Methods for Detecting and Monitoring of Sleep Disordered Breathing in Children using Overnight Polysomnography

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The University of Adelaide, Australia, 2015

Thesis submitted for the degree of

Doctor of Philosophy

in

School of Electrical & Electronic Engineering

Faculty of Engineering, Computer and Mathematical Sciences

The University of Adelaide

August 2019

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Contents

Abstract

Sleep is crucial for the health of every individual, especially children. One of the common causes of disturbed sleep in children is disordered breathing. Children who suffer from sleep disordered breathing are likely to have severe consequences for their physical growth, heart health and neuropsychological function. Sleep disordered breathing (SDB) comprises a spectrum of severity from a mild form of upper airway resistance syndrome (UARS) to severe form of obstructive sleep apnea syndrome (OSAS). While OSAS is considered clinically significant, UARS and its health consequences have been underestimated. The most common treatment for OSAS in children is adenotonsillectomy. However, breathing disturbances related to UARS may persist even after adenotonsillectomy. The current diagnostic marker for OSAS, the Apnea-Hypopnea Index (AHI) often overlooks the less severe conditions of breathing disturbances.

Therefore, the research objective of this thesis is to investigate the new alternative markers for SDB in children using non-invasive physiological measurements, such as thoracoabdominal signals and the photoplethysmogram. As the body experiences an array of complex changes, specifically in respiratory and autonomic nervous system activation during breathing disturbances, advanced signal processing and analysis techniques were used to identify the physiological variables that could reflect changes in those systems in children with SDB. Thoraco-abdominal asynchrony (TAA), heart period (HP) and pulse wave amplitude (PWA) were the three physiological variables were investigated. A total of five studies were conducted on two high-quality clinical research datasets to test the potential of the proposed physiological variables to effectively identify children with SDB.

Abstract

In the thesis: 1) Hilbert transform was applied for TAA estimation on the childhood adenotonsillectomy trial (CHAT) dataset; 2) symbolic dynamic analysis on HP was used to assess the effect of adenotonsillectomy on autonomic activations in children with SDB; 3) the conventional method of estimating PWA was combined with joint symbolic analysis of PWA and HP to analyse the effect of SDB on autonomic activation compared to healthy controls; 4) to improve the performance of the previous PWA measurement technique, a more robust and simpler method was proposed to estimate PWA using a simple envelope method, and a more extensive dynamic analysis method was created to capture more complete information; and 5) adding TAA and HP information with AHI, unsupervised machine learning method K-means clustering and linear discriminant analysis were used to discover the pathophysiology nature difference of children with SDB in CHAT dataset.

The main results from this thesis suggest that children with SDB have higher values in all three physiological variables, which indicates a high respiratory effort and elevated frequency of autonomic activation. Adenotonsillectomy showed to reverse the effects on these physiological variables, suggesting it assisted in the reduce of pathophysiological symptoms in those children. Interestingly, TAA was found inversely correlated with quality of life and unreported baseline difference in HP in children who had their AHI normalised spontaneously. These findings further indicate the limitation of AHI as the only marker for paediatric sleep disordered breathing. By combining the TAA and HP information with AHI, the alternative proposed diagnosing approach could help doctors predict who may benefit from adenotonsillectomy or not.

In conclusion, this thesis provides new evidence that TAA, HP and PWA can provide additional information and may yield more effective markers for diagnosing paediatric sleep disordered breathing.

Statement of Originality

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

	31/10/2019
Signed	Dates

Acknowledgements

This thesis is one of the most challenging tasks I have completed in my life so far. I could not be able to finish it without all those people who have supported, assisted and encouraged me. Here, I would like to take this opportunity to show my gratitude to all those people.

First of all, I would like to express my deepest gratitude to my supervisors, **Associate Professor Mathias Baumert** and **Professor Derek Abbott**, for their guidance. Particularly, my principal supervisor, **Associate Professor Mathias Baumert** for his continued guidance and patiently supporting me throughout my candidature. Mathias provided his insight and knowledge as the fundamental resource in the field of my research. He also offered his understanding and support when I underwent many of my life difficulties. I would not have been able to successfully complete my study without him.

I also like to thank my co-investigators Dr Sarah Immanuel, Dr Yvonne Pamula, Dr Declan Kennedy, Dr James Martin and Dr Mark Kohler for providing me with the valuable dataset and critical feedback on my research findings which I have built upon in this thesis.

Additionally, I would like to thank the postgraduate coordinator Dr Withawat Withayachumnankul, for his care and support in the last two years of my candidature. He has not only provided necessary information regarding my candidature but also care to my general health and wellbeing as a sincere friend.

I want to thank the head of school Prof Wen Soong who approved and provided the financial opportunity presenting my work at an international conference in Europe.

Special thanks go to all my friends, colleagues and staff from the Electrical and Electronic Engineering for their support throughout my candidature.

