were entirely different from what this study had found in the majority of OSA patients in this study. Although the p-value in this test was > 0.05, as a preliminary study it is suggested that future studies could increase the sample size for further analysis.

It is believed that the phase relationship of thoracic and abdominal signals was able to detect breathing status as promptly as a nasal airflow signal because the accommodation of respiratory volume changes according to displacement of the rib cage and the abdomen. Hence, the primary concern in this section was the accuracy of the signal, rather than time delay.

Other factors may also affect the performance of using this signal. In this study, it was found that the phase relationship can be affected by the tightness of the thoracic and abdominal belt. Prior to the test, the subjects were asked to sleep in the supine position and then the thoracic and abdominal belts were adjusted. However, when the subjects were asked to sleep in a lateral position, the belt became less fitted, especially in obese subjects. This is not, however, of primary concern in this study since in approximately 80% of sleep studies subjects sleep in the supine position. To conclude, in-phase and counter-phase patterns can still be found in both OSA and normal breathing.

Conclusion

This study aimed to prove whether the phase relationship of the thoracic and abdominal signals could be used to effectively and promptly indicate obstructive sleep apnoea (OSA). The results in the study suggested that there is nearly a 50% chance of accurately indicating the occurrence of OSA by using the phase relationship analysis of thoracic and abdominal signals, even though the signal had a good performance in identifying OSA events promptly only in an individual subject. Overall, it seems that the phase conditions of thoracic and abdominal signals, in this test, were not likely to identify the occurrence of OSA events in the majority of OSA patients.

7.5.4 Performance of mean absolute amplitude of thoracic and abdominal signals

In this test, the proposed number of samples of positive and negative events was 25 for each subject. In other words, 250 positive and 250 negative events were to be captured for all subjects. Patients who had severe OSA, however, may have had insufficient samples of the normal breathing (negative) events. Hence, only 228 negative events were available for analysis in this test.

After obtaining the mean absolute amplitude of the thoracic signal (TS), the abdominal signal (AS), and the combination of thoracic and abdominal signals (CTAS) at 10 seconds before and during the onset of OSA, ROC analysis was performed using SPSS 15.0.

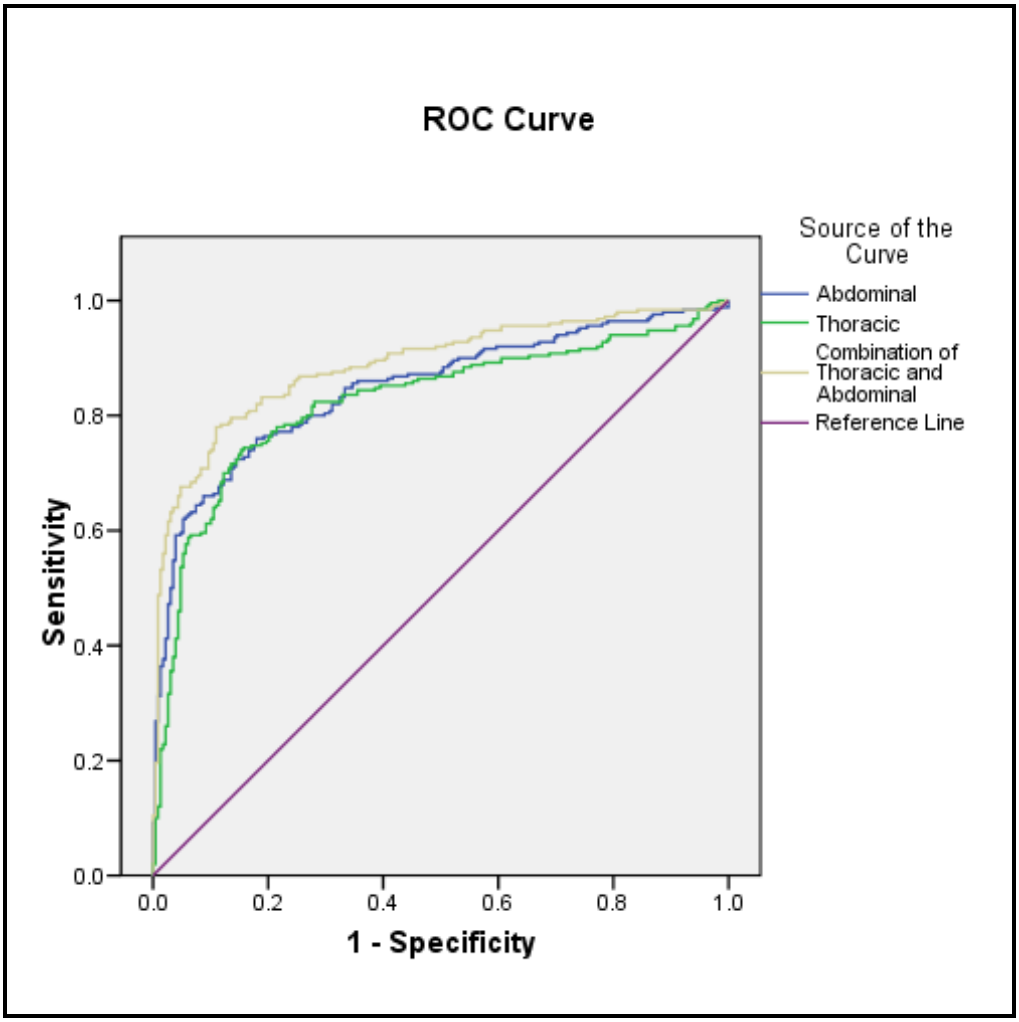
ROC values with a 95% confidence interval of the three types of signal are shown in Table 7. All of the signals have ROC values higher than 0.8 with a p-value less than 0.05.

Table 7 *ROC value, and significance (with a 95% confidence interval) of the thoracic signal (TS), abdominal signal (AS) and the combination of the thoracic and abdominal signals (CTAS)*

	TS	AS	CTAS
ROC Value	0.825	0.847	0.888
Significance (p-value)	0.000	0.000	0.000

After obtaining the ROC values in this test, ROC curves of the 3 types of signal were derived and are shown in Figure 27.

Figure 27 *Plotting of ROC curves of thoracic signal (green colour), abdominal signal (blue colour) and the combination of the thoracic and abdominal signals (yellow colour) with a 95% confidence interval*



As continuous data (that is, the percentage change of mean absolute amplitude rather than presence or absence of OSA event) were used to calculate and compare the mean absolute amplitude before and during the onset of OSA, the output of the ROC analysis in this study was able to select the optimum cut-off value (or, the threshold value) using the SPSS software.

Table 8 illustrates the sensitivity and the specificity of the 3 types of signal in the optimum cut-off value.

Table 8 *Sensitivity and specificity values and optimum cut-off value of the thoracic signal (TS), abdominal signal (AS) and the combination of the thoracic and abdominal signals (CTAS)*

	TS	AS	CTAS
Cut-off value	-0.2316	-0.2526	-0.2508
Sensitivity	0.78	0.78	0.82
Specificity	0.78	0.76	0.82

This study also attempted to evaluate the performance of the 3 types of signal in individual subjects, the results of which are shown in Table 9. Performances were evaluated based on the area of a 95% confidence interval of ROC value. The results were divided according to thoracic signal, abdominal signal (AS) and the combination of thoracic and abdominal signals (CTAS). The ROC value with a 95% confidence interval $\geq$ 80% was regarded as a good performance; 60-79% was regarded as a fair performance; and<60% was regarded as a poor performance [216].

Table 9 *Distribution of individual subjects according to various types of performances of the thoracic signal (TS), abdominal signal (AS), and the combination of thoracic and abdominal signals (CTAS)*

Signal / Performance	TS	AS	CTAS
Good	20%	30%	60%
Fair	50%	50%	30%
Poor	30%	20%	10%

Discussion

As there were no previous studies to investigate the possibility of using mean absolute amplitude of thoracic and abdominal effort to indicate the occurrence of OSA, this test was a first attempt not only to evaluate the performance of using this type of signal, but if possible to also identify the optimum threshold. With reference to Table 7, ROC values of the 3 types of signal were higher than 0.8 and the results were highly significant (p-value < 0.05) in indicating the occurrence of OSA events. An ROC value higher than 0.8 can be regarded as an excellent performance in a diagnostic test [216]. From these 3 types of signal, the combination of thoracic and abdominal signals (CTAS) achieved the best performance when compared with thoracic signal (TS) and abdominal signal (AS). Interestingly, AS achieved a better overall performance compared with TS.

With reference to the ROC curves of the 10 subjects that are shown in Figure 27, the green line indicates TS [93], the blue line indicates the AS, the yellow line indicates CTAS and the purple line is the reference line. With reference to the ROC curves, it would seems that all of the three types of signal achieved an

overall good performance as the turning points of the ROC curves close to the upper left corner of the ROC plot. This is because the larger area under the ROC curve means better effectiveness in using these types of signal to correctly distinguish OSA from a normal breathing event.

Apart from evaluating the performance of the three types of signal, it is also essential to identify the optimum threshold with maximum sensitivity and specificity. In Table 8, the cut-off values of the 3 types of signals are ranged from -0.23 to -0.25. This means that using a 23%-25% reduction of the mean absolute amplitude of the signals as the thresholds would make the sensitivity and specificity around 0.8 for all 3 types of signal in this test. Also, both sensitivity and specificity of CTAS was over 0.8 with a threshold value at -25%, which means that this signal had good performance in classifying both OSA and normal breathing events.

A series of ROC analyses were also carried out among individual subjects, the results of which are stated in Table 9. Although the 3 types of signal have overall good performance according to the results that are presented in Figure 27, only 20% of subjects have good performances using the mean absolute amplitude analysis of TS and 30% for AS, as seen Table 9. Again, CTAS achieved the best performance when compared with TS and AS with 60% of subjects having ROC values higher than 0.8.

Among these signals, CTAS achieved the best performance overall as well as in individual subjects. The indications using thoracic and abdominal effort were just as fast as the nasal airflow signals. In this test, the identification of positive and negative events was based on the nasal airflow signals. Mean absolute amplitude was calculated either during the cessation of airflow or during normal breathing. In other words, the reduction of mean absolute amplitude of thoracic and abdominal signals and the cessation of nasal airflow occurred concurrently.

Based on the results in this test, it is expected that an intervention could be applied once the reduction of the mean absolute amplitude of thoracic or abdominal effort met the predefined threshold (for example, -25%). In this case, the indications would be ten seconds after the onset of nasal airflow since the mean absolute amplitude was analysed every ten seconds for each event in this test. Sleep apnoea is defined as the cessation of nasal flow for ten seconds [2, 139]. If the mean absolute amplitude of thoracic and abdominal signals were to be used to indicate the occurrence of OSA, the intervention would not be too late.

Another concern was the tightness of the belt of the subjects. As mentioned in the previous test, these two factors may affect the performance of the signals generally. The belt may become less tight when the subject sleeps in a lateral position due to the effects of gravity [213]. However, it was found that around 80% of the time the subjects were in the supine position in this test; hence, overall the signals were not affected.

Usually medical practitioners do not regard thoracic and abdominal effort as one of the key parameters in identifying the occurrence of sleep apnoea events; however, they have used these two signals as an important parameter to distinguish obstructive, central and mixed sleep apnoea. This is because signal patterns of thoracic and abdominal effort are not remarkably different between normal breathing and OSA events as compared with nasal flow signals. In order to develop a management system for sleep apnoea patients, one of the approaches is to identify the crucial parameter. This parameter will be able to trigger the intervention in a timely manner in order to manage the symptoms of sleep apnoea. Patients are required to continuously monitor their respiratory status when they are using this system. In this case, a sensor with minimum discomfort to the users is preferable. It is believed that patients will have better

sleep using the thoracic and abdominal sensors (such as a belt or a smart shirt) than a nasal flow sensor.

Conclusion

This test evaluated the performance of mean absolute amplitude analysis of the thoracic signal (TS), abdominal signal (AS) and the combination of thoracic and abdominal signals (CTAS) in the prompt indication of the occurrence of sleep apnoea using the ROC analysis.

The results of this study showed that the mean absolute amplitude of CTAS achieved the best overall performance for subjects and even for individual subjects. A 25% reduction in the three types of signal usually had sensitivity and specificity values of higher than 0.8. Also, by using mean absolute amplitude analysis of TS, AS and CTAS to indicate the occurrence of sleep apnoea, intervention could be provided at 10 seconds after cessation of the nasal airflow signal. This study shows that using only thoracic and abdominal signals to promptly indicate the occurrence of obstructive and central sleep apnoea events is promising. Using the parameters identified in this study for TS, AS and CTAS, nurses may be able to identify high-risk patients and be proactive in managing sleep apnoea before apnoeic events occur.

7.6 Summary

This chapter aims to select the SpO_2 level, the thoracic and abdominal signals and to test the ability of using these signals to instantly indicate the occurrence of a sleep apnoea event in a group of OSA patients. This study used the nasal airflow signal to classify OSA and normal events in this test. Overall, it seems that the performance of using the mean absolute amplitude analysis of thoracic and abdominal signals to indicate the occurrence of sleep apnoea was good according to the results in the ROC analysis. As compared with the SpO_2 signals and the phase relationship of thoracic and abdominal signals, the mean absolute amplitude of thoracic and abdominal signals is likely to provide timely and accurate indication of OSA events with ROC value higher than 0.8.

Chapter 8

Methodology: Evaluation of the Efficacy of Instantaneous Meridian Point Stimulation for Managing Sleep Apnoea

8.1 Introduction

This chapter presents the clinical trial methodology, which is conducted to evaluate the efficacy of applying electrical stimulation on the Lieque (LU7) meridian point to manage symptoms of obstructive sleep apnoea (OSA). This chapter is divided into three parts. The first part focuses on the design of the clinical trial. The second part outlines the procedures of the clinical trial and the third part discusses the methods of statistical analysis.

8.2 Study Design

As one of the research questions is whether meridian point stimulation would produce a managing effect on the symptoms of OSA and improve sleep quality of patients, hence, a clinical trial was set up and divided into 2 stages; a pilot study and a main study.

This experiment is a pre-post study, which means that measurement of the outcome parameters took place without and during intervention. As it is believed that symptoms would be managed once intervention is applied, it is meaningful to study the pre-post effect of the intervention on the symptom. Thus, subjects have to spend two nights in the sleep laboratory, with a baseline sleep study and test study.

As the early stage of the clinical trial, the pilot study was intended to test the practicality of the process of the experiment with applications of low voltage electrical stimulation on the meridian point of the subjects and if the subjects woke up as a result of electrical stimulation. During the baseline and test studies, the physiological parameters in terms of respiration and sleep status were monitored and it is important to ensure that the location of the sensor and stimulation electrodes was correctly identified. It was also important to ensure that the intended signals were able to be recorded and analyzed. Also, the pilot study was conducted to test for any problems related to the experiment procedures or report adverse effects by the subject due to the intervention.

The main test was conducted followed by the pilot test. The main test is a single-blinded randomised control trial. Subjects were randomly assigned into three groups. One group received electrical stimulation on LU7; henceforth, designated as the meridian point stimulation group (MPSG). One group received electrical stimulation on the non-meridian (sham) point; henceforth, designated as the sham group (SG). One group received no stimulation; henceforth, designated as the control group (CG). To compare the pre-post effects of intervention, subjects had to undergo two nights of sleep study, with a baseline study (without any intervention) and a test study (may or may not receive any intervention, depending on the results of the group allocation) in the sleep laboratory.

The majority of the previous studies tend to use randomised placebo controlled and pre-post trials to evaluate the efficacy of different therapies for treating sleep apnoea [58, 170]. Also, most of the previous studies that applied acupuncture preferred to include a SG in their studies [119]. These studies usually applied a needle with a certain depth of insertion and only the location differed. The purpose of including a SG is important in comparing if the effect on symptoms of sleep apnoea is due to the intervention on the specific meridian point or purely

due to electrical stimulation. The purpose of including a CG is also important to verify if the effect on symptoms of sleep apnoea is due to the intervention or purely by chance.

With reference to the treatment objectives of sleep apnoea in Chapter 2 which is to alleviate symptoms of OSA and improve the sleep quality of the patients, evaluation of the efficacy of the intervention on sleep apnoea is mainly divided into (1) overall effect in terms of the severity of OSA and sleep quality and (2) immediate effect on the pulse oximetry level and sleep. Details of the quantitative measurement of the severity of OSA, sleep quality and immediate effect on the pulse oximetry level will be explained in section 7.8.

8.3 Inclusion and Exclusion Criteria

Subjects aged between 18 and 65 were invited to receive the baseline sleep study. Subjects were included in this research only if the "Apnoea Index" (AI) was larger than five in the baseline study.

Subjects who were pregnant, diagnosed with mental illnesses, used a pacemaker, had obstructive lung diseases, severe skin diseases, and unable to provide informed consent were excluded. They were also excluded if they received any acupuncture or meridian point stimulation three days before the sleep study. These exclusion criteria refer to studies which evaluated the efficacy of electrical stimulation on the hypoglossal or genioglossus nerves or muscles on sleep apnoea [96, 141]. Electrical stimulation may affect the heart rhythm for patients with pacemakers and thus they were excluded. As subjects have to discontinue other treatment (such as CPAP) for sleep apnoea during the sleep study, they were excluded if they could not tolerate the avoidance of using such treatments during the test study.

8.4 Subject Recruitment

Subjects were recruited by two methods. The first method was convenience sampling and the second method was recruiting subjects through posting an advertisement at the Hong Kong Polytechnic University (HKPU). The proposed target group was not only the students or staff in the university, but also their relatives and friends who were diagnosed with or suspected to have OSA.

8.5 Randomization and Blinding

This clinical trial is a single blinded, pre-post randomised control trial. Each subject was assigned a subject code. Randomisation was implemented by sealing the subject codes and putting them inside a box. Drawing was done by an individual who was not associated with the study and by following a sequence of MPSG-SG-CG, and MPSG-SG-CG and so on. Subjects were informed about the group division, but they did not know the type of intervention that they received during and even after the experiment.

8.6 Preparatory Works

The ethical approval of this experiment was obtained by the Human Subject Ethics Sub-Committee at the HKPU.

Prior to the clinical trial, the researcher received three training courses. The first training course consisted of a demonstration session on using the polysomnography device (PSG) and consultation sessions on the theory of sleep stages and breathing disorder events. The training took place in the Sleep

Disorders Unit at the Queen Elizabeth Hospital, Adelaide. The second course was conducted by an experienced local TCM practitioner for two sessions. One session involved the practise of meridian point stimulation which included the theory of meridian, skills of manipulating the stimulation device, and the required intensity and duration of performing the stimulation. Another session was the identification of the exact location of the meridian point. The third course was related to first aid and laboratory safety which was held by the university.

Prior to the experiment, all subjects were required to attend an introductory course individually. In this introductory course, participants were briefed on the background information of sleep apnoea, aims, venue, procedures, expected benefits and safety precautions of the study (Appendix 1). The duration of the introductory course was approximately 30 minutes for each subject. During the introductory course, subjects were informed about the group division in the experiment, but they were told that they had an equal chance of being assigned into one of three groups. If the subject agreed to participate in the study, they were asked to sign a consent form. Afterwards, the subject was invited to complete a questionnaire. This questionnaire mainly asked participant personal information, medical history, and current treatments received which are related to sleep apnoea, such as the CPAP device, oral appliance or acupuncture (Appendix 2). Subjects were told to avoid using the CPAP device during the sleep study, refrain from drinking alcohol or tea one day prior to the study, and try to stay relaxed during the sleep study. Also, the aim of conducting the introductory course was to gather information about the background of the subjects, in order to screen out those who fit the exclusion criteria.

8.7 Study Protocol

Subjects were invited to the sleep laboratory at the HKPU three times for one introductory session and two sleep studies.

The first night is called the baseline study. During the baseline study, subjects receive no intervention or treatment. Only the physiological signals are recorded.

The second night is called the test study. During the test study, the physiological signals are recorded. Meanwhile, subjects receive either electrical stimulation on LU7 or a non-meridian point once a sleep apnoea event is detected or they receive no stimulation during the entire period of the test study.

8.7.1 Procedures of the Baseline study

The baseline study is the first night of the sleep study without any intervention. The baseline study acts as a control which aims to compare the pre-post effects of the intervention on sleep apnoea. The baseline study in this experiment follows a protocol which is shown in Figure 28.

Figure 28 Protocol of the baseline study

- Brief the subject about the procedures of the sleep studies
- Inform the subject about the emergency exit
- Measure weight and blood pressure of the subject
- Attach the PSG sensor
- Ensure that the sensors are well connected to the skin surface
- Record room temperature and humidity
- Start the PSG recording for a minimum of 6 hours
- Stop the PSG recording
- Score the respiratory events, arousal events and sleep stage of the sleep study

8.7.2 Procedures of the test study

The second night was a test study. Subject received either meridian point, sham or no stimulation during the test study. Subjects in all groups were required to wear the PSG sensors and stimulation electrodes.

Prior to the sleep study, subjects were invited to select the level of intensity for the intervention. Subjects in the CG were also required to wear two electrodes on the meridian points and select the intensity even though the electrodes did not release any electrical stimulation during the experiment.

Stimulation intensity was selected according to the maximum acceptable level of the subjects. After the subject started to sleep, the sleep study was recorded at a minimum of six hours in duration. A real time nasal airflow was used to monitor the nasal airflow signal with less than 0.1 second time delay and released intervention accordingly once the occurrence of an OSA event was detected. The intensity of stimulation could be adjusted during sleep if the cessation of breathing continued after the intervention unless the subject restored breathing, the subject had complaints due to the strong stimulation intensity or more than five arousals were detected after the stimulation. No other intervention was involved during the test study. Subjects were allowed to eat and drink prior to the sleep study. Figure 29 shows the procedures of test study.

Figure 29 Protocol of the test study

- Brief the subject about the procedures of the test study
- Measure weight and blood pressure of the subject
- Attach the PSG sensors
- Subject select stimulation intensity
- Ensure that the PSG sensors are well connected to the skin surface of the subject
- Check the signal from the real time nasal airflow sensor
- Synchronise the time of the PSG device with the stimulation program
- Record room temperature and humidity
- Start the PSG recording for a minimum of 6 hours
- Stop the PSG recording
- Score the respiratory events, arousal events and sleep stage of the sleep study

8.7.3 Polysomnography monitoring

The overnight sleep study was performed using standard full PSG techniques. The PSG signals included electroencephalograph (EEG) (C4/A1; C3/A2), electrocardiograms (ECG), electro-occulogram (EOG), submental electromyogram (EMG), nasal pressure flow, nasal and oral temperature flow, limb movements, thoracic and abdominal efforts, pulse oximetry levels and sleep positions. An infrared video recording was used to monitor the body movements and sleeping positions of the subjects. Tracheal breathing sounds were recorded by a microphone attached to the skin overlying the cervical trachea. All variables were recorded continuously with a minimum duration of six hours and maximum of eight hours.

8.7.4 Positions of the polysomnography sensors

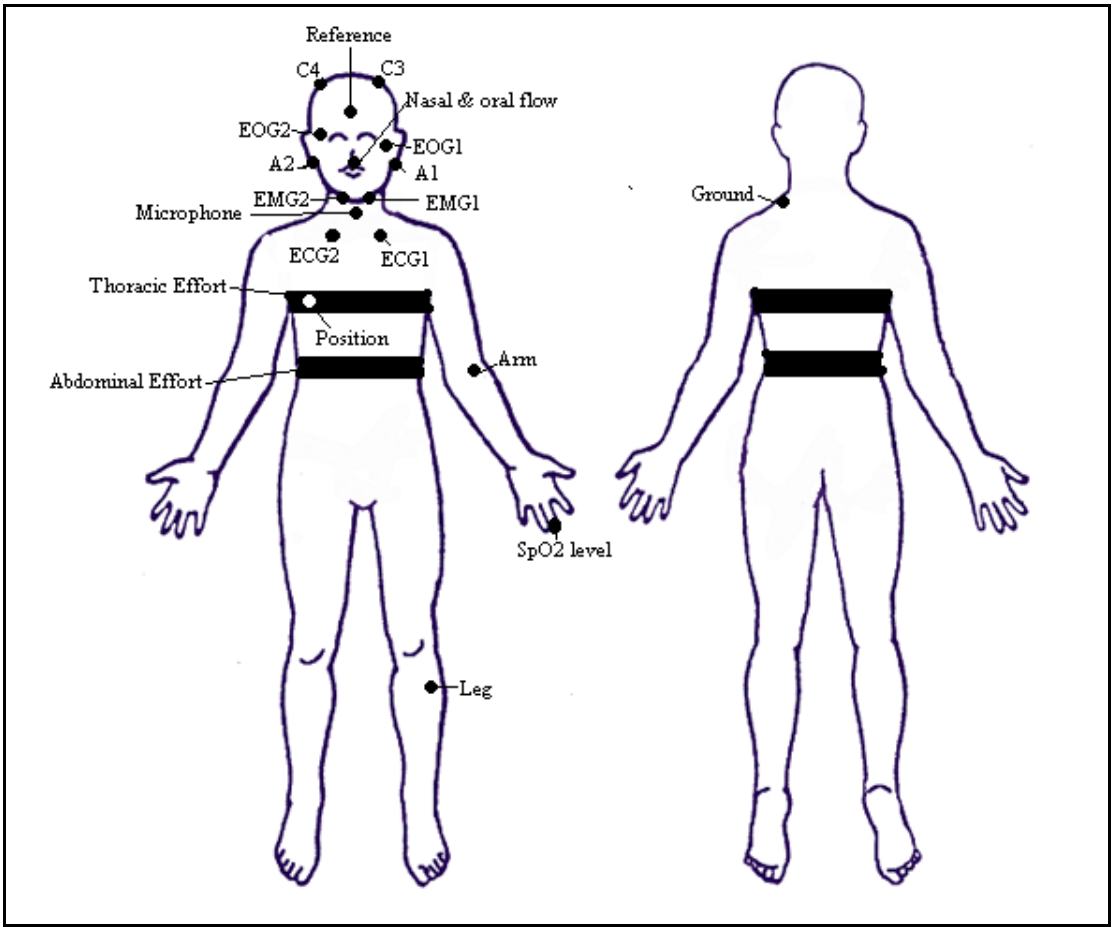
Table 10 describes the location of PSG sensors and Figure 30 illustrates their position in a diagram.

Table 10 Descriptions about the location of the PSG sensors

Signal	Location
C3	On the scalp in accordance to the 10-20 system
C4	On the scalp in accordance to the 10-20 system
A1 / A2	Behind the left ear / Behind the right ear
EOG 1	Lower outer canthus of the left eye
EOG 2	Upper outer canthus of the right eye
EMG 1	Left chin / Right chin
ECG 1 / ECG 2	Left clavicle / Right clavicle
Ground	Upon the left shoulder
Reference	On the forehead

Oral and Nasal Airflow	Underneath the nose
Nasal Temperature Flow	Underneath the nose
Thoracic Effort	Around the thorax
Abdomen Effort	Around the abdomen
Pulse Oximetry Level	On the middle finger of the left hand
Arm Movement	Upper arm
Leg Movement	Lower leg
Position	On the thoracic belt
Microphone	Overlying the cervical trachea

Figure 30 *Illustration of the location of the PSG sensors*



8.7.5 Intervention Setting

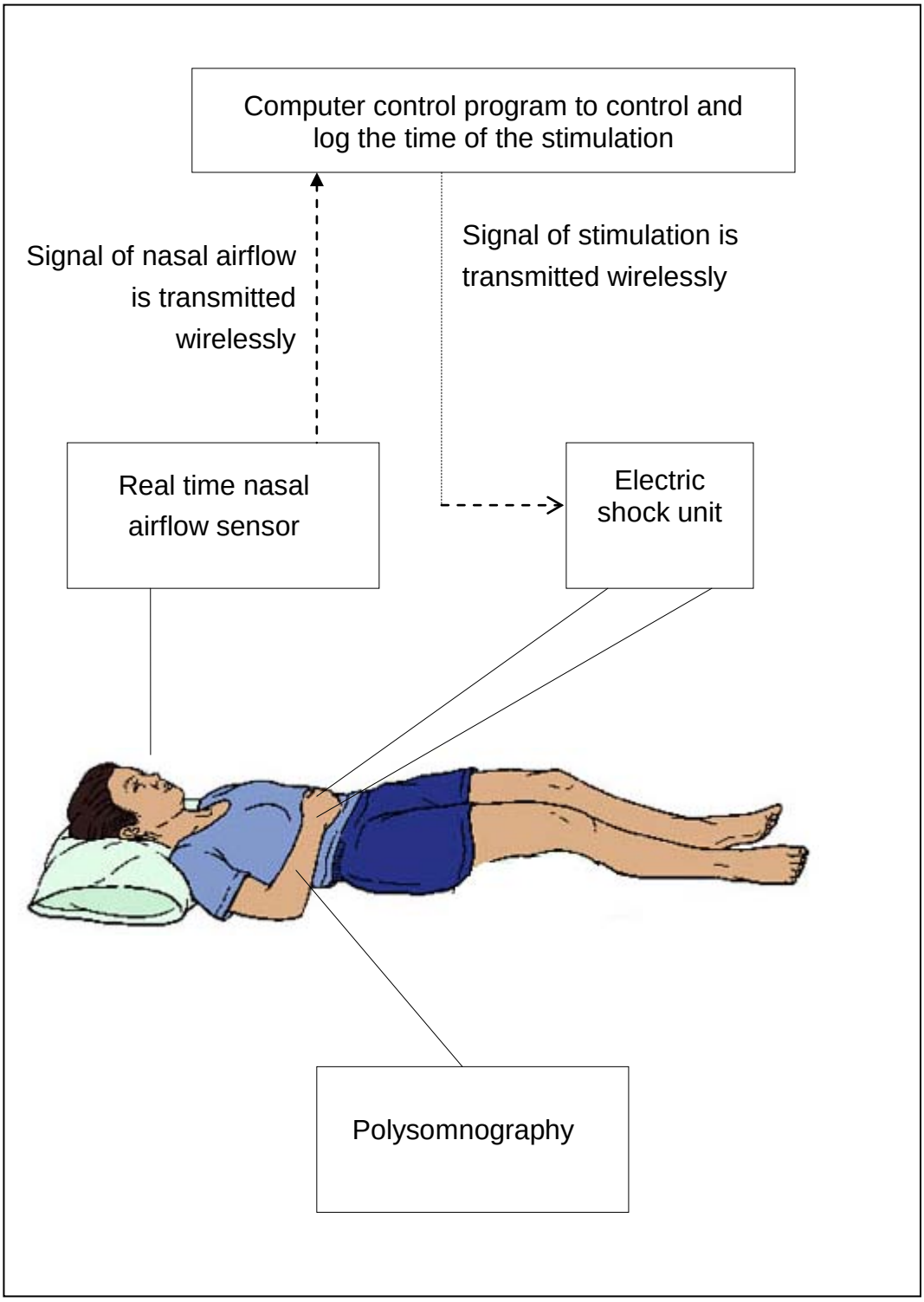
There are four components in the setting. They are a computerised program, electric shock unit, real-time nasal airflow sensor and PSG device. The computerised program controls the intensity and time of electrical stimulation automatically based on the real time nasal airflow signals. This computer program can log the time and intensity of the stimulation. The electric shock unit is able to release low voltage electrical currents through the electrodes onto the skin surface of the subject. The PSG is used to continuously monitor and record the physiological signals of the subject.

During the test study, the real-time nasal airflow sensor monitored the respiratory condition of the subjects and sent the signals continuously and wirelessly to the signal receiver in the computer. The computer controlled program analysed the signals of nasal airflow and decided when to trigger the intervention. The output signal of nasal airflow in the computer was shown in terms of voltage. Once the real time nasal airflow signal met with the threshold, i.e. a sleep apnoea event was detected, the computer control program sent the stimulation signal to the electric shock unit. Shortly after that, the electric shock unit released low voltage electrical stimulation on LU7 or a non-meridian point of the subject. The PSG device recorded the physiological signals of the subject continuously throughout the study.

The stimulation device and real-time nasal airflow meter were developed by our technical team. The reason for developing a real-time nasal airflow sensor is because there is a time delay for displaying the nasal airflow signals in the PSG device of ten seconds. If the nasal airflow signal in the PSG device is used as an indicator to trigger the stimulation, the subjects will have at least twenty seconds of sleep apnoea before receiving any stimulation. Therefore, our team finally developed a real-time nasal airflow sensor and the time delay was less than one

second in order to ensure that a prompt intervention was provided after the occurrence of sleep apnoea. The stimulation electrode was a disposable electrode cut into 1 cm diameter in size and attached onto the stimulation area of the subject. It acts as a media to transmit electrical voltage from the stimulation device to the skin surface. This is actually an ECG disposable electrode. The three-end nasal cannula, which is different from the traditional one, with one end connected to the PSG device, one end connected to the real-time nasal airflow meter and one end connected to the nasal area of the subject was used in this experiment. Figure 31 shows the system of intervention.

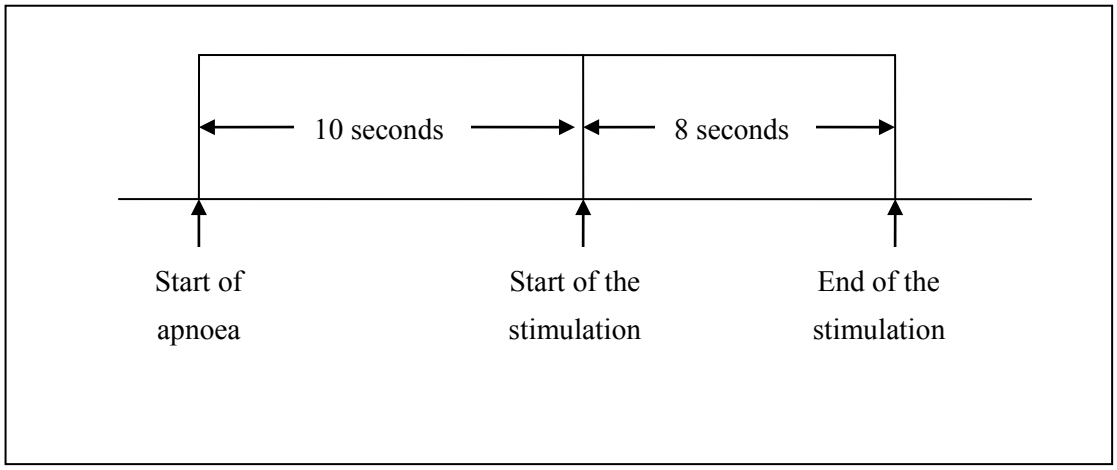
Figure 31 *System of Intervention*



8.7.6 Stimulation mechanism

Electrical stimulation was activated when a sleep apnoea event was detected by the real time nasal airflow meter. A sleep apnoea event could be identified when the nasal airflow signal was lower than a predefined threshold for ten seconds. The threshold was defined as the cessation of breathing with reference to the real time nasal airflow signal. The duration of the stimulation was eight seconds. The process of stimulation in response to an OSA event is shown in Figure 32.

Figure 32 Stimulation time of an OSA event



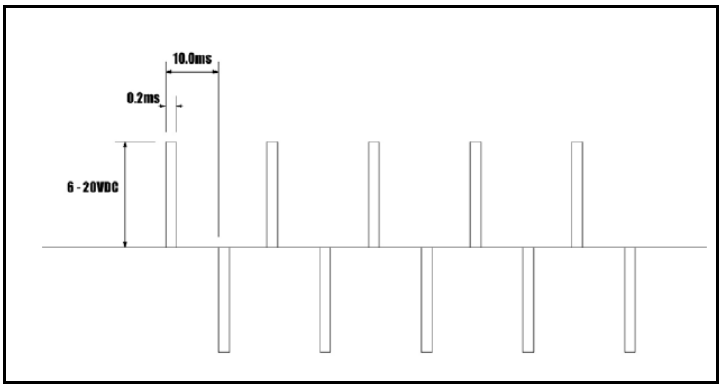
If sleep apnoea continues to occur after eight seconds of stimulation, another eight seconds of stimulation is released until the subject restores the breathing.

8.7.7 Specifications of the Electrical Stimulation

The optimal and reliable pattern of stimulation was set with reference to previous studies which applied electrical stimulation on the meridian point. According to Mesut et al. [140], closed loop stimulation is preferred to continuous stimulation and so this form of stimulation is selected in this study. In this regard, stimulation should be released once it is needed, rather than released continuously over the sleep study. It is because intensive activation of electrical stimulation may result in conversion of the fatigueable fibres to fatigue resistant ones in the long term. As suggested in previous studies which involved electrical stimulation on the meridian point, the criteria of stimulation is depicted in the following paragraph:

Bi-phasic pulse waves [27, 229, 230] and burst pulse chain were used [128, 131]. The pulse shape was in a square or rectangular form [27, 229, 230, 242, 243]. The pulse frequency within each burst was 100 Hz [128, 131, 208, 242, 243, 261, 270] and the pulse width was 0.2 ms [131, 229, 242, 243, 261]. The burst rate and width were 2 burst per second [128, 131] and 70 millisecond [128, 131] respectively. The intensity that was used in this study ranged from 0 to 20 mA and normally, an intensity between 10 and 11 mA is used [101, 229, 230, 242, 243, 261]. Figure 33 illustrates the waveform of the burst mode stimulation.

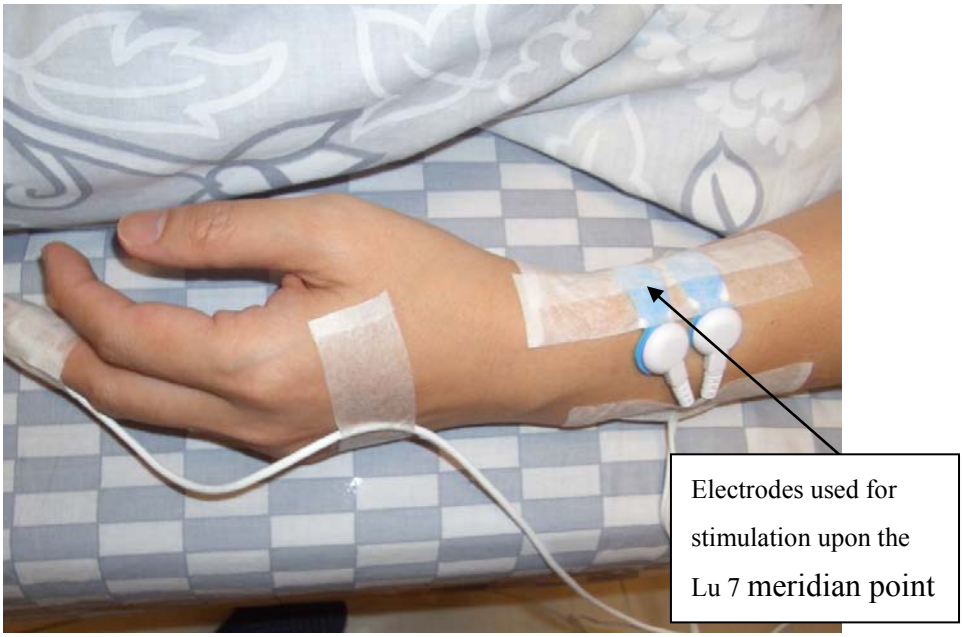
Figure 33 Waveform of the Burst Mode Stimulation



8.7.8 Location of the Lieque (LU7) meridian point

The selection of the meridian point in this research depends on the indication of the disease and location of the meridian point as mentioned in Chapter 3. LU7 is chosen because this meridian point can offer relief for respiratory problems, such as lung diseases, chest diseases, coughing, asthma and sore throat [251, 259]. In this research, the location of LU7 is defined as "at superior to the styloid process of the radius, at 1.5 cun above the transverse crease of the wrist between the brachioradial muscle and tendons of the long abductor muscle of the thumb" [40]. During the test study, subjects had to wear two electrodes, with one on LU7 and another one inch below LU7 along the lung meridian for grounding purposes. In order to confirm the location of the meridian point, subjects had to indicate if they felt sore, numb, extending or pain when the researcher pressed a specific point using a finger.

Figure 34 Example of the electrodes used for electrical stimulations during sleep



8.7.9 Location of the non-meridian (sham) point

The location of the sham stimulation is not recognized as a true meridian point in accordance to TCM theory. The s election of a non -meridian point in this research is that it should be close to the LU7. There are three meridians that run along the palmar side of forearm. They are the Lung (LU), the Pericardium (PC) and the Heart (HT) meridians. The LU runs along the radial side in the palmar aspect of the forearm. The PC runs along the middle of the palmar aspect of the forearm to cubital fossa and between the tendons of m. palmaris longus and m. flexor carpi radialis. The HT runs along the ulnar side in the palmar aspect of the forearm. In order to select a non-meridian point that is close to LU7, this study attempted to investigate the distribution of the meridian points along the lower inner arm. The distribution is shown in Figure 35.

Figure 35 Location of the meridian points along the lower inner arm

Radial side	Level of the cubital crease		Ulnar side
LI 11	LU 5	PC 3	HT 3
LI 10			
LI 9		Non-meridian point	
LI 8			
	LU 6		
LI 7		PC 4	
LI 6		PC 5	
			HT 4
	LU 7	PC 6	HT 5
			HT 6
LI 5	LU 8	PC 7	HT 7
Radial side	Distal forearm		Ulnar side

Figure 35 illustrates the location of the meridian points along the lower inner arm. The meridians found in this area are large intestine (LI), LU, PC and HT. LU7 is highlighted in yellow. The non-meridian point should not be close to other meridian points. Thus, a non-meridian point was chosen which was located at 3 to 4 cun distal to PC 3 (at the ulnar side of the tendon of m. biceps brachii) and at the ulnar side of the PC (the tendons of m. palmaris longus). The location of the non-meridian point is highlighted in red in Figure 35. As suggested by the TCM doctor, this point is the closest non-meridian point to the LU7 of 1 cm in diameter. The subjects in the sham group had to wear two electrodes that were placed at the ulnar side of the tendon of m. biceps brachii. Each electrode was located 0.5 cm away from each other. That is, one electrode was placed near the distal forearm and the other electrode near the cubital crease. The stimulation was performed on the left hand of the subject in the test groups as the location of LU7 was specified on the left hand of the subject in a review [250].

8.7.10 Environment

The sleep laboratory was designed to simulate the home environment with a living room, shower, bedroom and computer control room. During the sleep study, room temperature and relative humidity were set at a range between 21°c and 23°c and 60% to 80% respectively according to individual preference to ensure that the subject felt comfortable during sleeping.

8.7.11 Criteria of Scoring Respiratory Events and Sleep Stages

Scoring of all sleep stages was automatically performed using the PSG device and manually performed based on the "Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects" written by Rechtschaffen and Kales in 1968 [29]. The key points for scoring sleep stages in the study are summarised as follows:

Sleep stages were scored according to the amplitudes, frequencies and waveforms of EEG, EOG and EMG signals. There are two main stages in human sleep. They are non-rapid eye movement sleep (non-REM) and rapid-eye movement (REM) sleep. Non-REM sleep is divided into 4 sleep stages. They are stages 1, 2, 3 and 4.

Stage 1 is often regarded as "drowsy sleep" or "traditional sleep". In stage 1, EEG signals usually consist of alpha waves in low amplitude. Slow rolling eye movement, vertex waves, theta activity with less than 50 percent of alpha activity are the characteristics of stage 1. Vertex sharp waves are usually found in stage 1. Stage 2 is regarded as "light sleep". In stage 2, EEG signals usually consist of alpha waves with low amplitude. Sleep spindles and k-complexes can also be found. K-complex is a sharp wave with 2-3 phases, and can be found when there is sound or light stimulation that occurs in the vertex. Vertex sharp wave is a mono-phasic wave. Stages 3 and 4 are regarded as slow-wave sleep. Around 20-50 percent of delta-H waves can be found during stage 3 and more than 50 percent during stage 4. Saw-tooth EEG can be found during REM sleep. Intense dreaming occurs during REM sleep due to heightened cerebral activities. Muscles are usually paralyzed during REM sleep. During the REM stage, EEG waveforms are fast with low amplitude. EOG (left and right eye) are not flat. EOG tends to fluctuate with mirror images in the left and right ocular channels. Chin electromyogram (EMG) have little changes due to the paralysis of the

subjects. Non-REM and REM sleep occur repeatedly and cyclically. During wakefulness, more than 50% of alpha waves can be found. The frequency of alpha, delta, theta and beta waves are 8-13 Hz, 1-3 Hz, 4-7 Hz and 14-35 Hz respectively. In the awakening stage, EEG, EOG, EMG of subjects are usually fluctuated. On the other hand, subjects may also have intermittent arousals during sleep. In this case, paradoxical EEG, EMG and EOG waves can be found. Subject may also have little limb movement. The occurrence of saw-tooth waves during stages 2, 3 and 4 may help the researcher in predicting whether the REM stage is approaching or not. On the other hand, all the signals may have artifacts. The artefact is usually found in association to the movements of subjects (limbs, eye blinking, coughing and deep breathing) or poor contact of the electrode.

Scoring of sleep apnoea events referred to the definitions of sleep disordered breathing as suggested by Roux et al. [178]. Sleep apnoea events were excluded during the subjects' awakenings or appearance of signal noises. Sleep apnoea is defined as cessation of the nasal flow signal for at least 10 seconds along with four percent of oxygen desaturation [1]. OSA is the presence of thoracic and abdominal efforts during sleep apnoea. Central sleep apnoea is the absence of thoracic and abdominal efforts during sleep apnoea. To score the respiratory event, nasal airflow is a golden standard for diagnosing sleep apnoea in comparison with other signals, such as temperature flow, thoracic and abdominal movements in this study. OSA events are identified if the signal of nasal airflow is completely flat for more than ten seconds in association with three percent desaturation. Hypopnea events are identified if there is fifty percent reduction of the airflow for ten seconds in associate with three percent desaturation. Central apnoea events are identified if the nasal flow, thoracic and abdominal effort signals are completely flat for more than ten seconds plus three percent desaturation. Mixed apnoea is the combination of obstructive and central sleep apnoea. Events with signal artefact were excluded.

In 2007, the American Academy of Sleep Medicine has introduced a new manual regarding the scoring system of sleep stages and abnormal respiratory events. Difference between the scoring system used and the new AASM scoring manual in scoring the abnormal respiratory events are shown as below:

Scoring system used in this study:

Sleep apnoea: Cessation of breathing for ten seconds in associated with 4% oxygen desaturation.

Obstructive sleep apnoea: If the event meets apnoea criteria, thoracic and abdominal efforts are present

Central sleep apnoea: If the event meets apnoea criteria, thoracic and abdominal efforts are absent.

Mixed sleep apnoea: Initially appears with central sleep apnoea, then followed by obstructive sleep apnoea

AASM scoring system (for adults):

Sleep apnoea:

(1) Baseline amplitude has to be determined and there was no requiring of a minimum desaturation criterion
(2) There is a drop in the peak thermal sensor excursion by ≥90% of baseline
(3) The duration of he event lasts at least 10 seconds
(4) As least 90% of the event's duration meets the amplitude reduction criteria for apnoea

Obstructive sleep apnoea: If it meets apnoea criteria and is associated with continued or increased inspiratory effort throughout the entire period of absent airflow

Central sleep apnoea: If it meets apnoea criteria and is associated with absent inspiratory effort throughout the entire period of absent airflow

Mixed sleep apnoea: If it meets apnoea criteria and is associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event

8.8 Outcome Variable

Outcome variables are selected based on two aspects. The first aspect is the treatment objectives of sleep apnoea while the second is the outcome variables which were applied in previous studies. In the literature review, the treatment objectives were stated for reducing symptoms (such as AHI or oxyhaemoglobin saturation), to improve sleep quality or daytime sleepiness, and quality of life (such as moods). These objectives are particularly useful in evaluating the efficacy of different sleep apnoea treatments or measures. Analysis in this research is divided into two approaches. One approach is comparing the effect of the intervention on the physiological changes between the baseline and test study. The physiological changes are quantified into several indexes which are stated in section 7.8.1. Another approach is studying the instant effect of the intervention on the pulse oximetry level and EEG signals in which the methods of measuring these parameters are stated in section 7.8.2.

Previous studies measured different types of variables to evaluate the efficacy of treatment on sleep apnoea. The variables used were apnoea-hypopnea index (AHI), apnoea index (AI), daytime vigilance, cognitive function, adverse effects, satisfaction, daytime sleepiness, quality of life, sleep diary, upper airway closing pressure, snoring, pulse oximetry level, morning fatigue, sleep latency, number of arousals, sleep efficiency, and percentage of deep sleep. Of these parameters, AHI [99, 125, 186, 188, 218], AI [81, 85, 231], pulse oximetry level [85, 218, 227], arousals [78, 125, 195, 237], apnoea-sleep ratio [85] and sleep stages [100,

125, 188, 218] were commonly used to assess the outcome of treatment on sleep apnoea patients.

In consideration of the above parameters, this study selects the AI, apnoea-sleep ratio (ASR), average desaturation level (ADL), average respiratory arousal (ARA), sleep efficiency (SE) and percentage of deep sleep (PDS) as the measuring parameters in order to study the managing effects of the intervention on OSA.

AHI was not selected as a measuring parameter in this research because the intervention aims to manage the apnoeic event rather than the hypopnea event. AHI includes the average number of apnoea and hypopnea events per hour. AI is an index which has been found in some of the previous studies for evaluating the efficacy of the treatment for sleep apnoea. AI refers to the frequency of sleep apnoea episode per hour. However, as mentioned earlier, patients with a long duration of sleep apnoea may have lower frequency in terms of the number of episodes. Hence, this study also measures the ASR, which represents the total duration of sleep apnoea in total sleep time. Meanwhile, the ADL was measured which reflects the severity of OSA in a sleep study. ADL was used in most of the previous studies to reflect the degree of hypoxia of an individual.

As arousal is usually found after the cessation of an OSA event which may result in sleep fragmentation, this study also counted the average number of ARA during a sleep study. An arousal event is defined as a minimum of three seconds in duration of alpha waves in the EEGs, and there is ten seconds of sleep preceding the respiratory arousal event. On the other hand, the total duration of sleep in total recording time was measured and termed as SE. For an in-depth analysis of the sleep quality of the subject, this study also measured the total duration of deep sleep over the total sleep time which was termed as PDS. It was suggested in the literature that deprivation of slow wave sleep may worsen sleep

quality than deprivation of REM sleep [172]. Hence, the quantity of deep sleep may directly affect the quality of sleep. The definitions of these terms are summarized in Table 11.

Table 11 Definitions of the outcome variables

Variable	Abbreviation	Definition
Apnoea Index	*AI*	➢ Number of obstructive sleep apnoea events per hour over during sleep
Apnoea-Sleep Ratio	*ASR*	➢ Percentage of the total duration of sleep apnoea over the total sleep time
Average Desaturation Level	*ADL*	➢ Average percentage of oxygen desaturation level falls from the baseline level during a sleep study
Average Number of Respiratory Arousal	*ARA*	➢ Average number of respiratory arousal events per hour during a sleep study
Sleep Efficiency	*SE*	➢ Percentage of total sleep time (stage 1, 2, 3, 4 and REM sleep) over the total recording time
Percentage of Deep Sleep	*PDS*	➢ Total duration of deep sleep (stages 3 and 4) over the total sleep time

8.9 Sample Size

In this study, the estimation of sample size refers to an equation suggested by Chap (2003) [37]:

$$N = 4(Z_{1-\alpha} + Z_{1-\beta})^2 \frac{\sigma^2}{d^2}$$

This equation assumes that the total sample size is affected by the size α of the test, desired power (1-β), mean difference (d) and variance (σ) of the population. There are no previous studies which apply the meridian point stimulation in managing symptoms of sleep apnoea. Therefore, this study estimated the sample size based on information from a similar study: "The effects of transcutaneous electrical stimulation during sleep on obstructive sleep apnea" by Piao, 1998, and supposing that α and β is preset as 0.05 in accordance to the reference, the required sample size is

$$N = 4(1.96 + 1.65)^2 \frac{8.1^2}{23.1^2} \cong 6.4$$

This results in a minimum of total 7 participants in each group.