Acknowledgements

I am gratefully appreciative to all my close friends from my childhood, undergraduate days and accommodation building who have patiently encouraged and accompanied me on this journey.

Last but not least, I would like to thank my parents and family for their unconditional support and love in any situation.

Thesis Conventions

The following conventions have been adopted in this Thesis:

1. **Spelling.** Australia English spelling conventions have been used, as defined by the Macquarie English Dictionary, A. Delbridge (Ed.), Macquarie Library, North Ryde, NSW, Australia, 2001

2. **Typesetting.** This document was compiled using Microsoft Word 2016

3. **Referencing.** The Harvard style has been adopted for referencing

Publications

Journal Articles

LIU, X., IMMANUEL, S., KENNEDY, D., MARTIN, J., PAMULA, Y. & BAUMERT, M. 2018a. Effect of adenotonsillectomy for childhood obstructive sleep apnea on nocturnal heart rate patterns. Sleep. DOI: 10.1093/sleep/zsy171

LIU, X., IMMANUEL, S. A., PAMULA, Y., MARTIN, J., KENNEDY, D., KOHLER, M. & BAUMERT, M. 2018. Pulse wave amplitude and heart period variability in children with upper airway obstruction. Sleep Medicine, 50, 55-62. DOI: 10.1016/j.sleep.2018.05.020

LIU, X., IMMANUEL, S., PAMULA, Y., KENNEDY, D., MARTIN, J. & BAUMERT, M. 2017. Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea−hypopnoea index normalisation does not. European Respiratory Journal, 49. DOI: 10.1183/13993003.01177-2016

EL-HAMAD, F., IMMANUEL, S., **LIU, X.**, PAMULA, Y., KONTOS, A., MARTIN, J., KENNEDY, D., KOHLER, M., PORTA, A. & BAUMERT, M. 2017. Altered Nocturnal Cardiovascular Control in Children With Sleep-Disordered Breathing. Sleep, 40. DOI: 10.1093/sleep/zsx127

Publications

LIU, X., PAMULA, Y., IMMANUEL, S. A., MARTIN, J., KENNEDY, D. & BAUMERT, M. 2019. Utilisation of machine learning to predict surgical candidates for treatment of childhood upper airway obstruction. (Unsubmitted manuscripts)

Conference Article

LIU, X., PAMULA, Y., KOHLER, M. & BAUMERT, M. 2019, July. A Method for Estimating Pulse Wave Amplitude Variability in children with Sleep Disordered Breathing, In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE. (In press)

List of Figures

List of Abbreviation and Acronym

ABD	Abdominal
ACTH	Adrenocorticotropic Hormone
ADHD	Hyperactive
AHI	Apnea-Hypopnea Index
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
AT	Adenotonsillectomy
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BMIZ	Body Mass Index Z-Score
BP	Blood Pressure
BRIEF	Behaviour Rating Inventory of Executive Function
CAI0P	Central Apnea Index All Desaturations
CGI	Conners' Parent Rating Scale-Revised: Long Version Global Index
CHAT	The Childhood Adenotonsillectomy Trial
CPAP	Continuous Positive Airway Pressure
CRH	Corticotropin Releasing Hormone
DAS	Differential Ability Scales Ii
eAT	Early Adenotonsillectomy
ECG	Electrocardiography
EEG	Electroencephalography

EMG	Electromyography
EOG	Electrooculography
FIR	Finite Impulse Response
FL	Flow Limitation
GEC	Global Executive Composite
HP	Heart Period
HRV	Heart Rate Variability
LDA	Linear Discriminant Analysis
N2	Sleep Stage 2
N3	Sleep Stage 3
NREM	Non-Rapid Eye Movement
OAHI	Obstructive Apnea-Hypopnea Index
OAHI3	Obstructive Apnea Hypopnea (>=3% Desaturation) Index
OAI	Obstructive Apnea Index
OSA-18	The Total Obstructive Sleep Apnoea-18
OSAS	Obstructive Sleep Apnea Syndrome
PCTLT90	Percentage of Time < 90% Oxygen Saturation (Sao2)
PedsQL	Paediatric Quality of Life Inventory
PPG	Photoplethysmogram
PSG	Polysomnography
PSQ	Paediatric Sleep Questionnaire
PTT	Pulse Transit Time
R	Rapid Eye Movement
RC	Ribcage

REM	Rapid Eye Movement
RERA	Respiratory Effort-Related Arousal
RPCTCO2G50	Percentage of Total Sleep Time (Tst) Where End-Tidal Carbon Dioxide (Etco2) > 50 Mmhg
SDB	Sleep Disordered Breathing
SRBD	Sleep-Related Breathing Disorder Scale
TAA	Thoraco-Abdominal Asynchrony
TST	Total Sleep Time
UAO	Upper Airway Obstruction
UARS	Upper Airway Resistance Syndrome
WWSC	Watchful Waiting with Supportive Care

Chapter 1 Introduction

Children suffering from respiratory disorders during sleep in children can have crucial health problem later on in their life. Years of sleep research have conducted, and researchers have developed the current clinical criteria to diagnose children with sleep disordered breathing. However, the current clinical criteria have underestimated the severity of the mild cases. This Chapter introduces the background and motivation of the studies presented in this thesis.