The reasons of referring to Piao's study are:

(1) This study investigated the effects of transcutaneous electrical stimulation during sleep on obstructive sleep apnea syndrome, in which the aims and the objectives were similar to my study

(2) The primary outcome measurable was also using AI

(3) The target group was only the subjects with OSA

Figure 36 Sample size of other studies related to the treatment for OSA

Intervention / Source	Sample size (N)	No. of groups	Outcome
Dietary weight loss			
Smith et al, 1985	23	2 (weight loss and control)	• AHI reduced by 47% with 9% reduction in weight
Rubinstein et al, 1988	12	1	• AHI reduced by 75% with 20% reduction in weight
Schwartz et al, 1991	26	2 (weight loss and control)	• Number of apnoea episode/hour decreased from 83.3 +/- 31.0 to 32.5 +/- 35.9 • P_{Crit} decreased from 3.1 +/- 4.2 to -2.4 +/- 4.4 cm H2O with p less than 0.00001
Bariatric surgery			
Peiser et al, 1984	15	1	• AHI reduced by 89% with 31% reduction in weight
Herman et al, 1982	4	1	• AHI reduced by 98% with 47% reduction in weight
CPAP Device			
McArdle and Douglas, 2001	22	2 (CPAP and placebo capsule)	• CPAP: lower arousal index, less stage N1 and more N3
Engleman et al, 1994	32	1	• AHI reduced by 87%
Engleman et al, 1998	23	1	• Results in symptom improvement, sleepiness (multiple latency test), improved vigilance, cognitive function, quality of life and mood
McEvoy and Thornton, 1984	12	1	• AI reduced by 83%
Oral appliance			
Mehta et al., 2001	28	2 (Two-piece mandibular repositioning advancement and control plate)	• RDI in intervention group and control reduced by 53% and 10% respectively
Eveloff et al., 2004	19	Mandibular positioner	• AHI reduced by 68%
Clark al., 1993	24	Mandibular advancement	• AHI reduced by 75% • Less stage 1, more REM sleep
Gotsopoulos et al., 2002	73	2 (Two-piece mandibular repositioning advancement and control plate)	• RDI in intervention group and control reduced by 56% and 7% respectively
UPPP surgery			
Ryan et al., 1990	48	1	• More than 60% reduction of AI
Senior, 2003	37	1	• 40% of subjects reduced more than 50% respiratory event index
Electrical stimulation			
Schwartz et al., 2001	8	1	• Mean AHI reduced from 52 to 22.60

8.10 Analytical Method

The outcome variables will be compared (1) pre-post the experiment and (2) within the groups based on two important aspects. One aspect is the measurement of the improvement in the severity of sleep apnoea and the other is the measurement of sleep quality. AI, ASR, and ADL reflect the severity of sleep apnoea whilst ARA, SE and PDS reflect the sleep quality.

8.10.1 Subject characteristics

The first part of the analysis described the characteristics of subjects, including age, gender, BMI, AHI, and medical history, and if they were using other treatments for sleep apnoea. These characteristics help us in understanding the background of the subjects and generalise the results in accordance to the characteristics of the subjects.

8.10.2 Descriptive statistics

The mean and standard deviation of the outcome variables for each group and between the two nights were illustrated in error bar charts. The error bar chart provides a clear visual effect on the changes of the outcome variables between the two nights. As well, the trend of the average pulse oximetry level of the three groups during the first six hours of the baseline and test studies was plotted. The trend shows the change of the pulse oximetry level from time to time and it helps in understanding if there is any significant improvement in a specific period of time in the test study in comparison to the pulse oximetry level with the baseline study.

8.10.3 Influential statistics

SPSS software was used to perform one-way ANOVA (Analysis of Variance), MANOVA (Multivariate analysis of variance) and univariate analysis. One-way ANOVA analysis between groups evaluates if there is any significant differences in terms of each outcome variable among the three groups. If there is a significant difference in terms of the outcome variable among the three groups, the next task is to find out the difference between which two groups. The null hypothesis of ANOVA analysis is that there is no significant difference in terms of each outcome measurable among the three groups, where H_0: $\mu_1 = \mu_2 = \mu_3$. The confidence interval of all cases was 0.05 and $P < .05$ was considered as significant. The MANOVA analysis is used to identify the interactions among different independent variables and the association between dependent variables. In this study, the MANOVA is used to verify if there is an overall significant difference in terms of variance, considering the six outcome variables among the three groups. It is assumed that the dependent variables or outcome variables should be largely uncorrelated in the MANOVA analysis. Also, dependent variables should be normally distributed between groups. This study also attempted to investigate if there was any effect due to other influential variables (also called covariates), rather than the proposed intervention (that is, electrical stimulation) on outcome variables. A Univariate analysis was performed. Covariates were selected in this analysis according to literature review. Based on the factors that may potentially affect the severity of sleep apnoea, age, smoking habit, drinking habit, CPAP device, other treatment, sleeping position and weight change were selected as the possible influential variables in this study.

On the other hand, one-way ANOVA analysis was carried out to test if there was a significant difference between the trend of the SpO_2 level at the three points of time of each group during a sleep apnoea event with intervention. In the statistical analyses, the null hypothesis is that the intervention had no effect on each dependent variable. In this case, the null hypothesis is accepted. Results of the analyses were stated with an assumption of equal variance with 95% confidence interval of the difference and between the baseline and test study.

8.10.4 Analysis of the immediate effect of the intervention

This study also investigate the hit rate of the intervention in the MPSG and the SG during the test study. Hit rate is the percentage of correct firing (hit) during the test study, given that the stimulation is applied at 10 seconds during an OSA event. Meanwhile, the effect of intervention on managing symptoms of OSA was analyse by measuring the SpO_2 level at four time points: (1) right before the cessation of breathing; (2) at ten seconds after the cessation of breathing / the onset of OSA; (3) right after the stimulation and (4) one minute after the stimulation. Afterwards, one-way ANOVA analysis was carried out to compare if there is significant difference in terms of the average SpO_2 level at the four points in each group. On the other hand, arousal during the stimulation was observed and thereby calculated the percentage of arousal events triggered by the stimulation.

8.10.5 Illustrations of the PSG tracings

Apart from the statistical analysis, PSG tracings of a subject with meridian point stimulation during sleep apnoea were captured. Tracings include electroencephalogram (C3-A2 and C4-A1), electrooculogram (LOC and ROC),

pulse oximetry level (SpO_2), electrical stimulation (stimulation), nasal airflow and nasal temperature flow (nasal temp flow). All figures in the table of the result sessions are represented by mean (SD), unless otherwise specified. This study also investigated if there was a relationship between BMI and the final intensity selected for the stimulation.

8.10.6 Reported adverse effects

After the experiment, subjects were also asked if they had experienced any adverse reactions, such as pain, nausea, anxiety, sleep disturbance or skin allergy due to the interventions.

8.11 Summary

The chapter outlines the methodology of the clinical trial which aims to test the efficacy of applying meridian point stimulation to manage symptoms of OSA. The methodology includes trial design, subject recruitment, procedures and setting of the experiment. The analytical methods are depicted. The trial design, procedures and analyzing methods in this chapter are specifically designed for the main study. For the pilot study, a smaller scale of experiment is conducted which aims to test feasibility, possibility of acquiring the intended signals for analysis and if arousal occurs frequently due to electrical stimulation. In the pilot study, however, the signal which triggers the intervention is the sound level (occurrence of snoring). Details of the pilot study are stated in Chapter 8.

Chapter 9
Pilot Study

9.1 Introduction

In the pilot study, the feasibility of using the PSG device to obtain the intended physiological parameters was tested and the potential effects of the intervention on subjects was measured by applying a commercialised device which provides electrical stimulation when snoring episodes were detected. The procedures and outcome parameters in the pilot study are similar to those in the main study except for the intervention setting. This chapter is divided into four parts. The first and second parts introduce the aims and methods of the pilot study. The third part discusses the findings in the pilot study which include the change in terms of the output signals between the baseline study (night 1) and test study (night 2) and also verify preliminarily if the subjects will wake up due to the electrical stimulation. Eventually, the problems that are encountered by the researcher in the pilot study will be discussed and suggestions for the main study will be provided.

9.2 Aims

As an early stage of the experiment, a pilot study was conducted to test the feasibility of a clinical trial and verify if the proposed outcome parameter could be measured. Another purpose of the pilot study was to investigate whether electrical stimulation would cause any arousal on the subjects and thus worsen their sleep quality.

9.3 Methods

9.3.1 Subject

Subjects aged between 18 and 65 with symptoms of sleep apnoea were invited to participate in the pilot study. Subjects were recruited by convenience sampling. Subjects with symptoms such as breathing pauses and loud snoring during sleep which were reported by the bed partners, and daytime sleepiness, would be included. Subjects who were pregnant, diagnosed with mental illnesses, used a pacemaker, had obstructive lung disease, severe skin diseases, and unable to provide informed consent would be excluded.

9.3.2 Tools

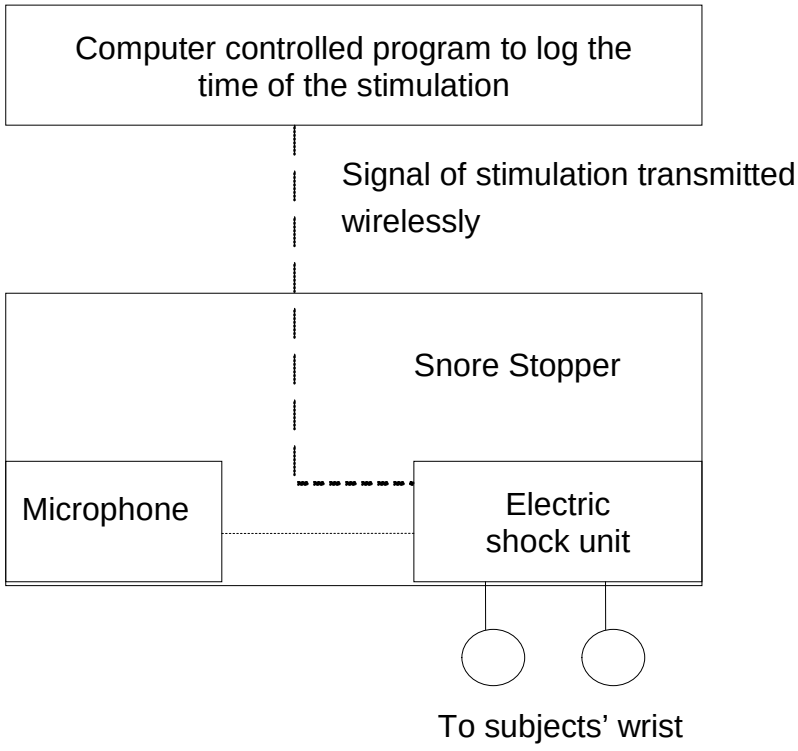
PSG

A PSG device was used to record the respiratory condition and brainwaves of the subjects during the pilot study. The PSG device monitored the EEG, ECG, EMG, EOG, chest and abdominal movements, nasal and oral air flow, body positions, pulse oximetry levels, sound levels (by microphone) and limb movements of the subjects. Meanwhile, subject movements were recorded using a video recorder and decibel levels were recorded using a decibel meter.

Intervention Setting

As the device for releasing electrical stimulation in response to sleep apnoea was under development in this stage, a commercialised device; namely, a snore stopper, which claims to release electrical stimulation on the meridian point in response to snoring, was used in the pilot study. The snore stopper aims to manage snoring using meridian point electrical stimulation and the location of stimulation is the Neiguan (PC6) meridian point. Stimulation is released only when three consecutive snoring events with decibels higher than 65 are detected. The pulse amplitude of the stimulation is 18uA and the pulse rate and width are 0.2 Hz and 800 uS respectively. Voltage of the stimulation ranges from 2.5 to 14 V. The waveform of the stimulation is a symmetrical bi-phasic square pulse. Figure 37 illustrates the block diagram of the experimental setting.

Figure 37 Block diagram of the experimental setting



9.3.3 Procedures

The subjects were invited to undergo two nights of sleep study, which consists of a baseline study (night 1) and a test study (night 2). The minimum duration of the recording of a sleep study was 6 hours. Physiological signals of the subject were monitored during the entire sleep study using the PSG device.

In night 1, no intervention or medication was given to the subjects. The aims of the baseline study are to assess the severity of sleep apnoea and snoring level of the subject.

In night 2, the subjects were required to wear the snore stopper during sleep and select the stimulation intensity prior to sleep. The intensity of stimulation was set at the maximum acceptable level for the subject. During night 2, stimulation was released on PC6 of the subject if three consecutive snoring episodes with decibels higher than 65 were detected. Meanwhile, the activation time of stimulation was recorded automatically using a computerised program. PC6 is located at 2 cuns proximal to the transverse cubital crease on the ulnar side of the tendon of biceps brachii [88]. Indications of PC6 are reduction of chest pain, nausea and pharyngitis [252]. The reason for stimulating PC6 rather than LU7 in the pilot study is that the location of the electrodes in the snore stopper is specially designed and cannot be adjusted. In other words, the snore stopper is wrapped on the wrist of the subject with the electrodes located upon PC6. As the pilot study attempted to measure the intended outcome parameters as well as the effect of sleep quality due to the electrical stimulation rather than the effect of electrical stimulation of LU7 on OSA, therefore, PC6 was chosen as the site for intervention.

Finally, data in the both two nights was analysed to generate the results in terms of AHI, average mean sound level, average pulse oximetry level, average number of arousal and sleep efficiency. Scoring of EEG signals was performed automatically by the PSG and manually. An EEG manual by Rechtschaffen and Kales (1968) was used as a guideline for manual scoring. The results were compared between the baseline and test studies.

9.4 Results

Three male subjects aged between 34 and 42 with BMI between 22.1 and 36.2 were enrolled in the pilot test. Two were OSA patients; namely, subjects A and B. One was a mixed sleep apnoea patient; namely, subject C. They had completed two nights of sleep study.

In the pilot study, the PSG signals were monitored and recorded successfully. However, the decibel level was not recorded occasionally due to the failure of the wireless signal receiver. The results of the outcome parameters in terms of AI, ARA, and ADL and SE are generated and shown in Table 12.

Table 12 Results of outcome parameter between night 1 and night 2 of the three subjects

Outcome Parameter		Subject A	Subject B	Subject C
AHI	*Night 1*	14.4	53.5	65.3
	Night 2	17.6	39.3	72.7
ARA	*Night 1*	39.5	58	148.6
	Night 2	22.1	71.7	210.7
ADL	*Night 1*	18	14	16
	Night 2	26	8	15
SE	*Night 1*	93.2	89.9	79.8
	Night 2	99.2	81.6	92.9

9.5 Discussion

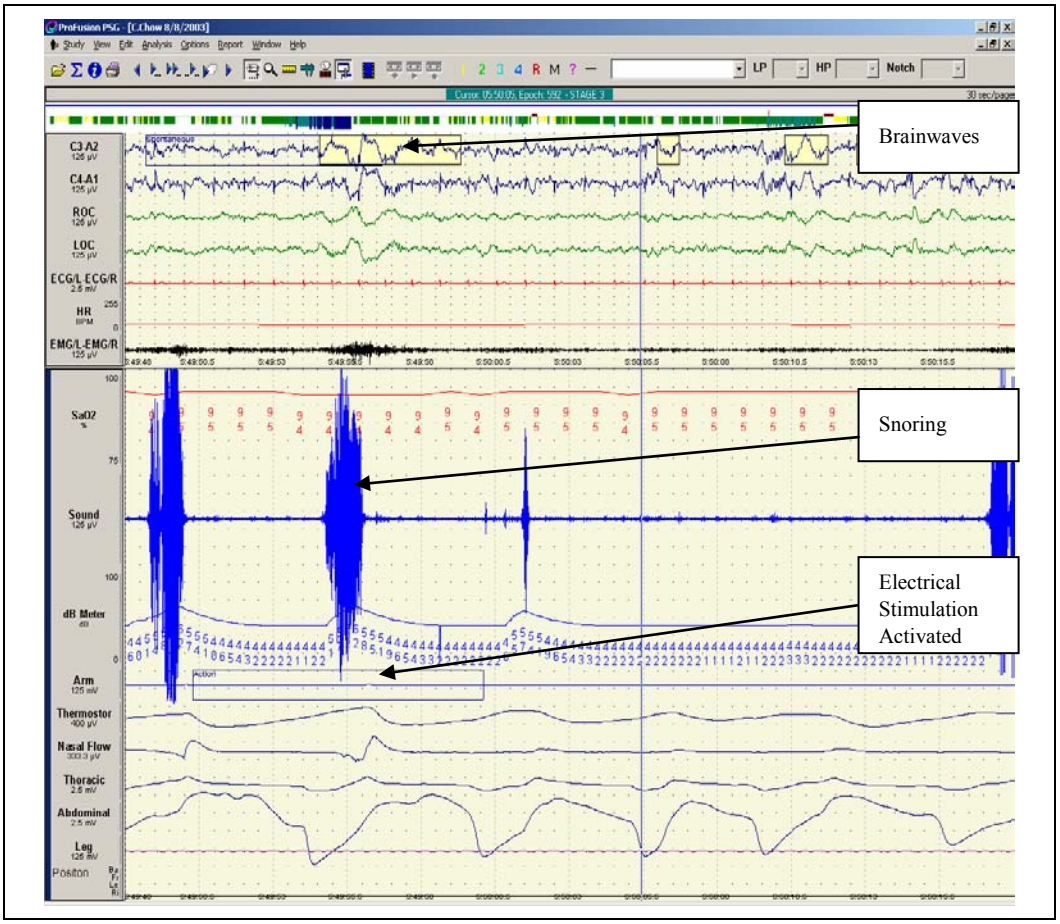
Using a computerised analysis of the PSG signals, AHI, ARA, ADL and SE were generated accordingly. By comparing the results between the two nights, it is found that AHI and ADL of subject B reduced remarkably after using the snore stopper, but the number of arousal increased and the sleep efficiency decreased at the same time. This may imply that this subject may have poor quality of sleep when he received the electrical stimulation. In this case, it is possible that the reduction of AHI may be due to the increased occurrence of arousal events and thus change the sleeping position of this subject. The AHI of subjects A and C increased and there was no improvement in terms of ADL during the test study. With reference to the SE of subjects A and C, it seemed

that the duration of sleep during the test study was longer than that in the baseline study. Meanwhile, the number of arousals decreased in subject A and increased in subject C. It seemed that stimulation had no effect on subject A in terms of sleep quality. A possible reason is that the intensity of stimulation was too low. In subject C, the stimulation intensity may be too strong which triggered many arousals and causes sleep fragmentation. The frequency of sleep apnoea was slightly increased at the same time.

This study also attempts to measure the average sound level of subjects during sleep. Unfortunately, the decibel meter was unable to record the decibel levels of subjects A and B occasionally during night 2 because of the instable connection of the signal transmission between the sensor and the PSG device. As the sound level is not the primary outcome parameter in the main study, it was not recorded in the pilot study due to the failure of the wireless signal receiver. However, for further studies, it is very important to ensure that the transmission of signals, especially those which are transmitted in wireless form, should be connected in a stable fashion without any signal disruptions.

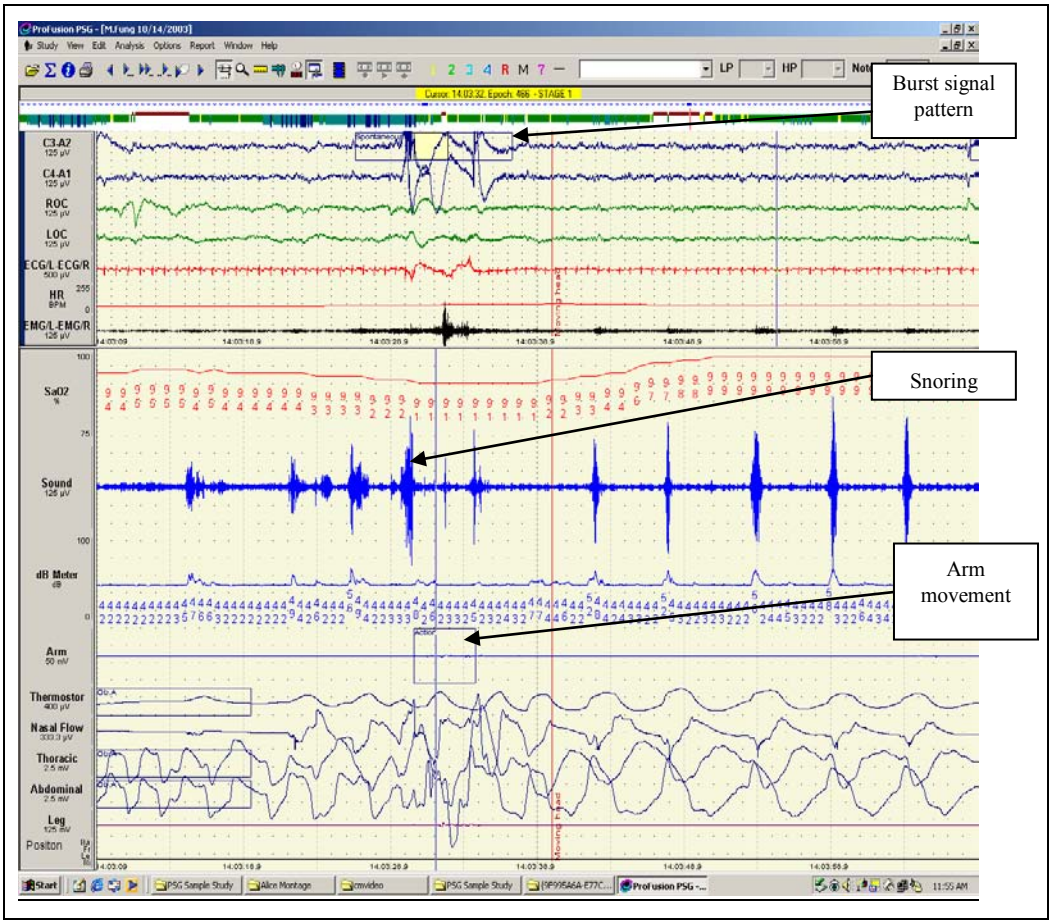
As the intensity of stimulation was selected by each subject, it is observed that there was no EEG arousal, especially in subject A during and well after the electrical stimulation. Figure 3 8 illustrates that subject A has no EEG arousal after stimulation. The first and the second channel of the tracings are the EEG signal. Figure 3 8 shows that stimulation is triggered after a snoring event in association to the arm movement. In this case, the EEG signal, blood oximetry level and volume of airflow have no significant changes, but snoring is stopped after the stimulation. During the stimulation and ten seconds after the stimulation, the subject was still experiencing sleep stage two.

Figure 38 *No arousal during the electrical stimulation*



However, EEG arousal was found frequently in subjects B and C during and well after electrical stimulation. As indicated by the EEG signals of subject B in Figure 39, stimulation is released at the time when there is arm movement. In the meantime, it is found that there are several bursts of EEG and EMG signal patterns which are interpreted as arousal and movement of the mouth. The body movement of the subject at this moment is further confirmed by referring to the video.

Figure 39 Electroencephalogram (EEG) arousal of subject B after the stimulation



As shown in Figure 39, it is found that the sound levels of subject B slightly improved by using the snore stopping device. Subject B stopped snoring immediately after the stimulation. Meanwhile, he altered his sleeping position.

With reference to the arousals in response to the stimulation in subjects B and C, it is found that the intensity of stimulation may not be the optimal level in the pilot study even though the level of intensity was selected by the subject prior to the experiment. Subjects may be aroused due to strong intensity of stimulation or cessation of breathing remained due to weak intensity of stimulation. In light of this issue, the researcher may have to adjust the level of intensity in response to the occurrence of OSA events or the arousal of the subject during the experiment

rather than using a fixed level of stimulation during the entire experiment in further studies. In other words, it is suggested that the intensity of stimulation would be increased if OSA remains as long as the subject is not aroused due to the stimulation.

The hit rate of the snore stopper was assessed by measuring the total number of three consecutive snoring events which was larger than 65 dB and the total number of stimulation when the subjects were using the snore stopper. The hit rate is an indicator which reflects the sensitivity of the snore detecting sensor. It is found that the hit rate of the snore stopper for subjects A, B and C are 22.3%, 12.8% and 48.9% respectively. The hit rate of the snore stopper is not satisfactory in this study as the snore detecting sensor was insensitive to the snore event with decibel levels larger than 65 most of the time.

It seems that the procedures suggested in the pilot study are able to measure the intended outcome parameters, such as the average pulse oximetry level, EEG arousal as well as nasal pressure flow. The stimulation time was able to be logged automatically using a computerized program.

9.6 Problems in the Pilot Test

Several problems were encountered during the pilot test. First, the brain waves of subjects changed abruptly when they altered their sleeping positions although they were not fully awakened by the stimulations. In this case, it was necessary to ensure that signals artifact due to movement should be identified in the main study. Secondly, the snore stopper only offered three levels of stimulation intensity. Thus, this may limit the choices for selecting the preferred level of stimulation by the subjects.

Also, the sensitivity of the sensor which triggers the intervention is very crucial so that the intervention would not be released during normal breathing conditions. However, it seemed that the microphone sensor in the snore stopper was not highly sensitive to snoring events. In the main study, it is important that OSA events should be identified promptly to ensure an effective management of symptoms. It is also important that subjects should try to stay relaxed in order to reduce the psychological burden due to the stimulation. Also, the electrodes which release electrical stimulation should be in close contact to the skin surface. Also of importance is the control of the stimulation intensity. As arousals were found in some events well after the electrical stimulation, it is very critical to control the stimulation intensity carefully so that the subject will not wake up in order to avoid sleep fragmentation. It is also important to test whether the management of symptom of OSA is not due to arousal of the subject after the stimulation.

9.7 Summary

The pilot test mainly tested the feasibility of using the PSG device to measure the physiological signals and the system for releasing stimulation which is triggered by snoring. The intended outcome parameters are measured successfully using the PSG device. Also, in some circumstances, EEG arousals are not found during electrical stimulation. It is very promising in applying this setting using OSA as an indicator for triggering the electrical stimulations and measuring as well as analyzing the results accordingly. Most importantly, the options of the level of stimulation should be increased so that the subjects will have more choices for selecting their preferred level of intensity.

Chapter 10

Main Study: Results and Discussions

10.1 Introduction

The main study of this thesis is conducted to evaluate the efficacy of applying electrical stimulation on the Lieque (LU7) meridian point to manage symptoms of OSA. This chapter discusses the results of the main study and its methodology that was also discussed in Chapter 7. This chapter is divided into 4 parts. The first part depicts the characteristics of the participants and average level of stimulation intensity that is used during the experiment. The second part compares the results between the baseline (night 1) and test study (night 2) in terms of the mean values of the outcome parameter. Results are also evaluated by using the paired sample t-test and one-way ANOVA. Afterwards, the trends of the mean pulse oximetry level and mean heart rate during the sleep study are plotted. The third part investigates the instantaneous effect of the intervention on the pulse oximetry level before, during and after an OSA event. Finally, the last part discusses the factors which may affect the outcome of the study.

10.2 Results

Twenty-seven subjects with baseline AI larger than 5 were enrolled in the main study. The subjects were divided into 3 groups, including the meridian point stimulation group (MPSG), sham group (SG) and control group (CG), each with 9 subjects. They had completed 2 nights of the sleep study, with a baseline study (night 1) and test study (night 2).

10.2.1 Recording duration and environment

The average duration of the sleep study was 7.2 hours. During the 2 nights of the sleep study, the mean values of room temperature and relative humidity were similar in all 3 groups, which were usually 22°C and 78 respectively.

10.2.2 Subject information

All participants in this test are Chinese adults. Tables 13 - 14 show the demographic information of the subjects in terms of gender, age, BMI, AI and the historical background of sleep apnoea treatment. The BMI and AI in Table 13 refer to the measurements taken during night 1.

Table 13 Gender and historical background of sleep apnoea treatment

	MPSG	**SG**	**CG**	**Total**	
Gender					
	N (%)	*N (%)*	*N (%)*	*N (%)*	
➢ *Male*	8 (32)	8 (32)	9 (36)	25 (100)	
➢ *Female*	1 (50)	1 (50)	0 (0)	2 (100)	
Historical Background of the OSA Treatment and Habits					
	N (%)	*N (%)*	*N (%)*	*N (%)*	*p*
➢ *With smoking habit*	2 (66)	1 (33)	0 (0)	3 (100)	0.129
➢ *With drinking habit*	3 (50)	2 (33)	1 (17)	6 (100)	0.346
➢ *Diagnosed with sleep apnoea*	8 (40)	4 (20)	8 (40)	20 (100)	0.798
➢ *Currently on CPAP*	5 (45)	1 (9)	5 (45)	11 (100)	0.018*
➢ *Tried CPAP, but stopped using now*	3 (33)	3 (33)	3 (33)	9 (100)	1.000
➢ *Tried other treatments for sleep apnoea, but stopped using now*	1 (100)	0 (0)	0 (0)	1 (100)	0.144
➢ *Currently using other sleep apnoea treatment*	1 (50)	0 (0)	1 (50)	2 (100)	0.352

Table 14 Age, Baseline BMI and AI of the subjects

	MPSG	**SG**	**CG**	**Total**	
	mean (SD)	*mean (SD)*	*mean (SD)*	*mean (SD)*	*p*
Age *years*	43.0 (5.9)	46.1 (11.5)	46.0 (8.5)	45 (8.7)	0.07
Baseline BMI *kg/m²*	26.0 (2.2)	27.1 (4.2)	27.1 (3.9)	27 (3.4)	0.286
Baseline AI *number of sleep apnoea/hour*	29.6 (19.6)	36.9 (19.7)	23.7 (17.3)	30.0 (19.0)	0.194

The majority of the subjects in this test are male and the overall mean age of the subjects is approximately 45. The youngest subject is 30 years old and the oldest is 61. Most of the subjects are obese with BMIs larger than 26. They are regarded as moderate to severe type of sleep apnoea patients with respect to the literature [103] as the mean value of AI in all 3 groups is close to 30.

Subjects in the MPSG and CG were previously diagnosed as OSA patients at a hospital. Afterwards, all were advised to use the CPAP device at home as a treatment. However, approximately 60% of these subjects continued to use the CPAP treatment. Three subjects tried other treatments, including weight management, sleeping with a special design pillow and oral appliance. It was also found that the majority of the subjects in the MPSG and SG smoke and drink in comparison to the subjects in the CG.

A chi-square test was conducted and it was found that there is no significant difference among the 3 groups in terms of their background information except for the use of the CPAP device.

10.2.3 Hit rate

It is important to know if intervention was applied at the right time (during sleep apnoea) in order to ensure that it is effective in managing the symptoms of sleep apnoea. This section calculates the number of sleep apnoea events with and without the application of electrical stimulation during the experiment. Also, it calculates whether stimulation is released during normal breathing. In night 2, the real time nasal airflow signals were monitored continuously with minimum time delay (less than 0.1 second) to detect the occurrence of sleep apnoea events. As the time delay of detecting sleep apnoea was short, stimulation could be released promptly after 10 seconds of breathing cessation. After the stimulation had been released on the subjects, the time for activating the stimulation was logged onto the computer. Figure 40 illustrates the program interface which is used to monitor the real time nasal airflow, controls the release of electrical stimulation and records the activation time.

Figure 40 *Demonstration of the program interface for releasing the stimulation and recording the stimulation time*

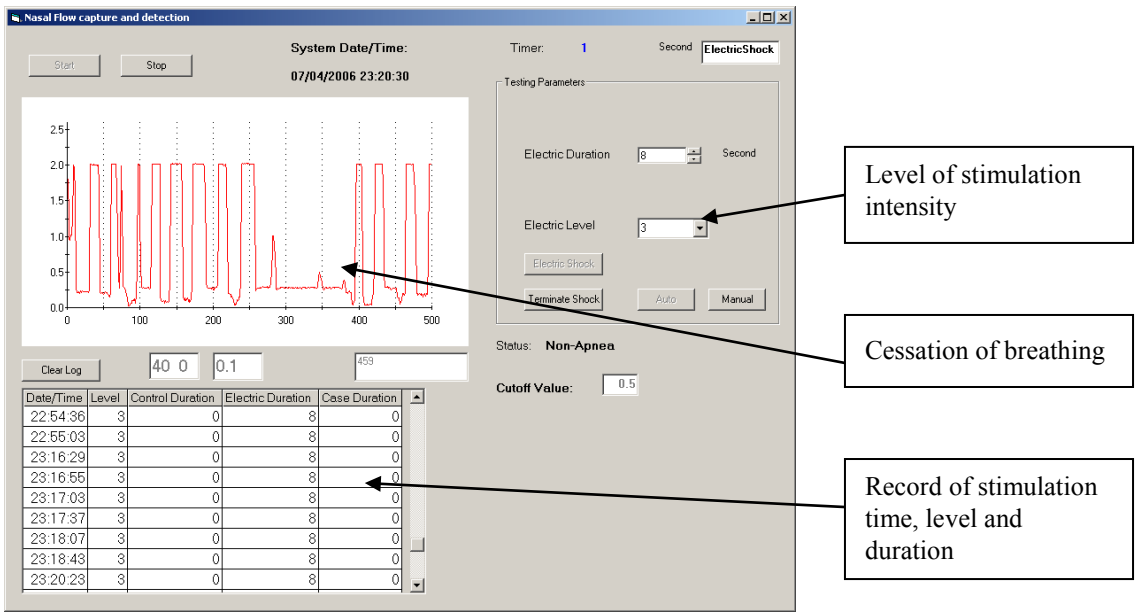


Table 15 summarises the number of stimulations which are released in response to the occurrence of an apnoea event and non-apnoea event, and also the number of an apnoeic event without the application of electrical stimulation. As intervention was started only after 10 seconds of breathing cessation, the term "cessation of breathing" in Table 15 is interpreted as the occurrence of cessation of nasal airflow, irrespective of the desaturation of the pulse oximetry level.

Table 15 *Number of OSA events with and without the electrical stimulation*

		Stimulation	
Group	**Episode**	**Yes**	**No**
MPSG	*Cessation of breathing*	1727	163
	Normal breathing	72	-
SG	*Cessation of breathing*	2020	211
	Normal breathing	115	-

Around 90% of sleep apnoea events with 10 seconds of breathing cessation were correctly identified using the real-time nasal airflow sensor. Stimulation was released during the events. In rare cases, stimulation was not released after the cessation of breathing. The reason is the incorrect measurement of the threshold value due to the detection error of the nasal airflow meter. The threshold value controls whether the intervention should be activated or not and it indicates when the subject stops breathing. In other cases, stimulation was also released during the absence of breathing cessation due to body movements.

10.2.4 Stimulation intensity

As mentioned in the methodology, there are 8 levels of stimulation intensity, ranging from 0-20 mA. Prior to the experiment, all subjects were asked to select their own level of intensity at a maximum acceptable level. The average level of the selected intensity in the MPSG and SG are shown in Table 16a. During the experiment, the researcher may have needed to adjust the level in accordance to the respiratory and arousal response of the subjects after stimulation. The mean level of intensity that is usually used during night 2 is shown in Table 16b.

Table 16a-b Summary of the level of intensity

	MPSG	**SG**
a. Selected Level of Intensity (mean ± SD)	2.44 ± 1.33	4.44 ± 1.42
b. Level of Intensity that was often used during the test study (mean ± SD)	4.44 ± 1.42	3.11 ± 2.47

Prior to the experiment, it was found that subjects in the SG tend to prefer a higher level of stimulation intensity whereas subjects in the MPSG tend to prefer a lower level of intensity prior to sleep. The maximum selected level is 5 in the MPSG and 4 in the SG. The minimum level in both groups is 1.

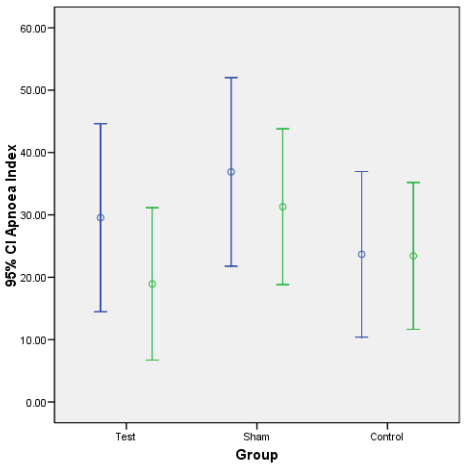
During the experiment, subjects in the MPSG usually received slightly stronger levels of stimulation than those in the SG. In both groups, the strongest level that was often used during the experiment was 7 and the lowest level was 1.

10.2.5 Change of the mean outcome parameters between the 2 nights

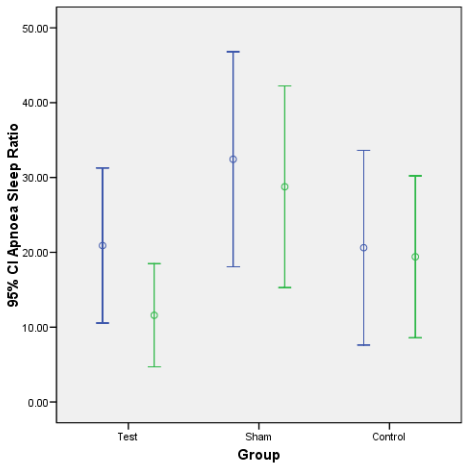
The physiological changes of the subjects were recorded successfully using the PSG device during the 2 nights of the study and the outcome parameters were generated accordingly. Figures 41a-h are a series of error bar charts which illustrate the difference in terms of the mean and standard deviation of AI, ASR, AAD, ADL, time with SpO_2 <90%, ARA, SE and PDS among the 3 groups between the 2 nights. In each graph, the 2 left bars belong to the MPSG group, the 2 middle bars belong to the SG, and the 2 right bars belong to the CG. The blue lines represent the results of night 1 while the green lines represent the results of night 2.

Figure 41 *Error bar charts showing (a) Apnoea Index; (b) Apnoea-Sleep Ratio; (c) Average Apnoeic Duration; (d) Average Desaturation Level (%); (e) Time (minute) with SpO_2 <90%; (f) Average Respiratory Arousal; (g) Sleep Efficiency and (h) Percentage of Deep Sleep of the 3 groups of subjects during night1 (the blue line) and night 2 (the green line)*

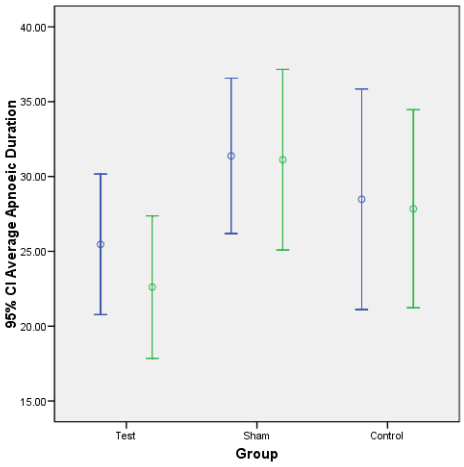
a



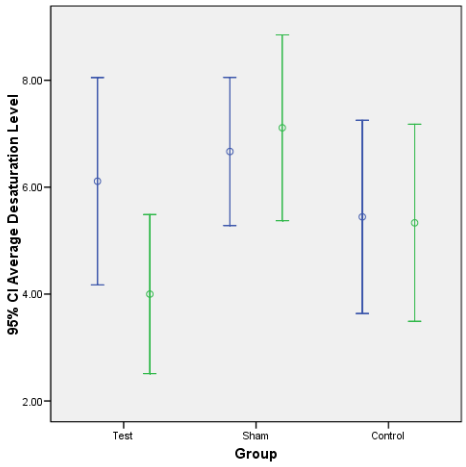
b



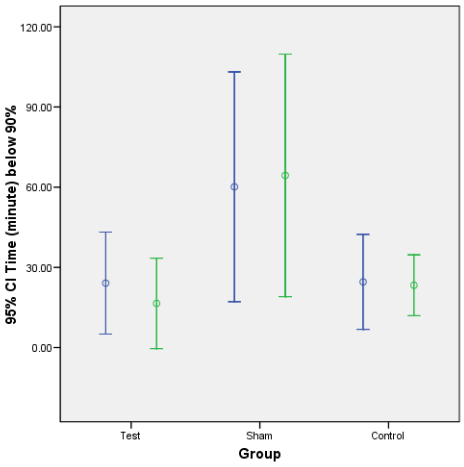
c


95% CI Average Apnoeic Duration
40.00
35.00
30.00
25.00
20.00
15.00
Test
Sham
Control
Group

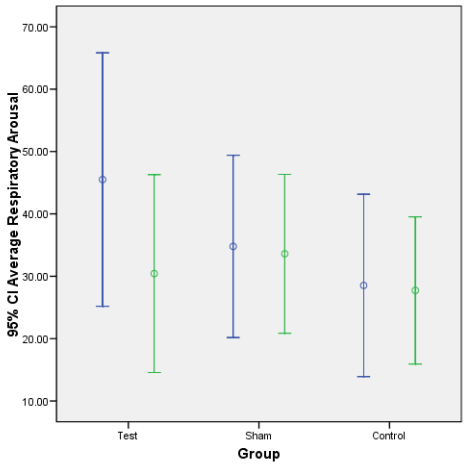
d


95% CI Average Desaturation Level
8.00
6.00
4.00
2.00
Test
Sham
Control
Group

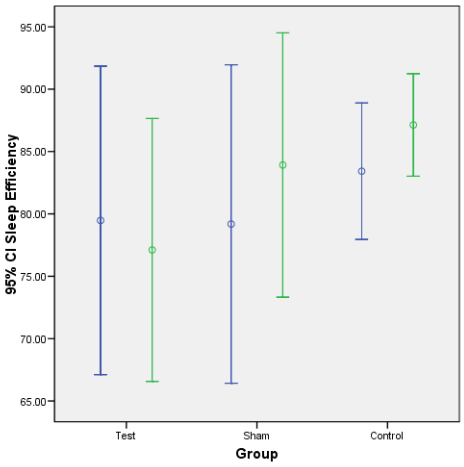
e


95% CI Time (minute) below 90%
120.00
90.00
60.00
30.00
0.00
Test
Sham
Control
Group

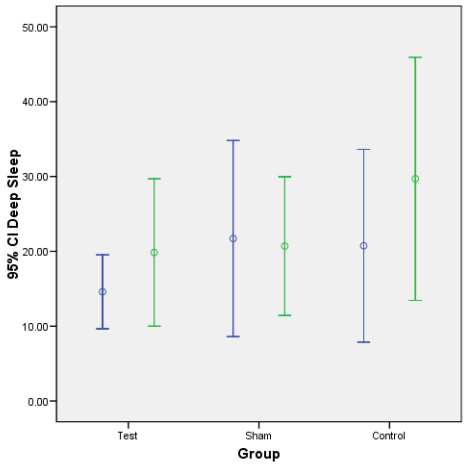
f


95% CI Average Respiratory Arousal
70.00
60.00
50.00
40.00
30.00
20.00
10.00
Test
Sham
Control
Group

g


95% CI Sleep Efficiency
95.00
90.00
85.00
80.00
75.00
70.00
65.00
Test
Sham
Control
Group

h


95% CI Deep Sleep
50.00
40.00
30.00
20.00
10.00
0.00
Test
Sham
Control
Group

As shown in Figure 41, the mean AI, ASR, AAD, ADL, ARA decrease from nights 1 to 2 in the MPSG. Overall, it seems that the severity of sleep apnoea in terms of the frequency, duration and average pulse oximetry level are improved by around 35%-45% after receiving meridian point stimulation. The "duration with SpO_2 less than 90%" slightly decreases only in the MPSG. Although SE slightly decreases by 2 % from nights 1 to 2 in the MPSG, the number of respiratory arousal decreases and the percentage of deep sleep increases slightly. It seems that the sleep quality in night 2 may be improved with the same amount of sleep during the 2 nights.

With reference to the results of the sham group, AI and ASR decrease from night 1 to 2 by 11% and 0.8% respectively. However, AAD and ADL of the subjects do not improve after they received the sham stimulation. It seems that the severity of sleep apnoea of the subjects is similar between nights 1 and 2 in the SG. On the other hand, the average number of respiratory arousals in night 2 almost remains the same as night 1. Although subjects in the SG tend to sleep longer in night 1, a smaller proportion of deep sleep is found during night 2.

With reference to the results of the control group, AI increases slightly in night 2 whilst AI, ASR, AAD, ADL and ARA do not change remarkably between the 2 nights. It seems that the severity of sleep apnoea is similar between the 2 nights as the subjects receive no intervention for both nights. However, patients in the CG tend to sleep more than the MPSG in night 2 with a greater proportion of deep sleep.

10.2.6 Results of the statistical analysis

A paired sample t-test was performed to compare if there is a significant difference in terms of AI, ASR, AAD, ADL, ARA, SE and PDS between the 2 nights within each group. This aims to analyse the pre-post effect on the subject due to the intervention.

The one-way ANOVA analysis compared if there was a significant difference in terms of AI, ASR, AAD, ADL, ARA, SE and PDS among the 3 groups. Furthermore, a post hoc test was carried out to analyse the effects of intervention on each pair of groups (i.e., MPSG-SG, SG-CG and MPSG-CG). Table 17 shows the results of the paired sample t-test and one-way ANOVA analysis.

Table 17 Results of the significant level in the paired sample t-test, one-way ANOVA and the independent sample t-test (= significant level < 0.05)*

Paired Sample t-test		**MPSG**	**SG**	**CG**
	AI	*0.005	0.219	0.932
	ASR	*0.005	0.202	0.666
	AAD	*0.025	0.838	0.624
	ADL	0.057	0.272	0.910
	ARA	0.081	0.772	0.740
	SE	0.555	0.277	0.158
	PDS	0.227	0.783	*0.021
One-way ANOVA		**MPSG-SG-CG**		
	AI	0.105		
	ASR	0.169		
	AAD	0.255		
	ADL	0.082		
	ARA	0. 097		
	SE	0.319		
	PDS	0.160		
Post hoc test		**MPSG-SG**	**SG-CG**	**MPSG-CG**
	AI	0.291	0.263	*0. 036
	ASR	0. 403	0.282	0.063
	AAD	0.129	0.821	0.191
	ADL	*0.034	0.630	0. 092
	ARA	0.052	0.872	0. 072
	SE	0.165	0.838	0.232
	PDS	0.228	0.472	0.061

According to the results of the paired sample t-test with 95% confidence interval, significant differences (p-value < 0.05) are found in terms of the mean of AI, ASR and AAD only in the MPSG. It seems that subjects who received meridian point stimulation better manage the frequency and duration of sleep apnoea in comparison with the night without any intervention. No significant improvement

is found between the 2 nights in terms of sleep quality in the MPSG. However, the outcome parameters in the SG and CG do not show any significant differences in terms of the severity of OSA between the 2 nights. Nevertheless, a significant difference in terms of the percentage of deep sleep is found in the CG.

None of the outcome parameters has a significant difference between the 2 nights of study according to the results of the one-way ANOVA. Furthermore, results in the post hoc test suggested that only AI is significantly different between the MPSG and CG, whereas ADL is significantly found between the MPSG and SG.

In this study, ANCOVA test was also performed. ANCOVA provides a way of statistically controlling for the effects of continuous or scale variables (or covariates) that the study is concerned but that are not the focal point or independent variable in the study. Covariates usually are variable that may cause the researcher to draw incorrect inferences about the prediction of the dependent variable from the independent variable, if not controlled.

10.2.7 Effect size and power

The power is obtained in accordance to the power table from "Power Analysis for Experimental Research" [9] and estimated based on the effect size, r (paired sample t-test), F pattern (one-way ANOVA) and the number of subjects per group in this experiment. In the paired t-test and using ASR as the dependent variable, the effect size of the MPSG was around 0.77 and r=0.863. The power was 0.88. In the one-way ANOVA test using ASR as the dependent variable, the effect size was 0.89. The F pattern was defined as High and the power was 0.5.

10.2.8 Univariate analysis

The Univariate analysis was conducted to examine the effect of other factors (or covariate) other than intervention, on dependent variables. In this section, only AI, ASR and PDS are chosen as the dependent variables for analysis because significant differences of these 3 outcome parameters are found according to the results of the paired t-test in Table 18. According to the literature as mentioned in Chapter 2, the contributing factors which may reduce the symptoms of OSA are weight management, pillow height and sleeping in a lateral position [95, 182]. In order to minimize the effect of the pillow height on the outcome parameters, the subject was required to use the same pillow during the 2 nights of the sleep study. However, "change in weight" and "sleeping position" could not be controlled by the researcher. Thus, there were attempts to test if these 2 factors, together with age, smoking, alcoholic consumption, and the use of CPAP at home, would contribute to the effect of the outcome in this study. The results are shown in Table 18.

Table 18 *Results of the univariate analysis on AI, ASR and PDS with significant level (* = significant level < 0.05)*

Factor	**AI**	**ASR**	**PDS**
Age	0.905	0.630	0.340
Smoking	0.301	0.098	0.763
Alcoholic consumption	0.268	0.073	0.407
CPAP treatment (at home)	0. 433	0.950	0.665
Sleeping position	0.336	0.590	0.890
Weight change	0.549	0.315	0.601

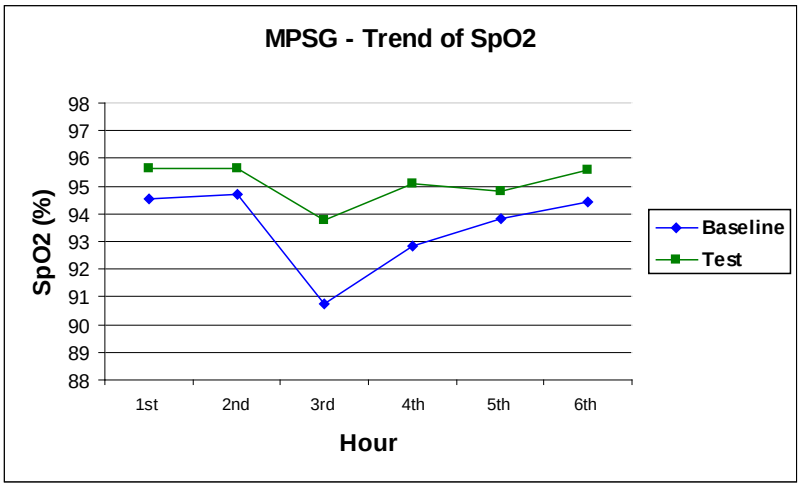
The results of the univariate analysis show that age, smoking, alcoholic consumption, CPAP treatment, sleeping position and weight change do not significantly affect the results on AI, ASR and PDS. The possible reasons are that usually the subjects slept in the supine position during the 2 nights of the sleep study. Thus, the impact of the sleeping position on the outcome parameters is not significant. Moreover, the subjects had completed the 2 nights for this sleep study within a month. Thus, their weight did not change dramatically within this period of time.

10.2.9 Trends of pulse oximetry level

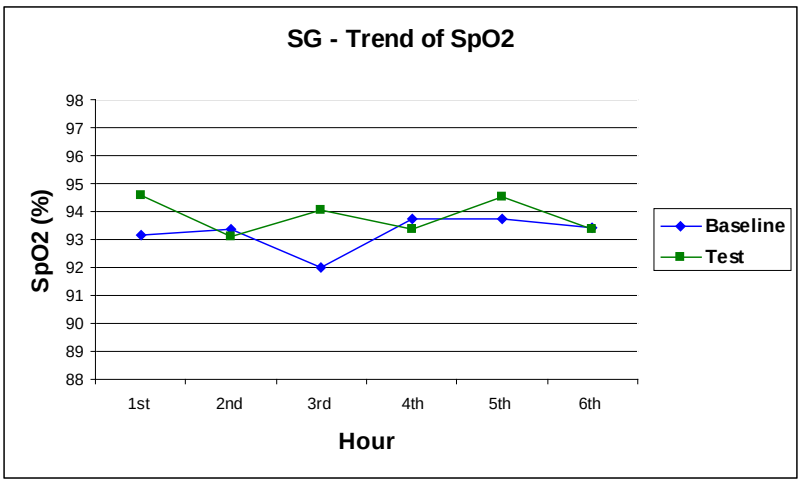
The trend of the average pulse oximetry level of the 3 groups during the first 6 hours starting from the onset of sleep in nights 1 and 2 is plotted in Figures 42a-c. The first hour is the time when the onset of sleep started.

Figure 42 *Plotting of the average SpO_2 level in (a) MPSG (b) CG during the first six hours of night 1 (the blue line) and night 2 (the green line) sleep studies*

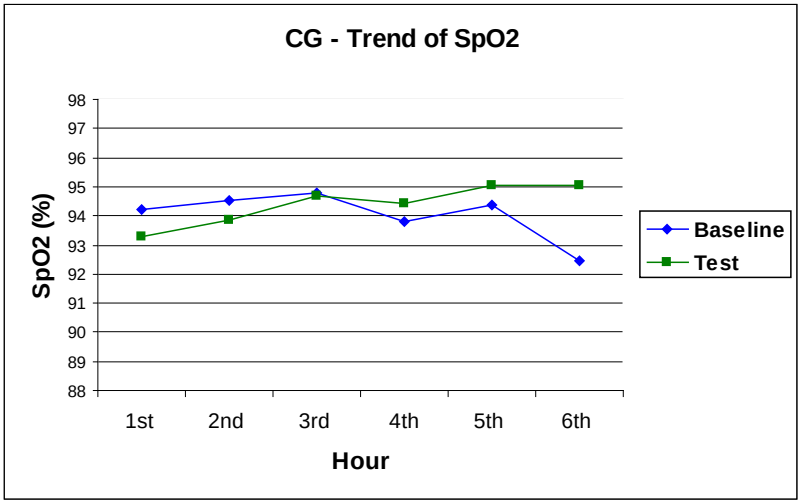
a



b



c



In the MPSG, the average SpO_2 level in nights 1 and 2 follows a rather similar pattern. The pattern is that the average SpO_2 level decreases sharply during the first 3 hours and increases after that. The lowest level in nights 1 and 2 is found during the 3rd hour of the sleep study. Overall, the average SpO_2 level increases by 1%-3% in night 2 in comparison with night 1. The lowest mean SpO_2 in night 1 is 91 and it increases to 94 in night 2.

In the SG, the pattern of the average SpO_2 level is not similar between the 2 nights. Also, a large difference of the SpO_2 level is found in the 1st and 3rd hour for both nights. A possible reason is the inducing of arousal by stimulation and thus, increasing the average SpO_2 level during the 2 hours. Overall, it seems that there is not a large difference in terms of the average SpO_2 level between the 2 nights in the SG.