1.1 Thesis Overview

This thesis comprises a total of seven main chapters and two Appendices. The main chapters include ONE introduction chapter, ONE method chapter, FOUR clinical studies chapters, and ONE conclusion chapter. The outline of each chapter is described below.

Chapter 1 introduces the main topic of sleep disordered breathing in children and reviewed the common physiological changes associated with the disease.

Chapter 2 describes the developed and applied physiological measurement methods in the thesis studies.

Chapter 3 investigates the effect of adenotonsillectomy for children with obstructive sleep apnoea on TAA using Hilbert Transform.

Chapter 4 explores the effect of adenotonsillectomy for children with obstructive sleep apnoea on autonomic activation using symbolic dynamic analysis on heart rate.

Chapter 5 investigates the effect of adenotonsillectomy for children with sleep disordered breathing on autonomic activation by analysing the joint symbolic dynamic of pulse wave amplitude and heart rate. It also explores the difference between the joint dynamics of children with sleep disordered breathing and healthy subjects.

Chapter 6 explores the effect of adenotonsillectomy for children with obstructive sleep apnoea using a data-driven approach that combines cluster analysis and linear discriminant analysis.

Chapter 7 summarises the work conducted in this thesis and provides possible prospective research directions.

Appendix A proposes a simple method on continuous pulse wave amplitude estimation and an alternative and more extensive dynamic analysis method

Appendix B shows the framework flow chart for TAA estimation presented in Chapter 2

1.2 Introduction

1.2.1 Normal sleep

Humans spend about one-third of their lifetime asleep. Good sleep acts as an important factor in the health of every individual. Before rapid eye movement (REM) sleep was discovered (Aserinsky and Kleitman, 1953), people believed during sleep the brain would be relaxed/inactive same as the body. In fact, our body and brain still keep busy during sleep. Four distinctive sleep stages were defined, which are sleep stage 1, 2, 3 and REM sleep stage(Altevogt and Colten, 2006). Stage 1, 2 and 3 are considered as non-repaid eye moment (NREM) sleep, where sleep stage 1 is a transition stage from wakefulness to sleep. Muscle tone starts to relax throughout the body and brain wave activity begins to slow down. The body is easily woken up during this stage. In sleep stage 2, heart rate slows down, body temperature drops, and the body prepares for deep sleep. Stage 2 indicates entry into a deep stage of sleep, and it is more difficult to be awakened compared to sleep stage 1. While during sleep stage 3, the body enters in slow wave sleep and muscles are fully relaxed, and it is even more difficult to arouse the body. There are significant physiological differences between non-REM sleep stages and REM sleep stages (Altevogt and Colten, 2006). During non-REM sleep, decreases trend of physiology activities, such as brain activities, heart rate, blood pressure, sympathetic nerve activity, body temperature and respiration. While limbs completely paralysis during REM sleep, the physiology activities are as active as awake. Sleep is a crucial process for our neurons and other cells to repair themselves, reset body

biochemical (hormones) and strength out the immune system. It turns on the glymphatic system (Jessen et al., 2015) which is the brain's waste-flushing system. The glymphatic system is close to 10 times more active than when awake (Xie et al., 2013). Critical hormones are released, for example, growth hormone released during slow-wave sleep (stage 3) (Sassin et al., 1969), and reset hunger hormone balance which could reduce the risk of obesity (Van Cauter and Knutson, 2008, Spiegel et al., 2009, Leproult and Van Cauter, 2010). Furthermore, sleep is important to mental health, such as memory conciliation, reconciliation and mood regulation. Especially in children, it is directly linked to children's growth, development, energy and happiness. However, not everyone experiences restorative sleep due to sleep-related breathing disorder.

1.2.2 Sleep disordered breathing

People who are suffering from sleep disordered breathing experience insufficient ventilation and abnormal breathing patterns during sleep. The obstructive sleep related disordered breathing is one of the most common types for this disease, and it is due to obstructed or narrow up airway. From obstructive sleep apnea syndrome (OSAS) to upper airway resistance syndrome (UARS), sleep disordered breathing consists of a spectrum of severity. Typically, obstructive respiratory events based on respiratory airflow are obstructive apnea, obstructive hypopnea and flow limitation (FL), where FL occurs with an increase of esophageal pressure without an increase of actual flow (Arora et al., 2015). While apnea and hypopnea are mainly used for diagnosing OSAS, FL is used for diagnosing UARS. The illustration for these events related to airway and respiratory flow is shown in **Figure 1**. Those that possess SDB are normally experience excessive daytime sleepiness/fatigue, and it is responsible for many accidents during driving and industrial work (Howard et al., 2004, Jordan et al., 2014).