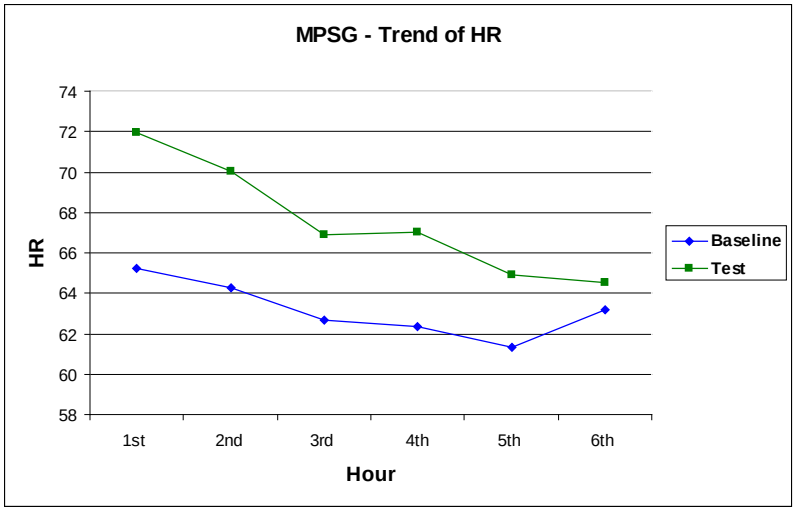
On the other hand, the patterns of the average SpO_2 level in the CG follow an opposite pattern, which means that the SpO_2 level decreases from the 1st hour to the 6th hour in night 1, and increases from the 1st to the 6th hour in night 2. Using the paired sample t-test, only a significant difference is found between the 2 nights of the sleep study in the MPSG ($p<0.05$).

10.2.10 Trends of heart rate

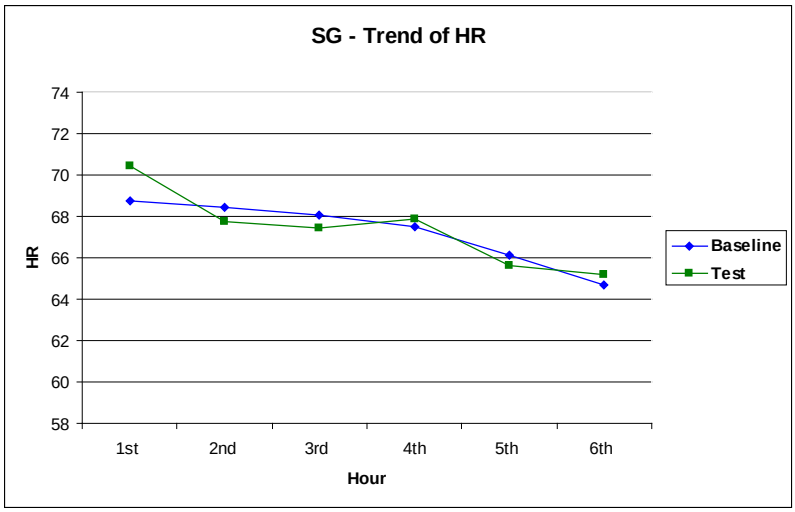
The trends of the average heart rate of the 3 groups during the first 6 hours of nights 1 and 2 are plotted and shown in Figures 43a-c. The first hour is the time that the onset of sleep started.

Figure 43 *Plotting of the average heart rate (HR) in (a) MPSG (b) CG during the first 6 hours of night 1 (the blue line) and night 2 (the green line)*

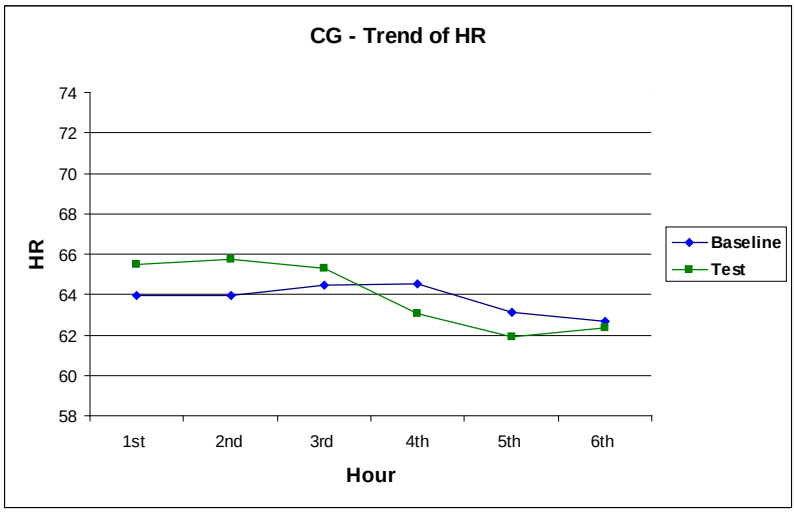
a



b



c



With reference to Figure 43, subjects in the MPSG tend to have a higher heart rate for night 2 in comparison to night 1. The difference in the heart rate for nights 1 and 2 narrowed down subsequently and it is small in the 6th hour of the sleep study. The heart rate trend tends to be constant (ranging from 81-85) in night 1 in the MPSG, but decreases more sharply from the 1st hour to the 6th hour in night 2.

The heart rate trend in the SG and CG is rather constant from the 1st hour to the 6th hour. Also, the mean heart rate of the SG and CG are similar. Using the paired sample t-test, only a significant difference is found between the 2 nights in the MPSG ($p<0.05$).

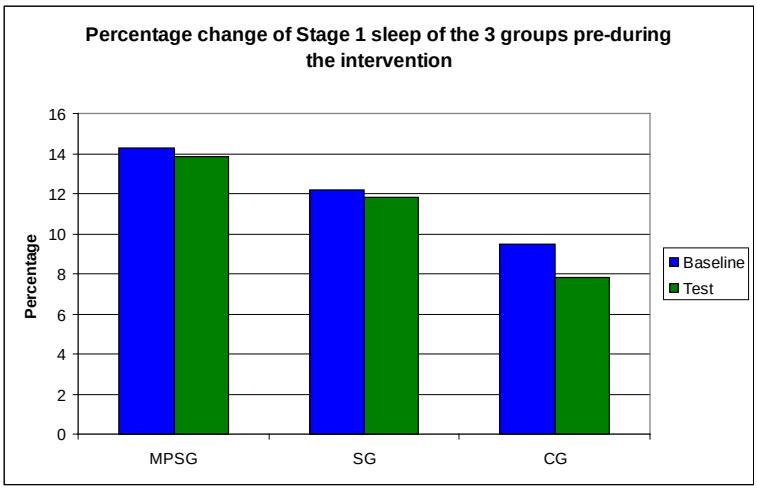
The results in Figures 42a and 43a suggest that subjects who received meridian point stimulation may have a higher mean heart rate during sleep and the mean SpO_2 level decreases at the same time.

10.2.11 Change in sleep stages during nights 1 and 2 in MPSG and CG

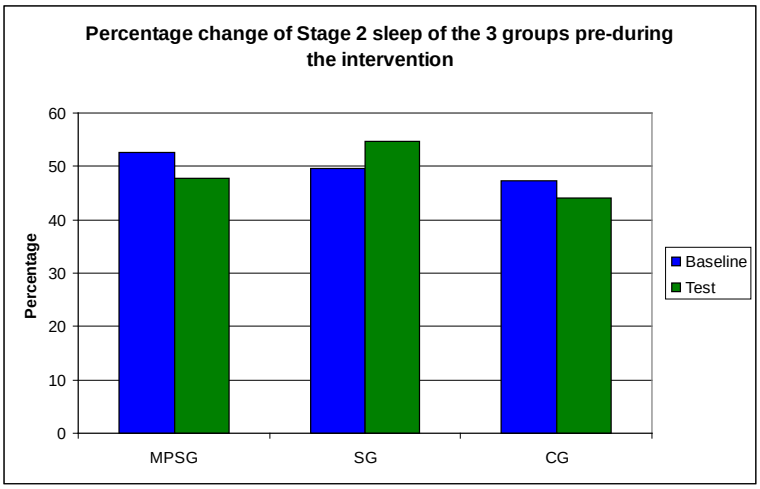
In order to understand the change of the sleep structure between the 2 nights of the sleep study in the 3 groups, the mean percentage of sleep stages 1, 2, 3, 4 and REM in total sleep time in each group are counted and shown in Figures 44a-e. The 2 left bars refer to the MPSG. The 2 middle bars refer to the SG. The 2 right bars refer to the CG.

Figure 44 *Change in sleep stage 1, 2, 3, 4 and REM during night 1 (in blue) and night 2 (in green) of the 3 groups*

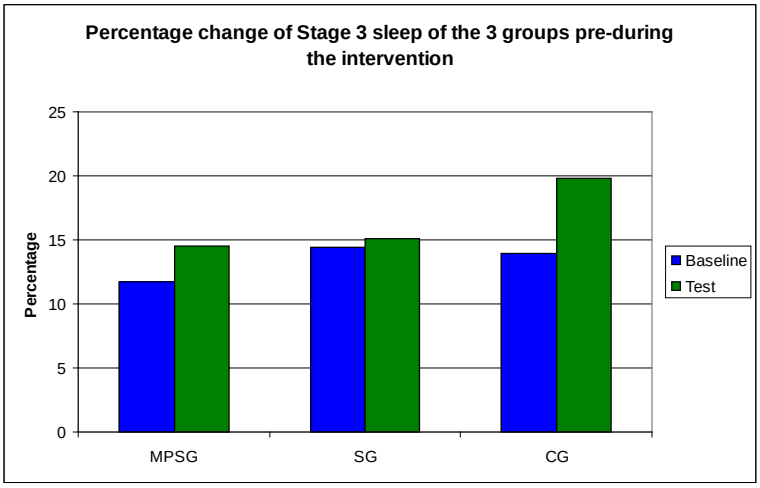
a



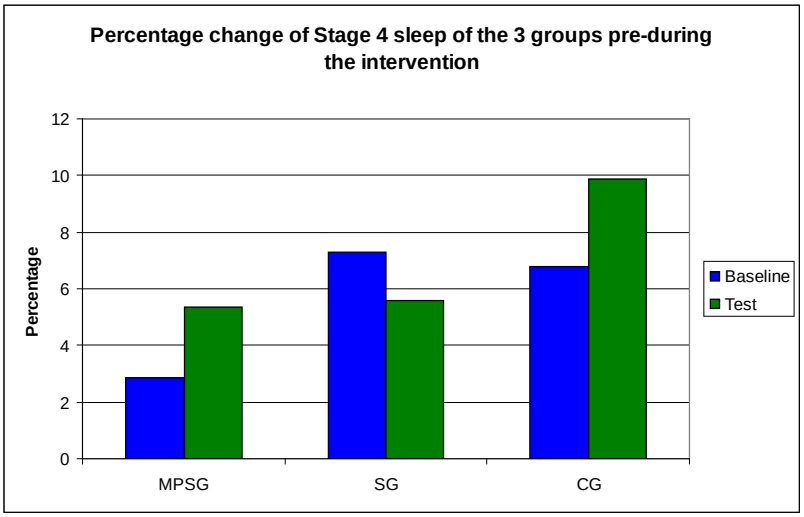
b


Percentage change of Stage 2 sleep of the 3 groups pre-during the intervention
60
50
40
30
20
10
0
Percentage
MPSG
SG
CG
Baseline
Test

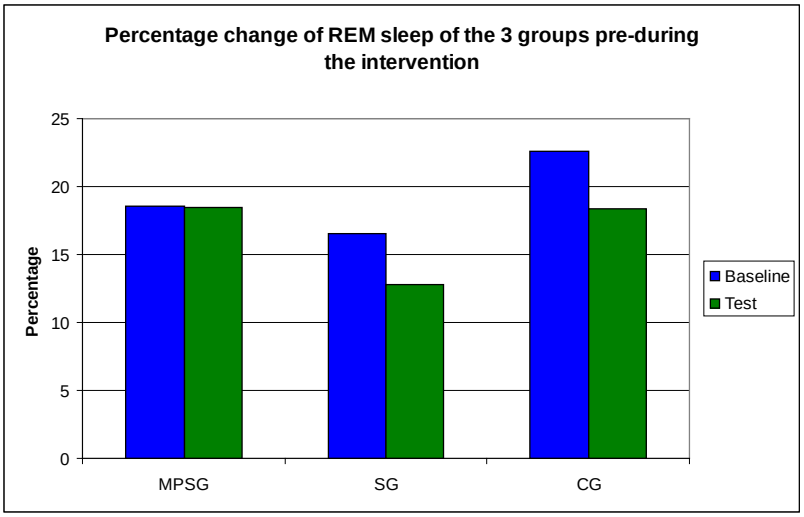
c


Percentage change of Stage 3 sleep of the 3 groups pre-during the intervention
25
20
15
10
5
0
Percentage
MPSG
SG
CG
Baseline
Test

d


Percentage change of Stage 4 sleep of the 3 groups pre-during the intervention
12
10
8
6
4
2
0
Percentage
MPSG
SG
CG
Baseline
Test

e



Sleep efficiency (SE) only determines the sleep quantity rather than considering the sleep quality of the subject during a sleep study. In order to further investigate the sleep quality between the 2 nights in the 3 groups, Figure 44 shows the sleep structure of the subjects. Each chart in Figure 44 represents the proportion of different sleep stages.

In the MPSG, the proportion of light sleep (stages 1 and 2) tends to decrease while the proportion of deep sleep (stages 3 and 4) increases from night 1 to night 2. REM sleep remains the same in both 2 nights. In the SG, only the proportion in stage 2 increases from night 1 to night 2. On the other hand, the proportion of deep sleep decreases during night 2. In the CG, the amount of light sleep tends to decrease and the amount of deep sleep increases by comparing the 2 nights, which is same for the MPSG. However, there is a reduction in terms of the amount of REM sleep in the CG.

From these results, it seems that electrical stimulation does not decrease and even increases the amount of deep sleep in the MPSG. Also, subjects in both the MPSG and CG groups tend to have better sleep quality in the second night than

the first night with a smaller proportion of light sleep and more deep sleep. With reference to the results in Figure 44f, it was found that subjects in the CG sleep more than the MPSG in night 2. However, both the MPSG and CG have more deep sleep in night 2 although the MPSG received electrical stimulation at the same time. In addition, subjects in the MPSG have less respiratory arousal in comparison with the CG in night 2.

Although the change in the percentage of various sleep stages during the 2 nights are plotted, this study also attempts to analyse if there is a significant difference in the different sleep stages between the 2 nights of the 3 groups using the one-way ANOVA and between any 2 groups using the post hoc test. However, it is found that there are no significant differences among the 3 groups or any 2 groups in all sleep stages.

10.2.12 Analysis of the immediate effect on the change of SpO_2 level

As stimulation is released once the cessation of airflow is detected, this study also attempts to measure if there are any changes in the pulse oximetry level prior to, during and well after a sleep apnoea event with receiving the stimulation in night 2. Measurements were taken place at 4 time points (TP): (1) prior to / well before a sleep apnoea event (2) 10 seconds after the cessation of breathing, (3) well after stimulation and (4) 1 minute after an OSA event. These are illustrated in Figure 45.

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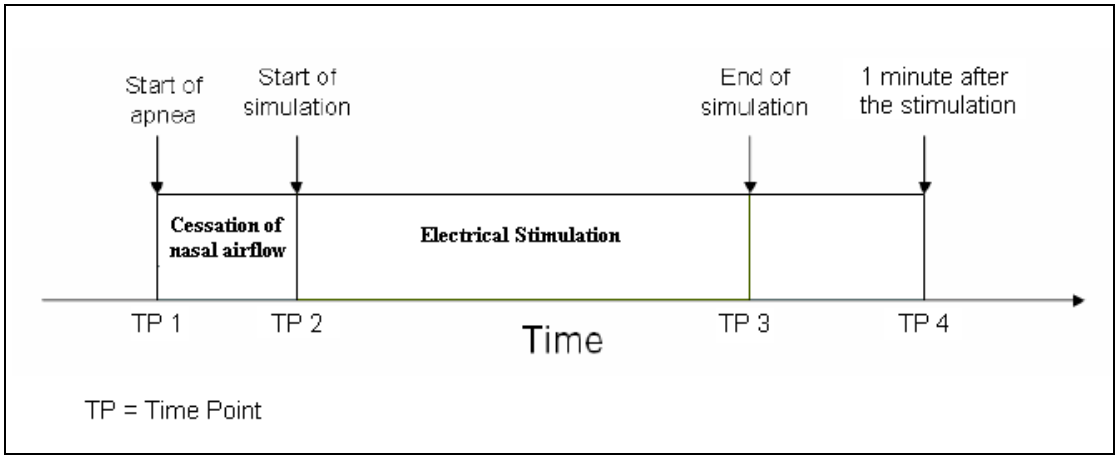
Figure 45 Illustration of the 4 time points (TP) during tan OSA event



The duration of a sleep apnoea event among the subjects in this study is usually around 30-60 seconds. In light of this reason, this study attempts to investigate the change in the SpO_2 level for 1 minute after stimulation. Figures 46 and 47 show the results of the changes of the SpO_2 level in the MPSG and SG at the 4 TPs.

Figure 46 *Changes in the mean SpO_2 level in the MPSG at 4 TPs*

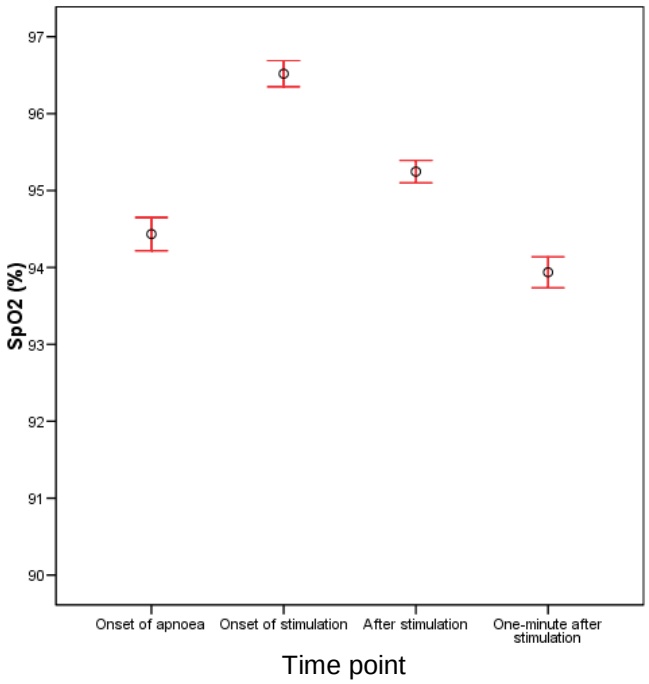
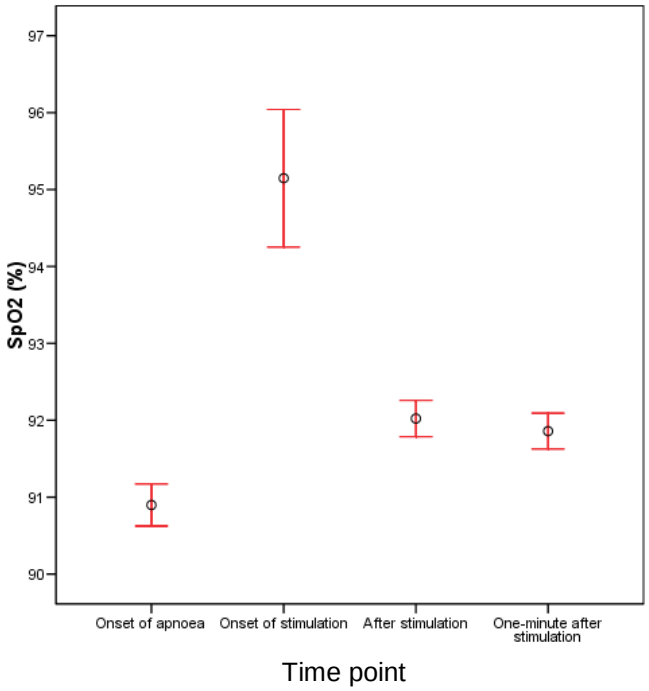


Figure 47 *Changes of the mean SpO_2 level in the SG at 4 TPs*



There are 1727 events and 2020 events for analysis in this part. Of all these events, a 10 second breathing was observed in each event and electrical stimulation was released accordingly.

Figure 46 illustrates the change in the SpO_2 level at 4 TPs in the MPSG while Figure 47 illustrates the change in the SpO_2 level at 4 TPs in the SG. The changes in the SpO_2 level in these 2 charts follow a similar pattern. The SpO_2 level increases from the 1st TP to the 2nd TP and decreases afterwards. It is found that usually the baseline SpO_2 level among the subjects is 98%.

As shown in Figure 46, the mean SpO_2 level of the MPSG is around 94% at the 1st TP, which is considered rather low (94%) in comparison with the other TPs. The reason may be due to the repeated occurrences of the OSA event during sleeping. Usually, a series of OSA events are found during different periods of time. In this case, the low SpO_2 level during the onset of OSA in the 1st TP may be affected by the previous sleep apnoea event. As suggested in Chapter 6, there is a time delay of the SpO_2 desaturation after OSA. After the 1st TP, the SpO_2 level returns from the lowest level to the baseline level. Thus, the mean SpO_2 level in the 2nd TP has already achieved the baseline level and is the highest among the 4 TPs. After stimulation, the mean SpO_2 level slightly decreases from 97% to 95%. However, the desaturation is less than 4% if 98% is considered as the baseline level. It is believed that the decrease of the mean SpO_2 level is due to the cessation of breathing as the stimulation is released only after 10 seconds. At 1 minute after stimulation, the mean SpO_2 level further decreases 1%, resulting in a mean of 94%. It is believed that the mean SpO_2 level is still slightly affected by the cessation of breathing.

As shown in Figure 47, the mean SpO_2 level is low (around 91%) in the 1st TP. It seems that the low level of SpO_2 at this TP is due to the effect of the previous OSA event. It was observed in this experiment that the duration of apnoea and level of desaturation are directly related. The mean SpO_2 in the SG at the 1st TP is lower than the MPSG, possibly due to longer mean duration of OSA in the SG as suggested in Figure 41. Similar to the 2nd TP in the MPSG, the 2nd TP in the SG also increases from 91% to 95% as the SpO_2 level recovered to the baseline level. In the SG, the increase from the 1st to the 2nd TP is even larger than the MPSG. However, the mean SpO_2 level in the SG at the 2nd TP is still less than the MPSG. After stimulation, the mean SpO_2 level in the SG decreases dramatically from 95% to 92%. A possible reason is that the subject may not recover breathing after the stimulation and thus the mean SpO_2 level keeps decreasing. At 1 minute after stimulation, the mean SpO_2 level is still around 92%, which is similar to the level at the 3rd TP. It seems that the mean SpO_2 level does not change dramatically between the 3rd and the 4th TP. However, the mean SpO_2 level usually continues to decrease since the 3rd TP and increases afterwards as the subject restores breathing. Therefore, the 3rd and 4th TPs have similar values in the mean SpO_2 level.

Although the mean SpO_2 level decreases from the onset of sleep apnoea to 1 minute after stimulation in the MPSG, overall, the pattern of the mean SpO_2 level before and after OSA events is more stable than that in the SG. However, as the stimulation is released after 10 seconds of cessation of breathing for both groups, the SpO_2 level still decreases due to the breathing cessation of the subject. In the MPSG, the mean SpO_2 level is usually around 94% to 96.5%, but a larger contrast of the mean SpO_2 level is found in the SG, ranging from 91% to 96.5%.

10.2.13 Limb Movements

The total number of limb movements during the 2 nights of the study are summarised by groups and the results are shown in Figures 48-50. The blue line indicates the number of limb movements in night 1 while the green line indicates the range of values in night 2.

Figure 48 *Number of limb movements during nights 1 2 in the MPSG*

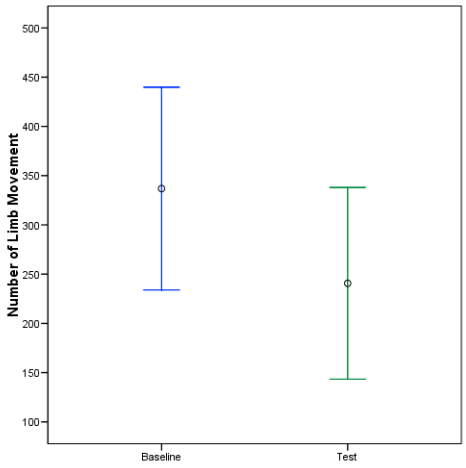


Figure 49 *Number of limb movements during nights 1 and 2 in the SG*

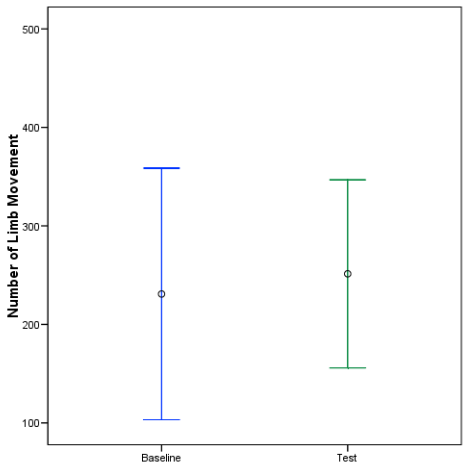
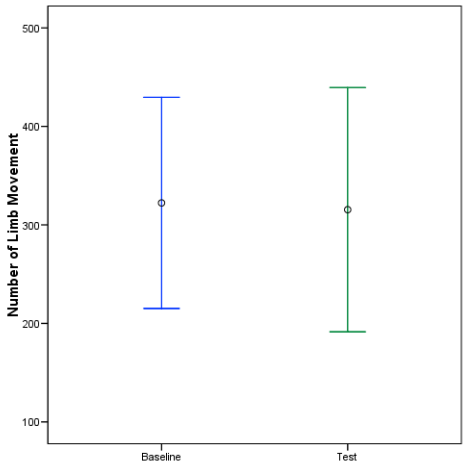


Figure 50 *Number of limb movements during nights 1 and 2 in the CG*



Apart from studying the effects of the intervention on respiratory status and sleep quality of the subjects, this study also investigates if the intervention will affect the number of limb movements. The reason for studying limb movements in this study is because it is suggested that periodic limb movements are associated with OSA which are usually induced by the respiratory effort related arousals (RERAs) [8]. The index of periodic leg movements (PLMI) larger than 10 is considered abnormal [156]. Several studies suggested that patients with moderate or severe OSA are likely to increase the frequency of limb movements while they are on the nasal CPAP, while patients with mild OSA decrease the frequency of limb movements after using the nasal CPAP [68, 111, 135]. However, in this study, it seems that the subjects who received meridian point stimulation have less frequency of limb movements during night 2 while the mean number of limb movements in the SG and CG is similar between the 2 nights. Using the paired t-test with 95% confidence interval, it was found that the difference in terms of limb movements between the 2 nights in the MPSG is significantly different.

10.2.14 Correlation between various factors

In this test, it is assumed that the subject (1) may have poor sleep quality if the level of intensity is high in night 2, and (2) may require a higher level of intensity if obese. Also, the intervention may have different effects in terms of AI and ASR in the subjects who have different levels of OSA severity. In order to investigate the relationships for the above issues, a series of correlation coefficient analysis are carried out and the results are shown in Table 19.

Table 19 *Results of the correlation coefficient analysis related to the level of intensity, the severity of OSA of the subjects and the effect due to the intervention*

Factors	*r*	*p*
Level of intensity & sleep efficiency	-0.089	0.660
Level of intensity & % of deep sleep	-0.137	0.496
Level of intensity & BMI	-0.192	0.337
Baseline AI & Change in AI	-0.582	0.004*
Baseline ASR & Change in ASR	-0.387	0.046*

Sleep efficiency, percentage of deep sleep was the value obtained in night 2 while baseline AI was the value taken in night 1. Change in AI and ASR are the difference of the value between the 2 nights. The main aims of this part are to determine if the level of intensity is related to BMI of the subjects, or the level of intensity is related to sleep efficiency and percentage of deep sleep in night 2, or the positive effect on AI or ASR in night 2 is related to the original severity (baseline AI and ASR) in terms of OSA of the subjects. After the correlation coefficient analysis, it seems that the level of stimulation intensity is not directly related to sleep quality in night 2. As it is possible that subjects who have thicker adipose tissue under their skin may need larger intensity of stimulation in order

to achieve a therapeutic effect, in this study, however, it was found that subjects with higher BMI do not tend to receive a higher level of intensity during night 2. On the other hand, subjects with lower baseline AI and ASR usually have more percentage of reduction in terms of AI and ASR during night 2 as the r-value is negative in this case. It is possible that subjects with less severe OSA tend to have better managing effects on OSA using meridian point stimulation.

10.3 Discussions

As suggested in the literature review, the efficacy and compliance of the present therapies for sleep apnoea vary in previous studies. Acupuncture has been reported as a promising method to effectively relieve the symptoms of sleep apnoea, but a needle has to be penetrated into the skin and the long-term effect on sleep apnoea remains unknown [256]. Another approach is to manage the symptoms of sleep apnoea by applying electrical stimulation inside the intra-oral area during the occurrence of sleep apnoea. The intra-oral area is usually sensitive to stimulation [55]. Thus, this study evaluates the efficacy of using electrical stimulation on the selected meridian point (LU7), rather than the intra-oral area on managing symptoms of OSA.

Subject Characteristics

As indicated in Tables 14 and 15, the majority of the subjects in this study are middle-aged males. Overall, the subject characteristics in terms of age, BMI and severity of apnoea are similar among the 3 groups. Almost all subjects in the MPSG and CG had been diagnosed as sleep apnoea patients in the hospital prior to this experiment. After the subjects received the sleep apnoea assessment in the hospital and sought medical advice from doctors, they tried to use the CPAP device at home. However, of these subjects, only 55% continued the CPAP treatment. The reasons for those who refused to use the CPAP device were due to experiencing discomfort, noise from the CPAP device and poor appearance of the subject after wearing the mask. The remaining 45% of the subjects who did not use the CPAP treatment tried other methods, such as weight control, sleeping in a lateral position, oral appliance, use of nasal allergy drugs and use of a special pillow. These subjects, together with those who were using the CPAP device during sleep, reported that they are still looking for other available

approaches to manage sleep apnoea. This is because they are still unsatisfied with the current methods. The complaints for using the CPAP device from the subjects in this study is similar to the opinions from the subjects in previous studies [133, 245]. The subjects in both studies suggested that they felt uncomfortable with the unfitted mask, nasal dryness and congestion after using the CPAP device.

Overall Effects of the Intervention

After 2 nights of the sleep study, the physiological signals of the subjects were recorded and analysed. With reference to the mean value of the outcome parameters between the 2 nights of the study and among the 3 groups as shown in Figure 40, it seems that there is an improvement in terms of the respiratory status and pulse oximetry level in the subjects who received the meridian point stimulation. However, subjects in this group tend to have a smaller proportion of sleep over the entire sleep study in the second night. Although the amount of sleep decreases during night 2, interestingly, the quality of sleep is better.

In this test, the subjects tend to prefer a lower level of intensity while the actual level of stimulation intensity during sleep is higher. This phenomenon is also found in a study using electrical stimulation of the lingual musculature, where subjects also preferred a lower level of intensity prior to sleep [50]. This study suggests that the pain threshold during sleep is larger than during waking moments.

As subjects in the MPSG received a relatively stronger intensity of stimulation than the SG, it is assumed that the decrease of AI, ASR and ADL in the MPSG may be due to the arousal induced by stronger levels of stimulation and thus restored their breathing. However, the number of arousals in the MPSG did not increase and it even decreased more than that in the SG. Due to less average events of arousal in the second night, meanwhile, subjects in the MPSG may experience a smaller degree of sleep fragmentation. Also, it is believed that subjects have better quality of sleep as the proportion of deep sleep increased in night 2 in comparison with night 1. In previous studies which released electrical stimulation on the submental or intra-oral area during OSA, symptoms of OSA were reduced while promoting deeper sleep [141, 166, 186, 234] . However, of these studies, stimulation intensity was selected by the subjects prior to the experiment and it was not adjusted during the experiment. It is possible that the submental and intra-oral areas are sensitive to stimulation and thus the pain threshold is different from other parts of the body. In this case, symptoms of OSA can be managed by requiring less intensity of stimulation.

However, subjects in the SG did not improve remarkably in terms of the frequency and duration of OSA. Also, the mean pulse oximetry level did not increase during night 2, possibly due to the lower level of intensity that the subjects had generally received in the SG. During night 2 for some subjects in the SG, there were attempts to increase the level of stimulation intensity when the cessation of breathing continued after stimulation. After increasing the level of stimulation intensity, arousals were observed immediately after stimulation. Thereafter, the level of intensity was fixed at a lower level to avoid arousal, but the apnoea events were recovered correspondingly. As a result, subjects in the SG usually have either no respiratory response after the stimulation or respiratory arousal after the OSA events.

The mean frequency and duration of sleep apnoea, and the mean pulse oximetry level of the subjects in the CG did not change dramatically from night 1 to 2. A possible reason is that subjects in the CG received no intervention during the 2 nights of sleep study and thus it is assumed that the severity of OSA was similar. Not surprisingly, subjects in this group had more and better quality of sleep during the second night of the sleep study.

In fact, the CG involved in this study aims to compare if there are differences in terms of the severity of sleep apnoea and sleep quality between the 2 nights of the experiment without applying any intervention. It is believed that sleep quality can still be different between the 2 nights due to the first night effect. The first night effect is the alteration of the sleep structure in an unfamiliar environment, especially in a sleep laboratory and the origin of first night effect is also due to the discomfort caused by the electrodes [22]. The first night of a sleep study is usually associated with more awakening events and less REM and deep sleeps than subsequent studies [22]. For this reason, it is not objective to compare the severity of sleep apnoea between the first and the second night of the sleep study, as it is expected that the subject may have less awakenings as well as more REM and deep sleep during the second night. It seems that this phenomenon is found in the CG as the percentage of deep sleep increased remarkably during night 2. Although the proportion of sleep remained the same in the CG, the sleep structure changed with more deep sleep than light sleep during night 2. The possible reason is that the subjects become more familiar with the environment. Thus, the first night effect may be present in this case as the subjects have better quality of sleep in the second night. However, subjects in the SG have a smaller proportion of deep sleep when they received the stimulation. In this case, it seems that the first night effect is not found as the sleep quality may even be worsened during the second night due to the stimulation. Subjects in the MPSG also received the intervention in the second night. The subjects in this group had a greater proportion of deep sleep than the

first night. In light of this issue, it seems that the first night effect is not a primary issue which will affect the results of the outcome parameters as it is not consistently present in all subjects. Other studies also suggested that first night effect was not presented in subjects as the AHI correlated significantly between the first two nights of sleep study (r=0.77, r=0.86) [58, 204]. On the other hand, it is believed that the subject's sleep may not be heavily affected by the environment as OSA subjects who possess the symptoms of daytime sleepiness and short sleep latency may be very easily to fall asleep during the 2 nights of the sleep study [165].

In the main study, it seems that there was an improvement in terms of the respiratory status of the subjects in the MPSG. Also, subjects in this group have around a 35% increase in deep sleep from night 1 to 2. By only referring to the mean value of the outcome parameters, it seems that the subjects who received meridian point stimulation are likely to have a positive therapeutic effect on OSA than the SG and CG. According to the results of the mean values of the outcome parameters, it seems that stimulation on the LU7 point is likely to improve the respiratory status of the subjects, slightly decreases the number of arousal and increases the percentage of deep sleep, but slightly decreases the proportion of sleep in the sleep study.

In previous studies, the CPAP device was found to decrease approximately 85% of the mean AHI in patients (N=32) with moderate OSA [61] and decrease approximately 83% of the mean AI in patients (N=12) with moderate or severe OSA [136]. The compliance of using CPAP device was not good, as patients in the previous studies also reported dramatic reversal of daytime hypersomnolence and minor nasal stuffiness after using the CPAP device at home for 12 months [136]. Subjects who used the CPAP at home experienced improvement in the severity of OSA by decreasing 50% of AI, but the mean pulse oximetry level had not significantly improved [136]. Apart from the CPAP device, patients with

mild or moderate OSA usually preferred to use the oral appliance [90]. A study found that the oral appliance reduces around 60% in terms of AI in a group of mild OSA patients. Apart from the oral appliance, another study also found that patients have more than 60% reduction in the mean AI at 3 months after receiving UPPP surgery [183]. The previous studies which applied electrical stimulation on the intra-oral area of the subjects also found that the stimulation reduces 63-80% of AI [141, 233]. Most of these previous studies used a 1 group pre-post study to evaluate the efficacy of various types of treatment and the p-values in these studies are usually less than 0.05. However, in comparison with other forms of treatment, meridian point stimulation in this research is able to reduce only approximately 36% of AI, which is considered less effective than other forms of treatment in managing OSA. On the other hand, subjects in the SG and CG have a 15% and 1% reduction of AI respectively. It seems that subjects with stimulation on non-meridian point areas or without stimulation are not likely to improve the frequency of OSA episodes in this study.

Although AI has been used as an important indicator for quantifying the severity of OSA, it only refers to the frequency of episodes per hour, while disregarding the duration of each episode. Thus, apnoea-sleep ratio (ASR) is also measured in this study. A previous study found that UPPP surgery reduces total apnoea/total sleep time by around 80% [183]. Another study found that the apnoea time/ total sleep time of the subjects decreases by 77% after using submental electrical stimulation [141]. In fact, there have been limited studies that evaluate the efficacy of other forms of treatment by measuring the total apnoea time against total sleep time. In this study, ASR (total apnoea time / total sleep time) is reduced by around 45% in the MPSG. Although ASR in the MPSG is reduced much more than that in the SG and CG, the degree of reduction is still less than submental stimulation and UPPP surgery.

Although the average duration of apnoea of the MPSG is reduced by 11% in this study, the improvement in terms of apnoea duration is not as effective as the CPAP treatment. In a previous study, the mean apnoea duration of the subjects was reduced by approximately 26% from night 1 to 2 [190].

Again, using the CPAP device as the intervention from other previous studies, the lowest pulse oximetry level increased by around 40% from night 1 to 2 [253, 271]. However, limited studies have compared the change in terms of the mean pulse oximetry level before and after the treatment. A study found that there is around 7% increase in mean pulse oximetry level at 3 months after UPPP surgery [257]. In this study, the mean pulse oximetry level of the MPSG increases by 2% after the intervention while the other 2 groups have no remarkable changes. The degree of improvement in terms of mean pulse oximetry level has less improvement in this study in comparison with the study which evaluated the efficacy of UPPP surgery.

Comparing the sleep quality of the subjects in the MPSG before and after the treatment, it was found that the average number of arousal decreases by 42% in a previous study for subjects using the nasal CPAP treatment [11]. In a study which also evaluated the efficacy of nasal CPAP, it was found that the arousal index (number of apnoea per hour) of the subjects is reduced by 72% and slow-wave sleep increases by 158% after the CPAP treatment [16]. A previous study suggested that the mean number of arousal also decreases by 67% using the nasal CPAP as the intervention [196]. However, in this study, the mean number of arousal decreases by only 33% and deep sleep (or slow-wave sleep) also increases by only 36%. Although the number of arousals decreases and the percentage of deep sleep increases in the MPSG, it seems that meridian point stimulation is not as effective as the nasal CPAP in improving the sleep quality of the patients. A possible explanation is that the intensity is insufficient to

stimulate the flow of Qi and thus improve the airway condition in some circumstances.

By observing the mean values of the outcome parameters among the 3 groups, there were improvement in terms of AI, ASR, AAD, ADL, ARA and PDS in the MPSG. The results of the paired sample t-test also suggested that there is a pre-post difference in terms of AI, AAD and ASR in the MPSG. However, the effects of the meridian point stimulation on managing symptoms of OSA and improvement of sleep quality are not as significant in comparison with the other 2 groups according to the results of the one-way ANOVA. The results of the post hoc test suggested that significant mean differences are found only in terms of the frequency of OSA in the MPSG and CG and oxygen desaturation between the MPSG and SG. The possible reason of inconsistent results between the paired t-test and ANOVA is due to the large variation of data range in terms of AI, AAD and ASR in the three groups which causes insignificance results of the ANOVA test. As this test utilised randomised control design, subjects with different levels of severity were assigned in each group and thus the variation of data is large. It is possible that the results of ANOVA test is significant if the outcome data were categorised by the level of severity (severe, moderate and mild). However, the sample size was imbalance with 2-4 subjects in each group with different levels of severity. In this case, the experimental precision may be inadequate to detect the true effect of the intervention among the three groups unless additional subjects were included in the test or if the analysis focuses on a group of OSA patients with a defined level of severity in each group.

To compare the effect size of this study with other forms of treatment in other studies, it is essential to classify its range. Usually, an effect size of 0.2 is considered small, 0.5 medium and 0.8 large [44]. The effect size of OSA treatment varies in different forms of treatment. It was suggested that the pool effect size in AHI for the CPAP treatment is 0.83 [1] and for the oral appliance, 0.96 [86] for the pre-post study. As the AHI is not the outcome parameter in this study, it is calculated and found that its effect size is 0.7, which is considered as medium to large, and similar to the CPAP and oral appliance treatment.

Although the power of paired sample t-test is over 0.8, the power of the one-way ANOVA is 0.5 in this study. Thus, the number of the sample size should further increase. Referring to the power table of the one-way ANOVA with an effect size of 0.89, the required sample size per group is 20 in order to achieve power=0.8. Because of the insufficient intake of subjects with baseline AI>5 and limited time, the number of subjects in each group is only 9 in this study.

In the Univariate analysis, several covariates were selected which may affect the outcome of the study, including age, smoking habit, drinking habit, CPAP device, other treatment, sleeping position and weight change. The results of the Univariate analysis showed that the effect of each covariate on each dependent variable (AI, ASR and PDS) were not significant. The ANCOVA analysis was conducted to test of the overall effect of the covariates on the dependent variable (AI, ASR and PDS). The potential effect of the six covariates on AI, ASR and PDS were not significant with significant values of 0.467, 0.313 and 0.619 respectively. The results imply that the assumption of homogeneity of variances has not been violated.

From the trend of the average oxygen desaturation (SpO_2) level during the first 6 hours of the sleep study in the 2 groups which is shown in Figure 41, it is found that the pattern of the SpO_2 level in a sleep study can be arbitrary and thus it is

believed that the occurrence of sleep apnoea event is unpredictable. Also, the average SpO_2 level may increase in night 2 in comparison to night 1 even without any intervention. This phenomenon occurred in the CG.

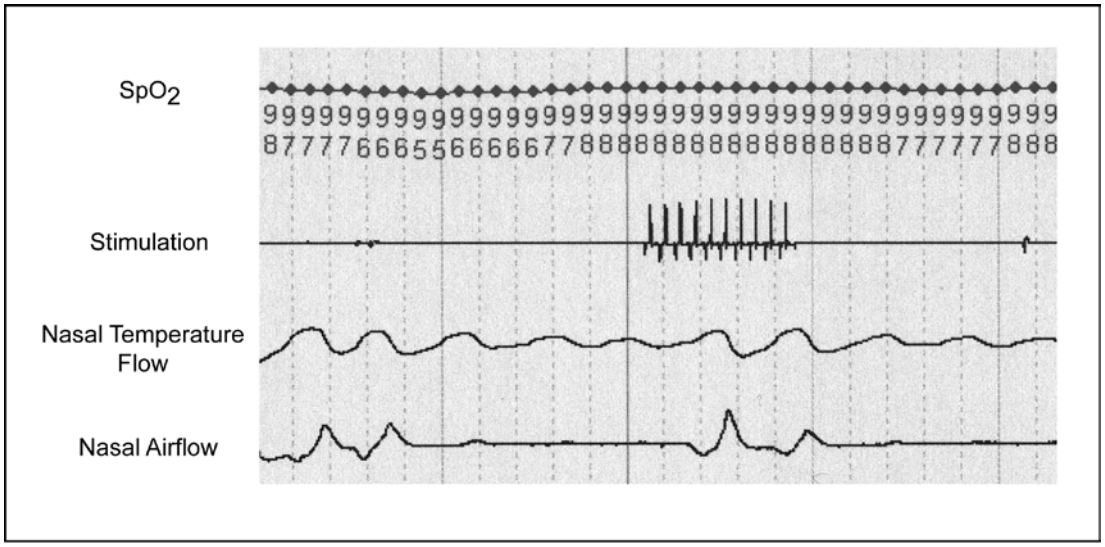
Referring to Figure 42, subjects in the MPSG tend to have a higher heart rate during night 2 than night 1. It is found that the heart rate is higher at the beginning of night 2, possibly due to the nervousness of the subjects. Also, the heart rate in almost all sleep studies tends to decrease from the beginning to the end. Most importantly, it is possible that meridian point stimulation may increase the heart rate during sleep. The findings in this study are different from those that applied electrical stimulation on the submental area, where it was suggested that AI, blood pressure and heart rate of the subjects (N=6) are reduced significantly after receiving stimulation [141].

Elevated heart rate is an important risk factor in cardiovascular disease [154] and thus sleep apnoea is often linked with the cardiovascular disease [118]. A higher level of sympathetic activity can be found during the occurrence of OSA, which may contribute to the elevation of heart rate [202]. Sumi et al. (2006) suggested that the mean heart rate of patients with OSA significantly decreases from 71.8 to 67.5 after using the nasal CPAP treatment for 3-4 days [202]. However, in their study, they only compared the heart rate before and after using the nasal CPAP device, rather before and during the use of the nasal CPAP device. As suggested in the literature review, bradycardia and tachycardia can be present during the occurrence and well after an OSA event. Thus, it is uncertain about the outcome of the mean heart rate due to the intervention during the experiment. In this test, the subjects who received meridian point stimulation tend to have a higher mean heart rate during sleep. The results in this study suggested that the mean heart rate may be elevated due to the meridian point stimulation and thus may add to the burden of the heart. However, the elevation of the heart rate in the MPSG group may also be caused by psychological factors. The repeated

effect of the stimulation on the mean heart rate in this study and also the effect of stimulation on the daytime mean heart rate are still unknown.

In this study, the frequency of OSA is reduced in the MPSG. The key reason of such improvement is that the meridian point stimulation reduces the oxygen desaturation and increases the mean pulse oximetry level. In this test, sleep apnoea is defined as 10 seconds of cessation of nasal airflow associated with 4% of oxygen desaturation. If a subject experienced 10 seconds of cessation of nasal airflow without 4% of oxygen desaturation, this is not regarded as a sleep apnoea event. In other words, when the stimulation is applied well after 10 seconds of cessation of breathing and the subject has recovered breathing immediately, the pulse oximetry level may decrease with less than 4% from the baseline level. Figure 51 illustrates an example of this phenomenon which is occasionally found in the MPSG.

Figure 51 *Illustration of an event with cessation of breathing after the meridian point stimulation*



As shown in Figure 51, the baseline pulse oximetry level is 98%. Referring to the stimulation channel, stimulation is applied at the time when there is a saw tooth pattern of the signals and after 10 seconds of cessation of nasal airflow. After the stimulation, the pulse oximetry level decreases by only 1%. In this case, this is not regarded as an OSA event in accordance to the scoring criteria of OSA. Thus, subjects with this phenomenon during a sleep study tend to have less frequency of OSA and a higher than average pulse oximetry level.

The quality of sleep is another key outcome parameter in this research in order to assess the efficacy of the meridian point stimulation. In the experiment, sleep quality was assessed based on the quantity of deep sleep and arousal events. As suggested in the literature, the subjective measurement of the sleepiness is not used in this research as the outcome will be affected by self-rated problem sleepiness [41], such as misinterpretation and bias [167].

In the literature review, it was found that the monitoring of sleep structure in terms of the sleep staging of an individual can help in quantifying sleep. [14]. Among different sleep stages, the quantity of slow wave sleep is often linked to the assessment of the sleep quality [172] than the other sleep stages. In this study, the percentage of slow wave sleep increases from night 1 to 2 in the MPSG and CG while light sleep decreases. Using the slow wave sleep as an indicator of sleep quality, patients have better sleep quality when they received meridian point stimulation or no stimulation, but the effect is not significant according to the results of paired t-test in each group. This result is similar to the results of a study that applied submental electrical stimulation in response to OSA events, where the proportion of light sleep decreases and deep sleep increases during night 2 [141]. As these studies aim to compare the mean value of AI and pulse oximetry level before and after the intervention, no information was found regarding the results of the statistical test.

As the number of arousals also decreases in the MPSG as shown in Figure 41, patients may have less sleep fragmentation. Although the number of arousals (or arousal index) is reduced remarkably from 45 to 30 in the MPSG, the arousal index is still over 10. According to the literature, an arousal index over 10 is still not regarded as normal [43].

To identify arousal events, one of the more difficult tasks is to ensure that the EEG should reflect the true status of sleep with minimum signal artifacts. However, electrical stimulation may affect the EEG signals during a sleep study because EEG is the measurement of the signal in terms of voltage in the brain. In this study, sleep stages are identified by a computerised program and manually in accordance to EEG signals. It was found that the amplitude and frequency of the EEG signals follow a constant saw-tooth pattern during stimulation. An example of the PSG tracing in this situation is captured during and 10 seconds after electrical stimulation, and shown in Figure 52. There are 2 timeframes in Figure 52. The timeframe in the upper tracing with 6 signal channels (C3-A2, C4-A1, ROC, LOC, ECG, HR and EMG) is 30 seconds. The timeframe in the lower tracing with 11 signal channels (SaO2, Sound, dB level, Arm, Thermistor, Nasal Flow, Thoracic, Abdominal, DEMG, Leg and Body Position) is 5 minutes.

Figure 52 *Illustration of PSG tracings with EEG, pulse oximetry, nasal airflow during a series of meridian point stimulation*

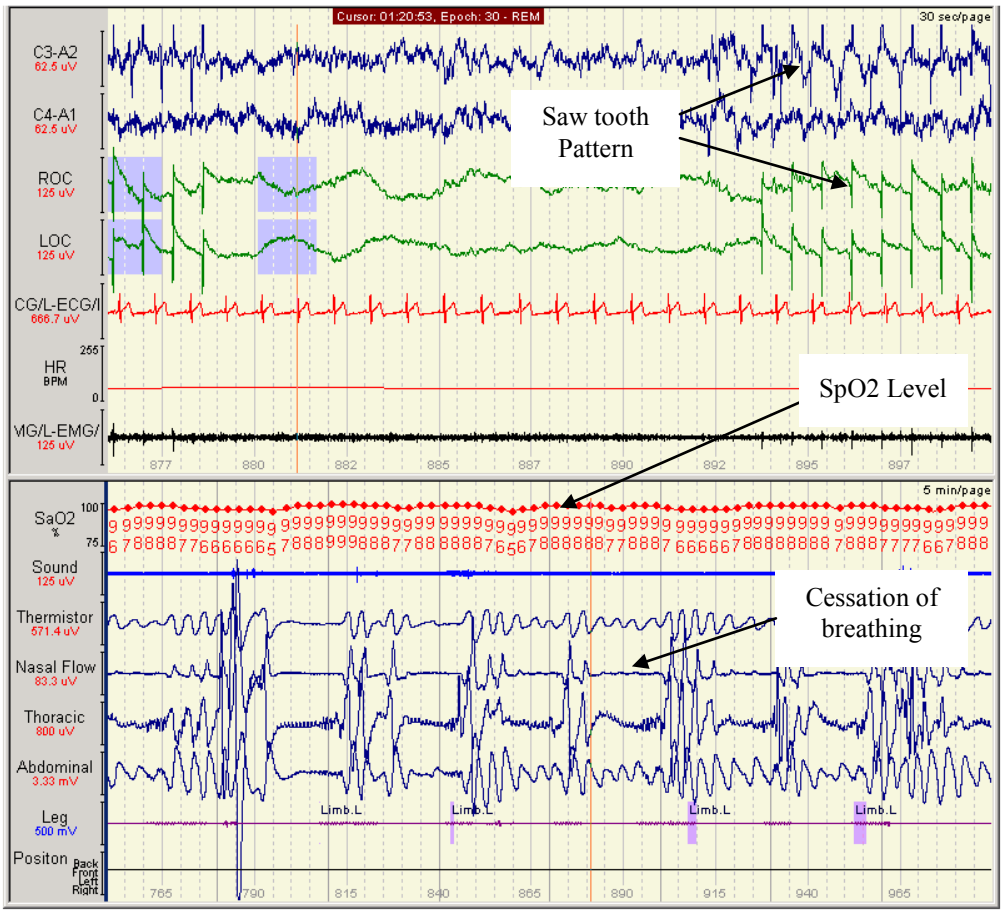
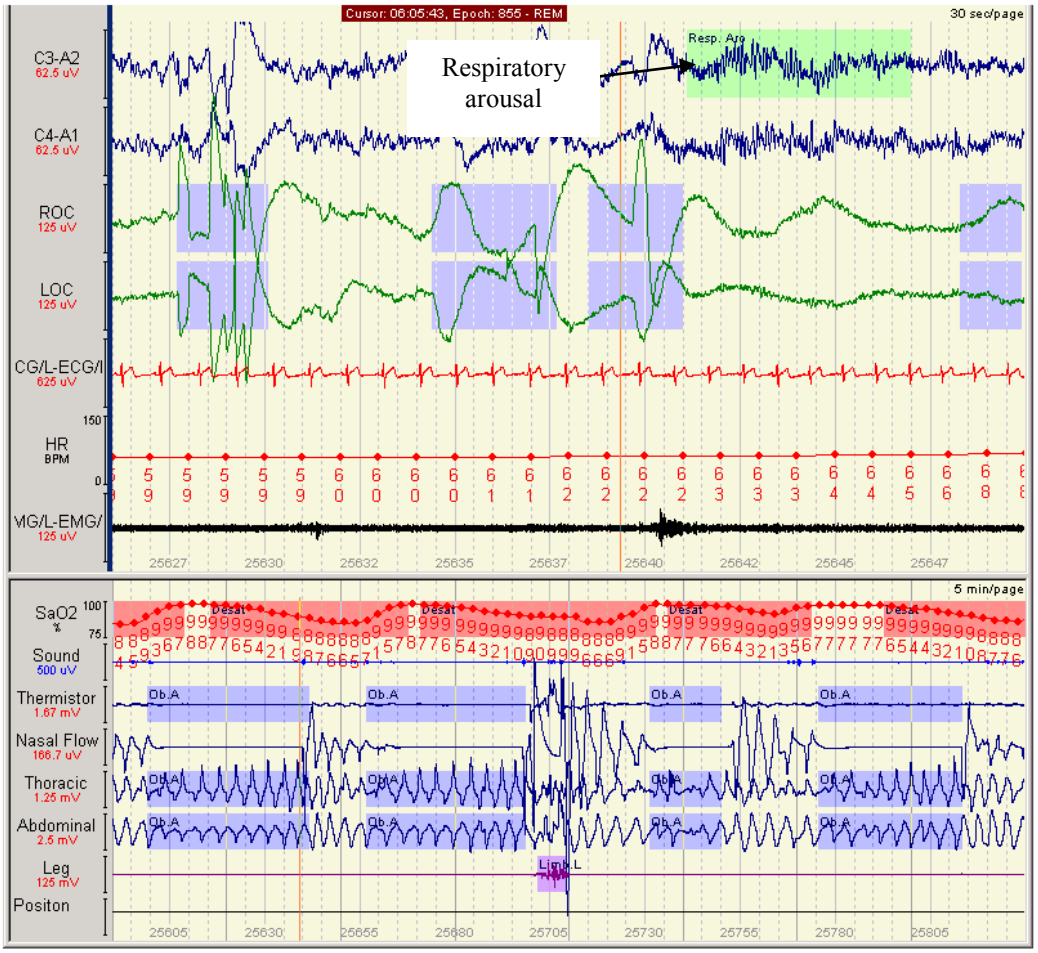


Figure 52 is captured during a series of events with cessation of breathing as well as meridian point electrical stimulation. The cessation of breathing occurs when the nasal airflow signal is flat. Stimulation is released at 10 seconds after the onset of the airflow cessation and the minimum duration of stimulation is 8 seconds.