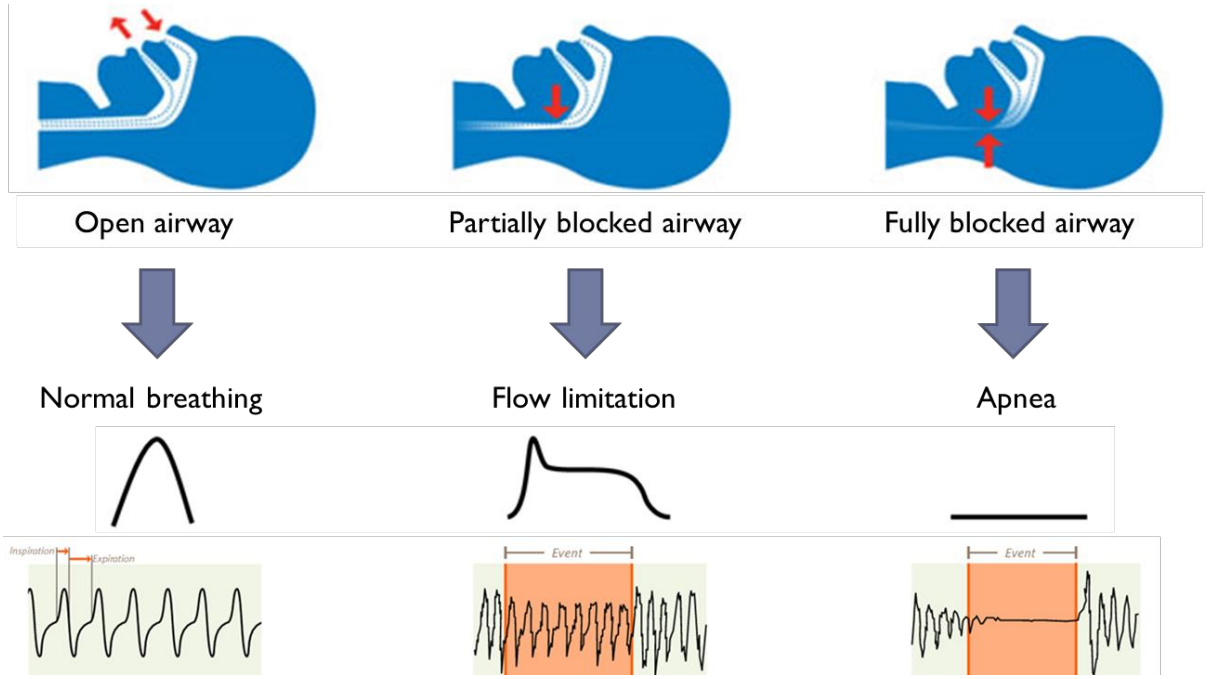

Figure 1. The fundamental of sleep and obstructive sleep apnea

The obstructive sleep apnea syndrome is a severe form of sleep-related breathing disorder disease, which is characterised by repetitive pauses in breathing during sleep (Jordan et al., 2014). In adults with OSAS, the condition is usually caused by the upper airway closure due to the relaxing of the throat and tongue muscle during sleep, or excess tissue resulting from obesity (Jordan et al., 2014). Patients with OSAS show symptoms of choking during sleep, recurrent wakening from sleep, excessive daytime sleepiness and impaired concentration (Fleetham et al., 2006). Evidence suggests an increased risk of fatal cardiovascular events in people who have obstructive sleep apnea (Punjabi, 2008). The number of apnea and hypopnea events occurring during an hour is called apnea and hypopnea index (AHI), which is a key assessment index for the diagnosis of OSAS. Combined with the symptoms, an individual that registers an AHI of five or above is considered as having obstructive sleep

apnea (Fleetham et al., 2006). Here, an obstructive apnea event is defined as airflow reduced to less than 10% of baseline for at least 10 seconds (Berry et al., 2012). An obstructive hypopnea is a clear 50% or more reducing in airflow amplitude that lasts for at least 10 seconds, or a clear decreasing in airflow amplitude with an arousal or least 3% oxygen desaturation following a putative event (Berry et al., 2012).

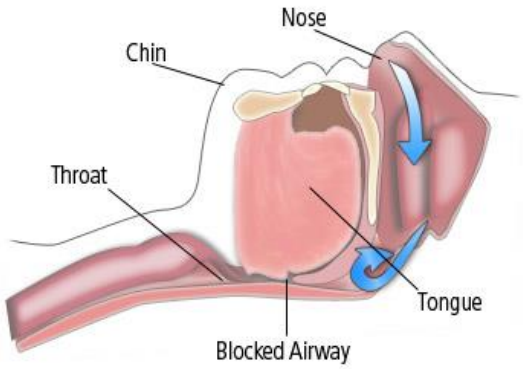

Figure 2. Completely blocked the respiratory upper airway (www.somnologymd.com)

The upper airway resistance syndrome (UARS) (Guilleminault et al., 1993) is defined as a mild level of sleep breathing disturbances. It causes inefficient breathing and increases the effort of breathing. UARS creates abnormal breathing patterns without a decreasing in oxygen saturation level and consists of very short transient arousals, which are not considered in OSAS. It is also known as respiratory effort-related arousal (RERA). UARS was found to be a cause of excessive daytime sleepiness (Guilleminault et al., 1993).

1.2.3 Sleep Disordered Breathing in Children

Similarly, SDB also exists in children. (Guilleminault et al., 1996). In clinical practice, SDB in children have been characterised differently than adults (Marcus, 2001), obstructive respiratory events and arousal are rarer in children because of the development of the body structure and neural control system (Marcus, 2001). In the present clinic scoring rules for

children, apnea and hypopnea are defined as events during which the peak of airflow signal drop at least 90% and 30% away from baseline with duration last at least two respiratory cycles (Berry et al., 2012). Additionally, hypopnea scoring rules require one of the following events also occurs: a more than 3% oxygen desaturation or arousal during the event. RERA is defined if FL occurs and last over two respiratory cycles in children, where FL characterises a flattening inspiratory segment in nasal pressure airflow waveform with snoring or end-tidal PCO_2 related arousal (Berry et al., 2012).

Different from adults, the cause of OSAS in children usually is enlarged tonsils and adenoids, presented in Figure **3**. Large tonsils and adenoids naturally narrow down the upper airway, which reduces airflow. The standard treatment for children with OSAS is called adenotonsillectomy. It is a type of surgery for opening the obstructive upper airway by removing the large tonsils and adenoid tissue. Adenotonsillectomy has been proved that it can significantly improve the initial symptoms. However, residual of the initial symptoms from treatment could have similar symptoms caused by nonstandard breathing pattern (Guilleminault et al., 2004). Current clinical scoring rules disregard nonstandard breathing, such as UARS, the subtle form of the SDB (Guilleminault et al., 2004, Lin and Guilleminault, 2011). Since discrete scored events are less frequent in mild SDB, current clinic marker AHI is not sufficient enough to reflect the complete view of respiratory disturbances. Long-term remaining residual problems, the effects can still be significant, such as long-term learning problems, memory loss, poor growth, and heart-related diseases (Sinha and Guilleminault, 2010).

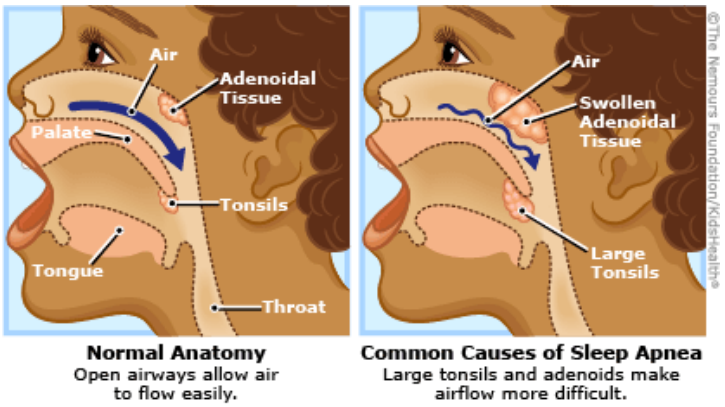

Figure 3. Respiratory upper airway for healthy children (left) and children with OSAS (right) (www.capitaltmjcenter.com, 2015)

The OSAS commonly has severe physiological and psychological impacts on children. Three main categories of resulting disease are generally related to children with OSAS, which are associated with metabolic, neurocognitive, and cardiovascular consequences (Katz and D'Ambrosio, 2010, Marcus et al., 2012). They are directly linked with physical growth, neuropsychological functionalities, and heart health. Many symptoms are related with OSAS in children, including snoring loudly, morning headaches, tiredness after sleeping, excessive sleepiness during the day, poor academic performance, unusual daytime behaviour, Hyperactive (ADHD), etc. (Guilleminault et al., 2005).