During the whole timeframe in Figure 52, there is no oxygen desaturation even though the cessation of airflow presented. In this case, the cessation of breathing is not regarded as an OSA event in this figure.

The justification of arousal in this case is also very critical which affects the outcome of assessing sleep quality of the subject. In this example, it is assumed that the subject is experiencing REM sleep and this subject did not experience arousal. The reasons are: (1) there were high frequency (10-13 Hz) of EEG waves in the whole time frame; (2) the mirror-image of wave pattern was found in the EOG during this period of time; (3) EEG waves do not increase tremendously within 5 seconds well after the stimulation as compared with the pattern of EEG arousal in the baseline study. Figure 53 captures the picture of respiratory arousal of this subject during the baseline study (night 1).

Figure 53 *Illustration of respiratory arousal during the baseline study (night 1)*



It is of interest to study whether the assessment of various sleep stages by the EEG was affected by the stimulation. It is because the EEG signals may interfere with noise due to the electrical stimulation and thus the assessment of sleep stages may be affected. As shown in Figure 5.2, EEG signals are in saw-tooth pattern during the stimulation. It is possible that the saw-tooth pattern of the EEG signals during the stimulation related to the intensity and the pattern of electrical stimulation as this saw-tooth pattern is consistently found in the EEG and EOG signals and the duration of the saw-tooth pattern corresponded to the time length of the electrical stimulation. As no awakening event was found immediately after the stimulation, it is believed that this subject may not be awaked by the stimulation and he may remain asleep during and well after the stimulation.

With reference to the instantaneous effect on the average pulse oximetry level prior to, during and after the intervention, it was found that both meridian point stimulation and sham stimulation does not increase the pulse oximetry level rapidly or tremendously after stimulation. The possible reason is that there is a time delay of deoxygenation after an OSA episode as suggested in chapter 6. Thus, the instantaneous effect of the intervention on the pulse oximetry level was not able to be observed instantly after the stimulation. However, the average pulse oximetry level at the 4 TPs was higher in the MPSG than the SG. As there are limited studies which investigate the instantaneous effect of other forms of treatment on the pulse oximetry level, there is no reference point for evaluating and comparing the instantaneous effect on OSA.

Mechanism of Meridian Point Stimulation using Theory of TCM

It was suggested that alternative therapy is preferred in some circumstances as western medicine may not work well for all occasions [107]. A report in the New England Journal of Medicine suggested that around 80% of the population in the United States are using alternative medicine, such as acupuncture, chiropractry, and massage therapy [56]. The central tenet of the theory of meridian point stimulation is that the body is able to heal itself by external stimuli [107]. The theory of TCM describes 361 meridian points that are distributed along 14 meridians in the body [19]. The meridian is a path that allows the flowing of "Qi", which is known as energy in the body [35]. Blockage of "Qi" causes imbalance of the body and results in illness [259]. Stimulation on the meridian point can activate the body's own defense mechanism and thus improve imbalance [19]. On the other hand, each meridian is related to a specific organ and hence, its name refers to a specific organ [19]. Kim [107] mentioned that the lung meridian has a superficial component on the upper limb, but also extends internally to the lungs. As suggested in the literature, stimulation on the lung meridian can regulate the flow of "Qi" and thus improve shortness of breath, cough or pain in the shoulder [259]. Although "Qi" is a theoretical hypothesis and cannot be observed or even measured using current sophisticated devices, the World Health Organization (WHO) has recognized that certain respiratory diseases or syndromes of the respiratory system, including acute sinusitis, tonsillitis and bronchitis, the common cold and bronchial asthma can benefit from acupuncture [107]. The effect of stimulation on managing OSA can be direct and instant. An example is a previous study which applied acupuncture to relieve cancer related breathlessness. This study found that 70% of patients have marked symptomatic relief following 10 minutes of acupuncture [66]. As it was suggested that the speed of propagation of "Qi" along the meridian is around 0.1 meter per second [255, 259, 260], stimulation on a meridian point may provide an instant managing effect, as long as there is the regulation of Qi. Meridian

point stimulation in studying cancer related breathlessness and this research both deviate from the traditional approaches of acupuncture. Traditionally, syndrome differentiation had to be conducted before acupuncture was performed on the patient. In TCM, the causes of OSA are mainly due to (1) the deficiency of the spleen "Qi", (2) blockage of "Qi" by phlegm and (3) masking of orifices. The practice of acupuncture in this case aims to cure the root of the disease in order to regulate the lung, reinforce the spleen, invigorate the kidneys and promote blood circulation. In this research, the managing effect is instantaneous, as it is believed that "Qi" is regulated accordingly after stimulation. However, a rebound effect will result once stimulation is discontinued.

Although it seems that the overall percentage of certain symptoms of sleep apnoea were reduced using meridian point stimulation, another question is whether the improvement in terms of sleep apnoea in this study is due to instantaneous management of the symptoms or sustained therapeutic effect of the stimulation which lasted for a set period of time. However, this issue cannot be further proven because stimulation is released once an apnoeic event is detected, rather than released continuously in a set period of time. The common practice for acupuncture is to retain needles into the skin for some time and the therapeutic effect is observed. In this study, it is believed that meridian point stimulation can produce an instantaneous managing effect on symptoms of OSA. However, it is unclear whether meridian point stimulation would cause a long-term therapeutic effect on OSA. Although sleep apnoea occurred unpredictably, it is still possible that sustained therapeutic effect and instantaneous managing effect on sleep apnoea co-exist but this issue needs further verification.

Other Possible Factors that Affect the Outcome of the Study

Factors, other than intervention, that may affect the outcome of the dependent variables are considered in this study. Some of the factors can be measured and evaluated if they have any effects on the outcome using statistical analysis. The potential factors are age, smoking and drinking, use of the CPAP device, weight change and sleeping positions. The results are shown in Table 19.

Results of this analysis showed that age, smoking, alcoholic consumption, use of the CPAP device, sleeping position and weight change do not significantly contribute to the changes in AI, ASR and PDS between the 2 nights.

However, it was found that a subject in the SG had strong improvements in terms of AI, ASR and ADL in night 2. Meanwhile, it was found that this subject is in the supine position for over 80% of the recording time during night 1. In night 2, for 80% of the time, this subject is recorded in the lateral position. In the literature review, the change in lateral sleeping position has been regarded as a conservative method to improve the collapsibility of the airway and thus reduce the severity of sleep apnoea. As there was only 1 subject with a significant change of sleeping position between the 2 nights of the study, the overall effect is not significant.

The habituation of the subject due to the repetitive episodes of electrical stimulation is a concern in this study. Habituation is regarded as the decrease in physiological response due to repeated times of stimulation [17]. As the average pulse oximetry level was consistently lower in night 2 than in night 1 in the MPSG, it is suggested that the effect of the intervention on OSA on the average pulse oximetry level have persisted from the 1st to the 6th hour, rather than only the first few hours of the sleep study. Thus, it seems that habituation may not be presented in this study. However, the assessment of habituation needs to be

further studied by conducting a trial with repeated measurement as the subjects in this study only received the stimulation for 1 night.

Another issue is the possibility of having learning effect in subjects after repeated exposures of electrical stimulation. Learning effect in this study is regarded as the physical change of the body after the stimulation in order to prevent the occurrence of the symptoms. In this test, it was found that learning effect may exhibit in a subject in the SG, as this subject altered his sleeping position from supine to lateral most of the time during night 2. It is possible that this subject may alter his sleeping position in order to prevent from being stimulated during sleep. In light of this issue, it is possible that this subject is benefit from the position therapy due to the learning effect.

Another question is whether obese patients may tend to receive a higher level of stimulation intensity during the experiment. Results in this study suggested that obesity and level of intensity do not seem to be related, which is similar to Miki et al. (1989), who suggested in their study that obesity and the level of intensity is not correlated [141]. Yang (2000) conducted a study which applied submental stimulation for OSA and they also suggested that skin thickness does not significantly affect the required stimulation intensity [233].

Sweating may affect skin conductivity and thus increase the level of intensity during stimulation. In fact, there is a strong correlation between conductivity measurement and the concentration of both Na^+ and Cl^- ions [21]. Also, sweat is rich in electrolytes and skin conductivity varies with changes in the rate of sweat secretion [116]. Sweating can be secreted anytime during the experiment although the room temperature was adjusted prior to the sleep study. Subjects covered with a blanket may increase their chances of sweating during sleep. Conversely, subjects with dry skin may have less skin conductivity. A limitation of this study is that the skin moisture or skin conductivity is not measured

continuously, as they may affect the actual intensity of intervention that the subject receives. However, subjects were asked if they usually sweated during sleeping at home and all subjects in the MPSG claimed that usually, they do not sweat during sleeping.

Psychological conditions during intervention can be another factor that affects the outcome of the study. Although the final stimulation intensity was adjusted by the researcher with respect to the effectiveness of the stimulation, psychological burdens due to the unexpected intensity of stimulation may affect the overall performance of the therapy. Subjects may experience insomnia or excessuration. In TCM, emotion plays an important role. Worrying or brooding over a period of time may weaken the lungs and cause the blockage of "qi", resulting in the formation of phlegm [107]. In the experiment, anxiety is found in several subjects. An example is that a subject who received meridian point stimulation reported that he could not sleep during the sleep study. However, the EEG waves showed that this subject actually did fall asleep. In this case, subjects were asked to stay relaxed before and during the sleep study.

The selection of threshold is also very critical as it may affect the outcome of the study. The threshold of intervention is 10 seconds of cessation of breathing. In fact, another study used 5 seconds of cessation of breathing as a threshold for releasing electrical stimulation [78]. It is believed that the severity of sleep apnoea can be further improved by shortening the length of the threshold, that is, 5 seconds instead of 10 seconds. In this case, AI and ADL may be improved significantly. However, shortening the length of the threshold may increase the chance of triggering false alarms. According to the definition of sleep apnoea in the literature review, sleep apnoea is defined as the cessation of breathing for at least 10 seconds. Unfortunately, no record was found to clarify the reason of using 10 seconds as the threshold to define sleep apnoea. In night 1, it was found that the minimum duration in most of the sleep apnoea events is 10 seconds.

Therefore, it is still believed that 10 seconds is an appropriate threshold, although some oxygen desaturation events are still found inevitably in some events with 10 seconds of breathing cessation after the stimulation.

A previous study released submental electrical stimulation to manage OSA according to breathing sound levels [141]. The reason for choosing breathing sound instead of nasal airflow signals is to avoid signal failure due to nasal obstruction or mouth breathing during sleeping. However, it is believed that signals can still be affected by displacement of the microphone. Also, breathing sound levels can be very low for some individuals. Sound levels can be even lower than the sound generated by the air conditioner in some circumstances. Hence, in this study, it is still preferable to use nasal airflow as the primary indictor to trigger the intervention.

Another concern is whether the meridian point stimulation affects a particular group of patients in terms of severity. A correlation analysis was carried out again to assess the relationship between the baseline AI, ASR and ADL, and the changes in AI, ASR and ADL between the 2 nights of the study. As no significant correlation was found, it is believed that the efficacy of meridian point stimulation varies among patients with different levels of severity of sleep apnoea.

This study tends to use objective measurements to assess the severity of sleep apnoea and sleep quality. Measurements were taken using the PSG device. In other previous studies, the Epworth Sleepiness Scale (ESS) and Multiple Sleep Latency Test (MSLT) were commonly used as subjective measurement tools to assess the sleepiness of subjects. The ESS asks subjects on the likeliness of falling asleep in different conditions in normal daily life. The events in daily life are supposed to be experienced by anyone. MSLT is counting the time that a subject takes to fall asleep. In fact, the results of these 2 tests can be affected by

some factors. First, ESS is based on just the estimation of sleepiness by subjects and the estimation is sensitive to misperception of sleep episodes [219]. Secondly, results of sleepiness may be affected by the psychological condition of subjects. In this study, a subject claimed that he did not sleep most of the time and saw the researcher entering the room frequently. In fact, EEG signals showed that this subject actually did sleep during the study and he may have dreamt about the experiment and researcher. As suggested previously, subjects who have OSA may be able to fall asleep promptly. The subject in this case may have dreamt about the experiment if they are nervous. On the other hand, results of both objective and subjective measurements of sleepiness can be affected by the activities that the subject participated in the daytime before the sleep study. For example, subjects may feel very tired after sporting activities or having a prolonged meeting. This may increase the chances of having bias in self-evaluation of daytime sleepiness. However, it is difficult to control the daily activities of the subjects in this study.

To conclude, the level of stimulation is very critical. In this study, it was found that the duration of OSA is shortened while the subjects do not experience arousal in some circumstances. However, none of these subjects in the MPSG is found with complete removal of OSA symptoms. As the OSA events are still found in all subjects, it is critical that the level of stimulation intensity should be selected precisely prior to sleeping. The same is found in another study [50] where subjects tend to select lower levels of intensity due to different pain thresholds between being awake and asleep, skin conductivity and psychological factors. In light of this issue, it is still very promising to apply meridian point stimulation for managing symptoms of OSA, given that the level of intensity is correctly chosen, but this issue still needs further verification.

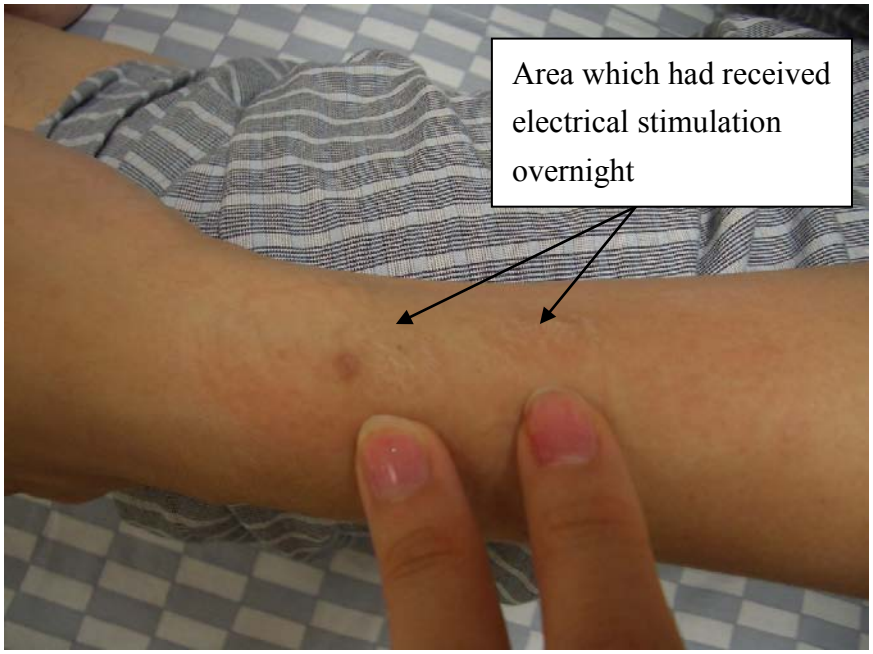
Safety Issues

Transcutaneous meridian point electrical stimulation has been regarded as an integration of acupuncture in Chinese medicine with physical therapy [131]. Transcutaneous electrical stimulation is characterized as a safe, convenient, practical and effective therapy for treating diseases [131, 208]. It is suggested that voltage should not be over 400 V for electrical stimulation on humans [34]. It is also suggested that people usually feel pain when the current of the stimulation is between 1-10 mA. People have difficulty with breathing when the current is 30 mA and they may experience cardiac arrest when the current is 4 A [24]. According to WHO, adverse effects, such as leukaemia or neurological disorders due to the exposure of low level ELF electric and magnetic fields are unlikely to occur. Hazards from test equipment operated at low voltage is minimal [15].

Another question is whether long-term low voltage electrical stimulation would produce harmful effects to humans, such as muscle or nerve fatigue. However, limited studies have been found that relate adverse effects to long-term low voltage electrical stimulation. It is believed that low-voltage electrical stimulation can be used every day to manage the symptoms of sleep apnoea which is the same for the application of stimulation to hypoglossal and genioglossus muscles. However, a large scale of clinical trials is required to verify the effect of long-term low voltage electrical stimulation on humans. On the other hand, electrical stimulation should not be applied to patients who are pregnant, have a cardiac pacemaker, have serious psychological disorders, or wounds in the stimulation area.

In this study, no adverse effects, such as skin irritation, skin burning, nausea, and fainting are reported during or well after the experiment. Figure 54 illustrates the skin area that received an overnight electrical stimulation. In this picture, no redness or skin rash is found in the area that received the electrical stimulation.

Figure 54 Illustration of the skin area after receiving electrical stimulation overnight



10.4 Summary

This chapter presents the results and discusses the findings of the main study. The aim of this main study is to investigate the efficacy of applying meridian point stimulation to manage the symptoms of OSA.

In this chapter, it was found that meridian point stimulation is likely to shorten the duration of an OSA event and thus increases the mean pulse oximetry level of the subject without experiencing arousal during and well after the stimulation in some cases (with approximately 35-40% reduction in symptoms). Afterwards, a one-way ANOVA test was conducted to compare if there is difference in terms of the symptoms due to the intervention among the 3 groups. It was found that the reduction of symptoms due to meridian point stimulation is not as significant when it is compared with the other 2 groups, possibility due to the large variation of data. However, the pre-post differences in terms of the frequency and duration of OSA and also the pulse oximetry level are significant only in the MPSG. Meanwhile, the mean heart rate of the subject increases. If the intensity of stimulation is carefully selected and controlled and if the elevation of the heart rate is due to psychological factors, it is still possible to apply meridian point stimulation effectively in managing symptoms of OSA, but this still needs further verification by further increasing the option of intensity levels. It is believed that meridian point stimulation is a more cost effective and user-friendly approach than the other available methods for patients with sleep apnoea as it is invasive and unobtrusive to the user during sleep.

Chapter 11 Conclusions

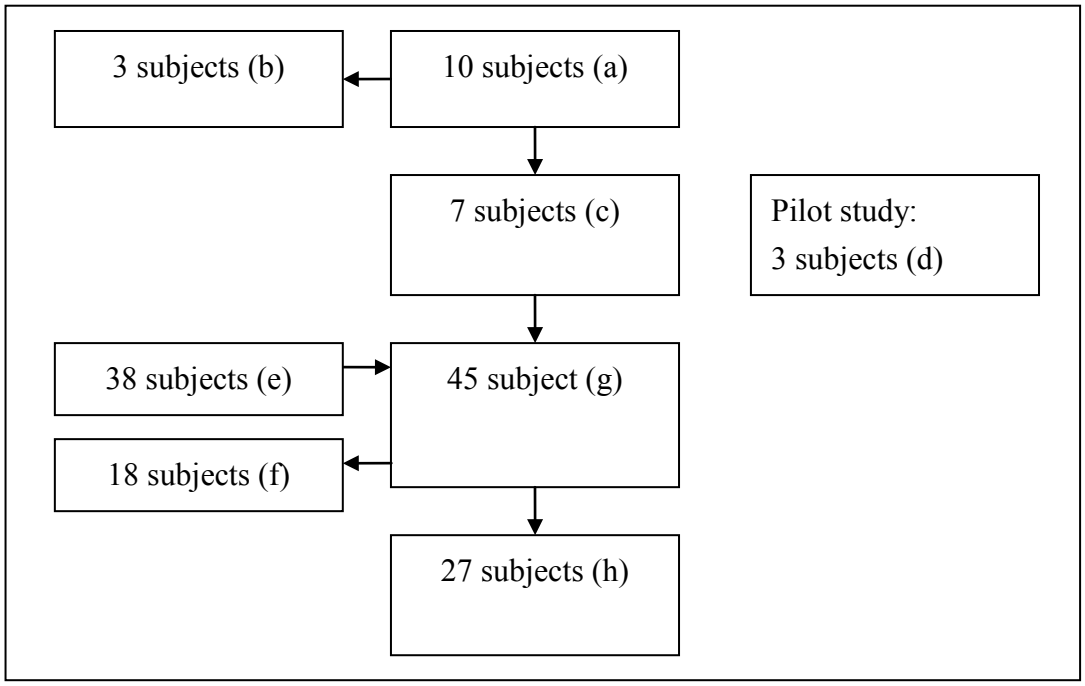
11.1 Introduction

This chapter is divided into 4 parts. The first part outlines the number of participants that enrolled, withdrew and were excluded in this research. The second part summarises the findings and limitations of the 2 studies in this research, including the identification of a critical signal and evaluation of the efficacy of meridian point stimulation on symptoms of OSA. Limitations related to the interpretation of the results and generalizability are identified and the possible contributions of this research to clinical or nursing practices are discussed. Finally, suggestions for making a smart anti-apnoea system are provided and a prototype is developed.

11.2 Participants

Overall, 58 subjects were interested in participating in this research program. Of these 58 participants, eighty-five percent were male between the ages of 26 to 61, with BMIs ranging from 19 to 32. In order to maximize the number of participants in this study, the recruitment of the subjects proceeded from the first study (identification of a critical signal) to the second study (evaluation of the efficacy of meridian point stimulation). Thus, there are a different number of subjects involved in the 2 studies. Ten subjects were enrolled in study 1 and 27 subjects in study 2. Figure 55 presents the flow of subject enrollment in this research. Further descriptions are provided in the next paragraph in accordance to the alphabet in each box.

Figure 55 Flow of subject enrolment in this research programme



Initially, 10 subjects were involved in study 1 (a), which aims to identify a critical signal for promptly indicate the occurrence of OSA episodes. After attending the first night of the sleep study, 3 subjects withdrew from the experiment (b). The analysis of study 1 was conducted at the same time. Afterwards, 7 subjects who were in the first night of study 1 continued to participate in the experiment of the second study (c). Meanwhile, 3 additional subjects were enrolled in the pilot test (d). In the main study, 38 additional participants (e) wanted to join the study 2. Together with 7 subjects brought in from study 1, there were 45 participants (g) who were willing to join the study 2 (main study). However, 18 subjects (f) were rejected because their apnoea index (AI) was less than 5 or there was the presence of suspected abnormal ECG signals during night 1. These patients were given suggestions for a thorough medical check with a healthcare professional afterwards. Eventually, 27 subjects were enrolled in the main study (h).

11.3 Summary of Findings

The results of this research are summarized in several points. First, participants in this study are typically middle-aged male adults with a mean BMI around 30. This phenomenon matches the literature that indicates men and obesity are usually associated with sleep apnoea.

Secondly, similar to findings in the literature, subjects in this study usually complain that they experienced discomfort and nasal congestion while they were on the CPAP, it was noisy or physically unappealing with the nasal mask. For these reasons, patients are still looking for an effective and comfortable alternative for managing sleep apnoea.

Thirdly, a physiological signal which is able to trigger intervention in an appropriate time frame is identified. Nasal airflow is a prompt indicator that accurately detects the occurrence of sleep apnoea. However, the nasal airflow sensor may produce discomfort to the user as the sensor has to be put underneath the nose during sleeping. According to the literature, pulse oximetry level, phase relation and amplitude of the thoracic and the abdominal signals are likely to indicate the occurrence of sleep apnoea without causing discomfort to the user. After carrying out the signal analysis, it was found that there is around 20 seconds of time delay between the onsets of sleep apnoea using the 3% of oxygen desaturation from the baseline level as a threshold. On the other hand, phase relation of the thoracic and abdominal signals is unlikely to accurately indicate sleep apnoea events according to the findings in this study. Lastly, it is found that the mean absolute amplitude of thoracic and abdominal signals is likely to instantaneously indicate the occurrence of sleep apnoea events with around 0.8 sensitivity and specificity values (lower bound), using -25% as a cut-off point. To analyze these signals, absolute amplitude must be summated every ten seconds. The sensor for the thoracic and abdominal signals is only a

piece of soft fabric which is comfortable when worn during sleep. It is very important to ensure that this sensor is able to discriminate motion artifact in order to avoid false alarms and the threshold to trigger the intervention should be carefully calibrated for each subject prior to sleep.