1.2.4 Diagnostic tests

Overnight polysomnography (PSG) is the standard test for diagnosing OSAS. The PSG contains multiple bio-physiological signals recorded during sleep. The recording of bio-signals includes heart rhythm (electrocardiography – ECG), blood volume changes (photoplethysmogram – PPG), brain activities (electroencephalography – EEG), skeletal muscle activation (electromyography – EMG), eye movement (electrooculography – EOG), airflow, limb movements, oxygen saturation, chest movement (ribcage), belly movement (abdominal) etc. While current laboratory-based PSG test is considered the gold standard, it

can be burdensome for some patients in its intensity, and associated costs and long waiting times due to the limited facility (Van De Water et al., 2011). By reducing the numbers of recorded signals, it has become a common approach to overcoming the complexity of the laboratory-based PSG test, to make the test more accessible and convenient even in a home setting. (Flemons et al., 2003). So far, there are four different levels of sleep monitoring tests that are commonly used (Collop, 2017, Hamilton and Chai-Coetzer, 2019). Level 1 is the attended in-laboratory PSG test. This type of test records a minimum of seven channels, which requires a technician supervise the device during the test. This level of test is considered as the gold standard for diagnosing sleep apnea. Level 2, 3 and 4 tests use portable devices without technician attend during the test. These tests allow patients to be tested in a home-based environment. Level 2 is the comprehensive portable PSG, which is similar to the level 1 test but in a home environment. However, frequently detached sensor leads often cause data loss since the test is supervised. To simplify the level 2 portable sleep test, the recorded signals are minimised to four for the Level 3 modified portable sleep apnea testing. A common selection of recorded physiological parameters includes two respiratory signals (such as airflow and respiratory effort), a cardiac signal (heart rate/ECG), and oxygen saturation. Since both heart rate and oxygen saturation information can be derived from a pulse oximetry signal, the level 3 test can be simplified even more. Hence, the level 4 sleep test only monitors 1 or 2 channels, such as one respiratory signal and pulse oximetry. While physiological variables currently derived from level 3 and 4 are sufficient to detect respiratory events for OSAS, events related to UARS cannot be detected since EEGs are not included. Although home PSGs are becoming increasingly available, making relevant diagnosis more accessible, and less complicated and cheaper, the reduction of the number of recorded signals compromises the amount of information that can be obtained during sleep. Hence, physiological variables that can be derived from Level 3 and 4 sleep tests, for use as

more effective diagnostic markers for more complete SDB detection still require to be determined.

1.2.5 Research on sleep disordered breathing in children

Research related to sleep-disordered breathing has been conducted for approximately half of the century. In 1966, Gastaut et al. firstly discovered the obstructive sleep apnea associated symptoms in Pickwick syndrome patients (Gastaut et al., 1966). Afterwards, sleep-related studies have been widely conducted. The focus of the OSAS research was on adults at the beginning, until 1976, Guilleminault et al. have shown that the sleep apnea may also exist in children (Guilleminault et al., 1976). Since then, many studies have been conducted on OSAS in children to find out the physiological effects, the diagnosing rules for OSA, and the treatment options. The main recommended treatment is surgical (tonsillectomy and/or adenoidectomy).

Many researchers have reviewed adenotonsillectomy treatment and confirmed that adenotonsillectomy gives physiological improvement by relief of airway obstruction. However, a series of unexpected findings were reported. In 1982, Brouillette et al. discovered that prolonged periods of partial airway obstructive and shorter complete obstructive still exist in most subjects after adenotonsillectomy during sleep (Brouillette et al., 1982).

In the same year, Guilleminault et al. reported a concern with adenotonsillectomy (Guilleminault et al., 1982). The adenotonsillectomy can only be recommended as a treatment if there has a clear clinical evidence of obstructed airway. However, the narrow airway cases were ignored, which cannot be identified as an obstructed airway. Guilleminault and his colleagues highlight that this abnormal airway could cause an increased respiratory

resistive load by increasing endoesophageal pressure, and it could lead to significant impacts on nighttime sleep airflows.

In 1993, Guilleminault et al. defined this abnormal airway related syndrome in terms of UARS. They emphasised UARS is different from OSAS and required specific treatments (Guilleminault et al., 1993).

Two years after, another group, Suen et al. also evaluated the adenotonsillectomy treatment and confirmed the patients showed physiological improvements after the treatment (Suen et al., 1995). However, the respiratory disturbances were not completely eliminated from the surgery. They have noted that the outcome from the adenotonsillectomy is difficult to be predicted based on history and physical findings.

After UARS was recognised, OSAS and UARS have been combined and described as Sleep Disordered Breathing (SDB) to distinguish from other sleep disorder. Although they are different syndromes, they still have similar symptoms and hard to be distinguished (Guilleminault et al., 1996). Besides of the physiological impacts for children with SDB, such as failure to thrive (Guilleminault et al., 1996), it also could cause significant effects on children's school performance, such as poor learning abilities and unusual daytime behavioural (Gozal, 1998).

In 1996, Guilleminault et al. successfully investigated and proved that sleep breathing patterns are associated with sleep events (e.g. Apnea, Hypopnea) (Guilleminault et al., 1996). In the later years (Guilleminault et al., 2004), they also investigated sleep breathing patterns using nasal cannula pressure transducer based on clinical practice suggestion. They have further demonstrated that it is effective by using a breathing pattern to identify a range of breathing abnormalities which associate with apnea and hypopnea, as well as other non-

standard breathing patterns. They also have further proved those non-standard breathing patterns (e.g. flow limitation) other than apnea and hypopnea patterns commonly exist as an incomplete recovery for children with SDB after adenotonsillectomy compared with control children. The clinic PSG scored criteria have been questioned as they overlook those common abnormal breathing patterns. Researchers have suggested that further treatment might be necessary. Although alternative treatments have been recommended, for example, continuous positive airway pressure (CPAP) which is a non-surgical treatment (Marcus, 2001), adenotonsillectomy surgery is still commonly used as a clinical treatment for children with OSAS. However, the initial symptoms are still yet entirely resolved with adenotonsillectomy treatment. While the OSA have been clearly defined with clinic scoring rules, it is still necessary to effectively define the scoring rules related to hypopnea, flow limitation and breathing-related abnormality. The physiological and psychological consequence of other breathing disturbance during sleep is still under investigation. The efficacy of adenotonsillectomy and the clinic soring criteria are continuously evaluated (Marcus et al., 2012).

1.2.6 Monitoring the physiological changes associated with sleep disordered breathing

At the mild end of the sleep disordered breathing spectrum, the lack of discrete events could limit the true reflection of the physiology changes caused by breathing abnormalities by the AHI. The body experiences a variety of physiological changes during SDB, especially affecting respiration and autonomic nervous systems.

Respiration

Respiration is the process of body exchange gas with the outside environment. During inspiration, oxygen is inhaled into the lung to alveolus and exchange with carbon-dioxide

carried by blood capillary around each alveolus. A high concentration of oxygen contained in the blood when it leaves the hung and delivered to every cell in the body, meanwhile the exchanged carbon-dioxide is exhaled out of the system during expiration. The crucial biochemical process of respiration is to produce energy for the body, and it happens down in the cell level. In each cell, the oxygen will react with glucose and produce carbon dioxide, water and energy in form of adenosine triphosphate (ATP) (Hlastala and Berger, 2001). Abnormal breathing would cause the gas exchange to become inefficient, and this would result in a lack of oxygen and carbon dioxide would build up in the body. A low level of oxygen in the bloodstream would affect the process to produce sufficient energy for the cell. Furthermore, a high level of carbon-dioxide would decrease oxygen consumption and production of ATP. It would cause mitochondrial dysfunction in the cells (Vohwinkel et al., 2011) and eventually harm organs. Serious consequences, such as coma or death, would happen if an extreme level was reached. Therefore, respiratory ventilation is the most direct measurement in assessing breathing related disturbances. Airflow and thoracoabdominal movements are commonly used to measure respiration.

Airflow

Measurement of airflow is a direct indicator of gas exchange from respiration. There are two typical ways of measuring airflow, one is using thermal sensors (e.g. thermistor), and another is using air pressure sensors (e.g. cannula pressure transducer system). Thermal sensors measure the temperature change in airflow exchange during respiration to indicate airflow. Air pressure sensors measure the air pressure fluctuations associated with inhalation and exhalation airflow.

In the early studies, as breathing related abnormality is directly related to breathing airflow, the thermistor is used as a common tool for monitoring and assessing breathing related

disorder (Farre et al., 1998), because the thermistor is sensitive to absence of airflow, e.g. during apnea (Gehring et al., 2014). However, it is less suitable for detecting partial airflow, e.g. during hypopnea (Gehring et al., 2014, Flemons et al., 2003), and it is worse for UARS events detection, because it does not respond linearly to actual airflow (Rapoport et al., 2001, Flemons et al., 2003, Gehring et al., 2014, Farre et al., 1998).

Guilleminault et al. proposed the use of esophageal pressure recordings for recognising UARS and were able to distinguish it from OSAS (Guilleminault et al., 1996). They have shown that esophageal pressure traces can effectively recognise clinic defined sleep events, which include apnea and hypopnea, as well as upper airway resistance events. It was recommended for analysing abnormal breathing patterns during sleep and later was used as the gold standard (Montserrat and Badia, 1999). However, this invasive measurement method is hard to tolerate for patients, especially for children. In the meantime, the non-invasive method nasal cannula pressure transducer system was mentioned as an alternative tool for characterising SDB (Montserrat and Badia, 1999). Later on, it was demonstrated that nasal cannula pressure transducer system can be used to detecting all sleep events including UARS events, which gives same or better results as esophageal pressure signal (Ayappa et al., 2000, Hernández et al., 2001, Serebrisky et al., 2002, Hosselet et al., 1998). These studies proved a nasal cannula pressure transducer system provides more premising diagnosing results compare to thermistors. Nevertheless, many patients with the mild severity of OSAS are less likely to tolerate CAPA due to discomfort(Janson et al., 2000). While other believe there is not a single reason for a high non-adherence rate of patients on CPAP treatment, and it is more likely depend on the day time symptoms and performance (Weaver and Grunstein, 2008).