Fourth, findings of this research also suggest that subjects who received meridian point electrical stimulations present a better therapeutic effect in terms of AI, ASR, ADL and ARA than subjects who received sham (non-meridian point stimulation) and no stimulation, given that the location of stimulation is the Lieque (LU7) meridian point. Although there is a pre-post difference in terms of the frequency, the duration of OSA and mean pulse oximetry level in the MPSG, the effect of the meridian point stimulation on the respiration and sleep quality is not as significant when compared with the other 2 groups. On the other hand, although the overall pulse oximetry level during night 2 is lower than that in night 1 only in the MPSG, the heart rate increases at the same time. The instant effect of the meridian point stimulation on the pulse oximetry level in an OSA event is also investigated. It seems that the stimulation on the meridian point is not likely to reduce the pulse oximetry level instantly after stimulation as the pulse oximetry level may take time to decrease at a certain level. However, the overall pulse oximetry level increases as the duration of apnoea is shortened.

Other possible factors that may affect the results of this test are also considered. Although it seems that meridian point stimulation is likely to manage the symptoms of sleep apnoea, changes in the lateral sleeping position between nights 1 and 2 may also contribute to the change in the frequency of sleep apnoea in both groups. On the other hand, the level of intensity, threshold for triggering the intervention, sweating and psychological condition of subjects may also be factors that are uncontrollable and affect the results of this study.

According to the results of the statistical analysis, there are significant differences in terms of the frequency of OSA, the duration of OSA, and the mean pulse oximetry level between nights 1 and 2 in the treatment group. Around 30% of symptoms in terms of the sleep-apnoea ratio are reduced after receiving meridian point stimulation. Also, subjects who receive meridian point stimulation tend to have a lower SpO_2 level and higher heart rate in the whole sleep study. With reference to the EEG signals after stimulation, it seems that there is no arousal during the electrical stimulation. Apart from the meridian point stimulation, sleeping position may be another factor that affects ASR only for the patients who receive meridian point stimulation because ASR and increase in the lateral sleeping position are inversely related. However, it seems that sleeping position of the subjects was in supine usually and thus the effect of the sleeping position on OSA was not significant. For safety issues, it is believed that hazards due to the exposure of low level electrical stimulation are unlikely to occur. However, it is necessary to investigate if long-term exposure of low level electrical stimulation would produce harmful effects on human health, such as muscle or nerve fatigue.

Referring to the previous studies which investigated the efficacy of other forms of treatment on OSA, meridian point stimulation is not as effective when compared to the CPAP device. Overall, the CPAP device is able to reduce approximately 80% of AI while the instantaneous meridian point stimulation in this study is able to reduce approximately 35% of AI. Although OSA can be managed more effectively using the CPAP device, there is low compliance as suggested in the literature. The problems of using the CPAP device are nasal dryness, increased tossing and turning, sleep disruption, face irritation, embarrassment and less intimacy with bed partner [90]. In this study, subjects are willing to try meridian point stimulation and generally accepted this method more than the CPAP device. However, this issue needs to be confirmed with other studies. During the experiment, it was found that the subjects restore

breathing w ell a fter receiving m eridian point s timulation while the y do not experience arousal in some circumstances. It is still very promising to apply this method, given that the level of stimulation is carefully selected and controlled.

11.4 Contributions of Study

Contributions of this study are that the investigation may provide suggestions for medical practitioners and nurses on a completely new method to manage symptoms of sleep apnoea. It seems that the duration of sleep apnoea of subjects would shorten after receiving meridian point stimulation and the overall oxygen desaturation level would increase. On the other hand, sleep quality of patients would not deteriorate. In the long term, the cardiovascular condition of patients may improve because of lower cardiac burden due to prolonged oxygen desaturation; as long as the subject is in relax state. Certainly, this issue needs further justification. Apart from the CPAP, surgery or oral appliances, sleep apnoea patients may have an alternative choice for managing sleep apnoea. Also, the smart system would be more accepted by patients than other methods as the smart device is comfortable, utilizing only 2 pieces of smart fabric for sensing and actuating function. The smart device is portable and light-weight since it utilises smart textile technology, replacing traditional hard electronic components.

As the compliances and efficacies among the current management methods for sleep apnoea varied, medical practitioners and patients are still looking for a better alternative to minimize the symptoms of sleep apnoea and improve sleep quality of patients. In this study, subjects in the MPSG and SG did not experience much discomfort or any adverse effects during the testing, it is still very promising that meridian point stimulation is likely to provide a better managing effect on symptoms of sleep apnoea than sham point stimulation as the severity of sleep apnoea reduced without dramatically increasing the number of arousals as compared with the SG and CG. Findings of this research would suggest an alternative option for medical practitioners to manage symptoms of sleep apnoea and stimulate further studies on the topic of integrating western and Chinese medicine in managing sleep apnoea.

Findings of this research would help generations of the idea for the sleep researchers about the changes of electroencephalograph (EEG) during the meridian point stimulation and non-meridian point stimulation. On the other hand, the arousal threshold in response to the meridian point stimulation and non-meridian point stimulation would be very important in this study as it may affect the sleep quality of the subjects. According to the theory of latent propagated sensation along the channel as suggested in Chapter 3, lower skin impedance along the meridian were found which may require less intensity of stimulation and the threshold value may be lower. However, this suggestion needs further investigation. Although the periodic limb movement was not measured in this study, findings of the average number of limb movement would provide an idea about the possible correlation between meridian point stimulation and limb movement and between arousal and limb movement.

Nurses and medical practitioners are also able to monitor or screen sleep apnoea through constant monitoring of the patient's thoracic and abdominal signals using an abdomen belt or a t-shirt, rather than a nasal airflow sensor. Knowledge of these signals can help in developing other smart systems to provide instant management of symptoms or use as a critical parameter to trigger intervention through existing treatment methods. For example, the CPAP device is used to pump positive pressure continuously to the nasal and oral areas of patients. Positive pressure can also be pumped in case of sleep apnoea using the thoracic and abdominal signals as the indicator, in order to minimize the discomfort of patients. Findings in this study may also stimulate further studies related to the integration of bio-sensing technology and TCM for managing different health problems using smart sensors as well as smart actuators.

11.5 Limitation of Study

Study 1: Identification of a critical signal

For the first study which identifies a critical signal for prompt indication of OSA events, the limitations are that it only involves 10 subjects with the majority of the subjects being male. It is suggested that future research should further increase the sample size, study the mechanism of this phenomenon and standardize the device that is used in the clinical study. In order to conduct a meta-based analysis, it is essential to form criteria in defining sleep apnoea in terms of the phase relationship. In this research, 90% of the participants are severe male sleep apnoea patients with an AHI higher than 30.

Study 2: Evaluation of the efficacy of meridian point stimulation on OSA

Several limitations are addressed. First, this study employs convenience sampling by posting advertisements in the university, which may result in selection bias, and thus influences the results. The samples in this study only involve Chinese patients as it is conducted in Hong Kong. Moreover, the majority of these participants are mainly middle-aged males with obstructive sleep apnoea. Therefore, findings of this research might not be generalized to other groups, such as central sleep apnoea, females, teenagers and the elderly.

Secondly, the repeated effect of the intervention on symptoms of OSA is not observed as subjects spent only 1 night for the baseline study and 1 night for the test study.

Thirdly, this study mainly evaluates the performance of meridian point stimulation using an objective approach, whereas a subjective approach, such as self-evaluation of daytime sleepiness is omitted. Also, this study only assesses the efficacy of intervention by comparing only the severity of sleep apnoea and sleep quality of patients. However, quality of life, which is also an important indicator that reflects an individual's physical and mental well-being, is not studied in this research.

Reasons for suffering from sleep apnoea are not clearly defined prior to the study. Reasons may include obesity, craniofacial abnormalities, nasal obstruction or a large tongue. Subjects with different reasons of having sleep apnoea may have different reactions of sleep apnoea in response to the meridian point stimulation, but this study does not investigate this issue.

Another limitation is that the sample size is only 27 in the main study. Although the power in the paired t-test is over 0.8, the power in the one-way ANOVA analysis is 0.5. Subjects with different levels of severity were assigned into 1 group which results in a large variation of data. In the previous studies which investigated the efficacy of using electrical stimulation on the hypoglossal or genioglossus nerves or muscles, usually the sample size is also around 10 to 20. However, these previous studies utilized a 1 group single-blinded clinical trial design.

Ideally, a double-blinded design would be better in providing a more objective analysis. As one researcher is involved in performing the experiment and scoring of the OSA events and sleep, a double-blind design is not applicable for this study.

This study only observes the phenomenon of symptoms after intervention, and without studying the physical mechanism of the intervention. This study also does not investigate the immediate reaction of the nasal pharynx or upper airway resistance due to meridian point stimulation. In fact, these 2 parameters are able to indicate the condition of the airway and thus observe if there is improvement in terms of sleep apnoea due to the meridian point stimulation more directly.

Another limitation is that this study selects cessation of breathing for 10 seconds as a threshold for triggering intervention, without studying the effects of using other thresholds. The decrease in the threshold (such as 5 seconds) may exhibit a better managing effect on the frequency duration of OSA. This issue needs to be further investigated.

Ideally, the ultimate goal of this project is to evaluate the performance of using the smart system rather than available sensors and actuators to manage symptoms of sleep apnoea. However, the performance of smart textile materials still needs further improvement. Although the piezoelectric fabric possesses a property that electrical resistance changes by stretching it, the initial value of electrical resistance may change at different times under relaxed conditions. This fabric is also sensitive to sweating and temperature change. Therefore, it needs to be coated with special materials in a specific condition. The coating method is still under further investigation by the Institute of Textiles and Clothing in the Hong Kong Polytechnic University. In addition, the stainless steel fabric is highly electrical conductive and able to resist water. However, the performance of electrical conductivity on the skin surface without applying any gel is still unstable. It is found that the conductivity of the fabric changes in response to the change in humidity of the environment and sweating of the subjects. Also, electrodes can be located in the wrong position on the wrist due to frequent body movements during sleep. Therefore, this project only provides a conceptual

design of the smart system and the development of these materials needs further investigation in order to enhance its performance. Despite these limitations, findings in this study may offer directions for further areas of sleep apnoea and symptom management methods, which utilize the concept of TCM and smart textile technology.

11.6 Future Work

Study 1: Identification of a critical signal

Future work should investigate the possibility of using signals as the only indicator of sleep apnoea for mild sleep apnoea patients and also for female patients, or for hypopnea. It is also suggested that future work can study the possibility of applying other parameters as the indicator to promptly diagnose or even predict the occurrence of sleep apnoea. An appropriate intervention can be applied even before the occurrence of sleep apnoea in order to avoid any deoxygenation as well as arousal. Overall, it is important to consider the accuracy of using a specific parameter to indicate the occurrence of sleep apnoea without triggering false alarms.

Study 2: Evaluation of the efficacy of meridian point stimulation on OSA

Recommendations for future studies can be divided into several aspects. The first aspect is to increase the sample size and include different types of patients. The majority of samples in this research are middle-aged males with obstructive sleep apnoea. Future studies can focus on studying the critical signal and effect of meridian point stimulation in different age groups, levels of severity, female groups, and with central or mixed sleep apnoea in order to allow greater generalizability of the results. It is worth studying the effect of meridian point stimulation in other races, such as Caucasians. Possibly, Caucasian people may have different characteristics in terms of airway collapsibility, skin moisture and also the path of “Qi” flow and thus, have different responses to meridian point stimulation that can be observed. This needs further justification.

The second aspect is the recommendations for the methodology design of the clinical trial. In this study, there are only 2 nights of sleep study for each subject. It is recommended that the duration of sleep studies can be even extended from 2 nights to a week. Future studies can investigate the long-term effect of meridian point stimulation on sleep apnoea. For example, subjects receive a baseline sleep study for 1 night and several nights of treatment instead of 1 night. The outcome measurable would be the same as in this study and these parameters can be used to compare the effect of intervention during the several nights. This analysis helps in evaluating the reliability and consistency of the results. Also, study of the long-term effect of the intervention on sleep apnoea helps identify the possibility of habituation and learning the effect of nerves and muscles or if the results would be affected by the release of endorphins due to continuous stimulation. This issue needs further investigation. However, subjects may refuse to spend time travelling to the sleep laboratory frequently. Therefore, another suggestion for future research is that the experiment can be conducted at home instead of the sleep laboratory. A home PSG device is recommended for recording the physiological signals of the subject. Only a technician is needed to teach subjects the way to wear the sensors and actuators at home and provide technical support if necessary. This approach helps in evaluating long-term efficacy of meridian point stimulation. However, compliance will be an important issue in this case. A double-blinded randomised control trial is recommended in order to increase the objectivity of the results. In other words, both patients and the data analyst will be blind about the results of group division. Scoring or analysis can also be done by a separated data analyst. Furthermore, other meridian or meridian points along the lung meridian that may benefit respiration during sleep can also be studied. The selection of these meridian points definitely needs strong theoretical support.

The third aspect is to further extend the outcome assessment of the parameters used in evaluating the efficacy of the intervention. It is suggested that a comparison can be made between the efficacy of using the meridian point stimulation as well as the CPAP machine for managing symptoms of sleep apnoea. Also, other measurable outcomes, such as quality of life and daytime sleepiness, can be used given that only the daily activities before the experiment will not heavily affect the sleepiness of subjects. It is also suggested that signal artefact of the EEG signals due to stimulation will be filtered during the experiment in order to obtain more meaningful signals for further analysis. In addition, the skin depth of stimulation area can also be measured and investigated to determine if it affects the intensity of stimulation and the efficacy of the intervention. On the other hand, it is important to investigate whether the meridian point stimulation will directly affect the collapsibility of the upper airway or nasal pharyngeal area of the subject using an endoscope. The study of the relationship between the meridian point stimulation and upper airway resistance helps to further confirm the efficacy of stimulation on symptom management. Although it is expected that the method of meridian point stimulation should produce minimum discomfort to the user, it is still recommended that the difference between perception and tolerance of patients be evaluated. Studying this issue helps in predicting the long-term compliance of using this method.

The fourth aspect is the recommendations for product development. A clinical trial can also be conducted to test the efficacy of using the prototype for managing symptoms of sleep apnoea, given that the development of smart textile materials is mature and its performance is stable. Durability and washability of smart materials are important issues in developing smart sensors or actuators. On the other hand, the criteria of stimulation should be carefully controlled so that user will not underestimate or overestimate the pain threshold. As a result, user will be able to select an appropriate level of stimulation without any bias. It is

suggested that a clearly defined sensation scale with guidelines for selecting the intensity of stimulation will be provided to users prior to sleeping. Also, the level of intensity can be adjusted accordingly by the smart system due to the efficacy of stimulation during sleep. Signal artefacts due to body movements should be identified in order to avoid triggering false alarms. An important issue is that the smart textile materials or electronic components should not be overheated when using them continuously during sleep because it produces discomfort to the user and may be dangerous to human health. Electro-magnetic waves (EMW) generated due to the exposure of electrical stimulation and wireless transmission of the signals should not exceed a certain limit to minimize the effect of potential hazard to the human body in the long-term. It is also very important to obtain the opinions or suggestions of medical professionals and patients about the design of the smart system. Last but not least, although this method has plenty of room for improvement, it is still expected that it will be widely accepted by patients as it provides a completely new, safe, effective and user-friendly approach to managing symptoms of sleep apnoea.

11.7 Suggestions for developing a smart anti-apnoeic device

As the critical signal is selected and efficacy of meridian point stimulation tested, it is suggested that a device which utilizes the concept of this study can be developed and further tested. This device should consist of a smart abdomen belt as well as a wristband.

Although the combination of thoracic and abdominal signals is likely to be the most effective indicator for identifying obstructive sleep apnoea in accordance to the findings in this study, it is suggested that only the abdomen signal be monitored in this smart system in order to maximize the comfort of the user as the ROC value of only the abdomen signal is still around 0.8. An abdomen belt is responsible for the sensing part of the system. It is used to measure the signals of change in abdominal efforts as the conductivity of piezoelectric fabric changes when force is applied. In usage, the user has to wrap the elastic belt around the abdomen, and wrap the wristband around the wrist before going to bed. There are 3 pieces of fabric sensors in this abdomen belt. The middle sensor is placed on the belly button. The upper and lower sensors are placed at 1 inch up or down from the middle sensor. It is suggested that the user should wear the belt in the supine condition rather than in a sitting or standing position as there is a difference in terms of circumference of the abdomen in different postures. Also, this smart system should detect abdominal signals during motion (calibrate the signal such as the occurrence of extremely large or small in amplitude during use) in order to avoid triggering false alarms. It is important that this belt is supposed to be used to identify sleep apnoea only rather than both apnoea and hypopnea. Figure 56 shows the prototype of the smart abdomen belt. Apart from the abdomen belt, fabric sensors can also be directly sewn onto nightwear or t-shirt.

Figure 56 The Smart Abdomen Belt

Meanwhile, patients with OSA can wear the wristband as well as the abdomen belt during sleep. The wristband receives the signals from the abdomen belt and releases stimulation once the signals meet the threshold value. The user has to select the stimulation intensity prior to sleeping. The stimulation electrode on the wristband is made up of conductive fabric. The advantage of applying the conductive fabric instead of using traditional electrodes is that there should be conductive gel during use. Ideally, the fabric electrodes should be protruded as much as possible to ensure good dry contact with the skin surface. It is also important to ensure that the sensor is placed upon the LU7 and avoid displacement of the electrodes during sleep. Therefore, the casing of the wristband should be designed in a shape that merely fits the wrist and not be too heavy. The base fabric of the wristband should be breathable, soft and non-conductive to electricity. The stainless steel fabric can be washed under clean water, but not detergent. The stainless steel fabric is also very soft as the

diameter of the fibre is very small (about 10 microns). Figures 57 and 58 illustrate the prototype of the smart wristband.

Figure 57 Inner part of the wristband with 2 fabric electrodes

Figure 58 The smart wristband

11.8 Summary

Non-invasive meridian point stimulation for alleviating sleep apnoea is suggested and evaluated in this research. Overall, the results in the main test suggest that stimulation on LU7 is likely to reduce the frequency and duration of OSA by approximately 30-40% and also increase the average pulse oximetry level. A significant difference between the 2 nights of the study was found only in the MPSG. However, the effects are not significant when compared with the SG and CG. The possible reason is the insufficient sample size for ANOVA test and thus the variation of data is large. Also, this method may be less effective for the CPAP device in terms of reducing the frequency of apnoea with respect to the results in other previous studies. As it was found in some circumstances that meridian point stimulation is able to shorten the duration of sleep apnoea, prevent oxygen desaturation while not causing arousal of the subjects, it is still promising that the application of this method will manage symptoms of OSA, given that the stimulation intensity is controlled carefully. Future studies can further study the repeated and long-term effects of meridian point stimulation. Last but not least, as smart textile technology can be utilised in the device. This approach may provide a cost-effective and user-friendly solution for managing the symptoms of OSA.

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Appendix

Appendix 1 Questionnaire

V1 Record Sheet for Sleep Apnoea Patients

Subject Code: _____ Date: _____

Personal Information

Chinese Name: _____ _____ E nglish Name: _____ _____

HKID No.: __ _____ G ender: _____

Age: _____ M arital Statue: S ingle/ Married/ Others

Tel (Mobile): __ _____ E mail: _____

Date of Birth: ____ _____ O ccupation: _____

Weight (kg): ___ _____ H eight (meter): __ _____

BMI (kg/m²): _____ _____ E thnic: ___ _____

Epworth Sleepiness Scale: _____ A HI: _____

❒ Do you smoke? How often? ____ ❒ Do you drink alcohol? How often? _____

❒ Are you pregnant?

Medical History

Any of the below events:

❒ Cardiovascular Diseases:

❒ Hypertension 高血壓 ❒ Hypotension 低血壓

❒ Atrial Flutter 心房撲動 ❒ Angina Pectoris 心絞痛

❒ Coronary Artery Disease冠心病 ❒ Heart Failure心臟衰竭

❒ Arrhythmia 心律不整 ❒ Heart Failure 心力衰竭

❒ Rheumatic Heart Disease 風濕性心臟病

❒ Hypertensive Heart Disease 高血壓性心臟病

❒ Others, please specify: _____

❒ Respiratory Diseases:

❒ COPD 慢性阻塞性肺疾病 ❒ Pneumonia 肺炎

❒ Asthma 哮喘 ❒ Bronchitis 支氣管炎

❒ Emphysema肺氣腫 ❒ Lung Cancer 肺癌

❒ Tuberculosis 肺結核

❒ Others, please specify: _____

❒ Neurological Diseases:

❒ Convulsion 痙攣 ❒ Carpal tunnel syndrome 腕隧道徵候群

❒ Others, please specify: _____

❒ Skin Diseases:

❒ Skin allergy 皮膚敏感 ❒ Dryness of skin 皮膚乾燥

❒ Itchy Skin 皮膚發癢 ❒ Eczema 濕疹

❒ Skin Cancer 皮膚癌

❒ Others, please specify: _____

❒ Nasal Diseases:

❒ Allergic Rhinitis 過敏性鼻炎 ❒ Sinusitis 鼻竇炎

❒ Nasal Polyp 鼻息肉

❒ Others, please specify: _____

❒ Other Chronic Diseases:

❒ Diabetes 糖尿病 ❒ Stroke 中風

❒ Leukaemia 白血病/血癌

❒ Others, please specify: _____

❒ Remarks: _____

❒ Are you currently receiving sleep apnoea treatments or management?

Which treatment?❒ CPAP ❒ Oral appliances ❒ Surgery ❒ Drugs

❒ Others, please specify: _____

❒ Do you feel unacceptable if you don't have the sleep apnoea treatment for even one night?

❒ Did you receive any sleep apnoea treatment for relieving the problem of sleep apnoea?

Which treatment?❒ CPAP ❒ Oral appliances ❒ Surgery ❒ Drugs

❒ Others, please specify: _____

Appendix 2a Information Booklet (English Version)

Evaluating the Application

of

Meridian Point Stimulation for

Managing Sleep Apnoea

Subject Code: _____

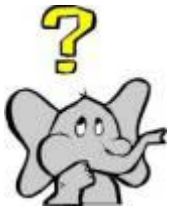
About Sleep Apnoea

Sleep apnoea is a common sleep disorder. It affects about 1-2% of the total population. Sleep apnoea is characteristised by the occurrence of repetitive episodes of partial or complete obstruction of the upper airway. Symptoms are loud snores, cessation of breathing and blood oxygen deoxygenation. Frequent awakenings caused by sleep apnoea may result in daytime sleepiness.

Other symptoms of sleep apnoea are morning headache, daytime sleepiness, poor memory and concentration.

Reasons to have obstructive sleep apnoea: Pharyngeal muscles normally relax during sleep; enlargement of the uvula, tonsil or tongue; elongation of the soft palate, and nasal obstruction. These will cause partially or completely blockage of the airway. Obstructive sleep apnoea is also commonly found in the obese people. Some people who have craniofacial abnormalities may also have higher chance to suffer from obstructive sleep apnoea.

Management methods of sleep apnoea: Patients should consult doctors for medical advices. People who have suspected sleep apnoea are recommended to have an overnight sleep assessment. Polysomnography will be used as a tool to diagnose sleep apnoea.



About This Research

Aims

A research student in the School of Nursing, the Hong Kong Polytechnic University (HKPU) is currently conducting research about sleep apnoea.

The main aims are to research the efficacy of applying meridian point stimulation for managing sleep apnoea and to explore the possibility of developing a lightweight and portable device for managing sleep apnoea.

Venue

Room MN043

The Sleep Laboratory in the HKPU (Please refer to the map in the next page)

Washroom, bathroom, TV, air conditioning will be provided.

Drinks and snacks will be provided.

* Time will be flexible according to subject's availability

Telephone Number (Sleep Laboratory)

2766-4537 (Emergency only)

About the Sleep Apnoea Test

Sleep apnoea test is a gold standard to diagnose obstructive sleep apnoea. Subjects will sleep in a laboratory and their multiple physiological parameters will be measured and recorded. Subjects are required to wear sensors on their faces, heads, limbs, chests and abdomens. It is expected that subjects should not

Procedures

Please confirm date of your attendance with the researcher 3 days prior to the sleep apnoea test

All sleep apnoea tests will be conducted in the sleep laboratory

Patients need to spend 2 nights in the sleep laboratory
Patients will receive 3 follow-up calls from the researcher
The whole investigation should not longer than 12 months

Patients may be required to attend the sleep laboratory again in case of data failure

* Please bring this booklet along with you during each visit

Procedures

Research Process

		Approximate Duration	Tasks	Date	Remarks
Initial Conversation	Call 1	15 minutes	• Briefly introduce research aims • Acquire Patient's medical background and contact number • Confirm the date of the first visit		
First Meeting	Visit 1	30 minutes	• Introduce research aims, procedures and handle the enquiry • Introduce the facility of the sleep laboratory • Confirm the date of the second visit		
Baseline Study	Call 2	10 minutes	• Remind the time of visit and what they need to bring		
	Visit 2	1 night	• Provide the booklet • Session briefing • Signing the consent form • Sleep apnoea test		
Testing the efficacy o f the m eridian point	Call 3	10 minutes	• Remind the time of visit and what they need to bring		
	Visit 3	1 night	• Session briefing • Wear the electrodes/ wristband for meridian point stimulation • Adjust the stimulation intensity • Sleep apnoea test		

Information

What you need to bring during each visit?

- Comfortable pajamas (note that nightshirts or nightdresses are not suitable)
- Any medication you are using
- Your toothbrush
- If you like, your own pillow, slipper, soap and shampoo

Suggestions

- Prior to attending please wash your hair and do not apply gels or conditioner
- Please remove make-up, moisturizers and nail polish, as these will interfere with our recording
- Please have your evening meal before the sleep study
- Please avoid drinking too much water during the day of visit

When you arrive and leave the sleep laboratory?

Arrival Time: 20: 30 (Please confirm if you need to take a shower in the laboratory and arrive 30 minutes prior to the sleep study)

Leave Time: 07: 30

Cancellation of the appointment

If you are unable to keep your appointment, please contact the researcher as soon as possible to arrange a new appointment date

Others

CPAP machine will not be used during the day of visit and using the prototype at home; If you feel too uncomfortable when you use the prototype, please stop using it and contact the researcher immediately so that we can help to correct the problem

Please feel free to contact Ms. Alice Ng at 2766-4534 for any information

You have every right to withdrawn from the study before or during the measurement without penalty of any kind.
If you have any complaints about the conduct of this research study, please do not hesitate to contact Mr Eric Chan, Secretary of the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University in person or in writing (c/o Human Resources Office of the University).
If you would like more information about this study, please contact
Ms. Alice Ng (researcher), on tel. no. 2766-4534.

or Contact Project Supervisors
Prof. Thomas Wong: 2766-6397
Dr. Danny Gohel: 2766-7883
Dr. Winnie Yu: 2766-6525

Thank you for your interest in participating in this study.