Thoracoabdominal movement

Beside of airflow, thoracoabdominal movements are more easily measured and commonly used, which contains ribcage and abdominal signal. During normal breathing, ribcage and abdomen should expand or contract in the same direction simultaneously, which gives a baseline of the ribcage and abdominal breathing signal pattern. However, when abnormal breathing happens, the amplitude of ribcage and abdominal signals would reduce significantly, or thoracoabdominal paradox would occur. Here, thoracoabdominal paradox means that the ribcage and abdominal signals are out of phase due to asynchrony movements (Berry et al., 2012).

Two ways of using these measurements are often applied to detect breathing abnormality in clinic practice. One is the sum of thoracoabdominal movements by assessing the relevant amplitude difference of two signals compare to baseline. Another is thoracoabdominal asynchrony by evaluating the phase difference between two signals (Berry et al., 2012).

Sum of thoracoabdominal movements is also recommended for sleep breathing abnormality detection, especially for UARS, instead of using esophageal pressure signal (Montserrat and Badia, 1999, Masa et al., 2003). While sum of thoracoabdominal movements can detect apnea and hypopnea, the central or obstructive events cannot be distinguished.

Alternatively, studies have shown thoracoabdominal asynchrony can be used for measuring both server and subtle upper airway obstruction (Sivan and Newth, 1990, Immanuel et al., 2014). Although thoracoabdominal movement measurements have used for apnea and hypopnea detection in the currently defined clinic scoring rule (Berry et al., 2012), they still have not been included in RERA detection rules.

Autonomic nervous system

When the body perceives stress or danger, unconsciously amygdala sends a signal to the hypothalamus to release corticotropin releasing hormone (CRH), which triggers the pituitary gland to release adrenocorticotropic hormone (ACTH). Adrenal glands will respond to this hormone by release more adrenaline in the blood. Adrenaline will cause numbers of physical changes, which include increased heart rate, breathing and blood pressure. These series of responses are mediated by sympathetic nervous system activation, which is a part of the autonomic nervous system. When the body experiences upper airway obstruction during sleep, negative intrathoracic pressure increases, this results in stimulated baroreceptors and increases sympathetic tone (Miglis, 2016). Studies showed the autonomic system become abnormal in children with disordered breathing during sleep (Walter et al., 2013, Nisbet et al., 2013, Liao et al., 2010, Kwok et al., 2008) and daytime (O'Brien and Gozal, 2005). Increase of autonomic activation has been identified as an important cause of cardiovascular abnormalities in children with OSAS (Ng et al., 2005, Montesano et al., 2010). Although cortical activation is included in the current scoring manual by scoring the arousals using EEG signal, cortical activation is less frequent and shorter in children during sleep compared to adults. Alternatives measurement, such as autonomic activation, were recommended for improving the scoring for arousal in children (Paruthi and Chervin, 2010). ECG and PPG signals are commonly used to extract autonomic activation, by measuring the altered heart period (HP), pulse wave amplitude (PWA) or pulse transit time (PTT) (Alian and Shelley, 2014, Allen, 2007, Catcheside et al., 2001, Pitson, 1998).

Heart rate variability

The timing of every beat adjusts based on the demand of the body responds to the change in the environment. The variation of the heart beat to beat interval is a good reflector of the

autonomic activities (Berntson et al., 1997). However, conflicting findings are reported in the literature about how cardiac autonomic control changes in children with OSAS by measuring heart rate variability. In an early study with a small dataset, children with OSAS had dysfunctional cardiovascular and autonomic activities. A variation change in heart rate variability (HRV) was found based on the different heart rate interval dispersion in children with OSA during events include sleep data, an increased HRV found at lower heart rate intervals, vice versa, a decreased HRV found at higher heart rate intervals (Aljadeff et al., 1997). On the one hand, children with OSAS were shown to have a lower HRV compared to controls and demonstrated reduction in HRV that may indicate an increased sympathetic or decreased parasympathetic activities during wakefulness (Montesano et al., 2010) and event-free sleep (Liao et al., 2010). While others showed prolonged heart rate delay in response to increased blood pressure variability and this suggests the increased sympathetic and decreased parasympathetic activities (Walter et al., 2013). An early study based on frequency analysis of HRV in children with OSAS demonstrated the increased power in lower frequency HRV in children with OSAS through all sleep stages and even during awake at the beginning of the study than control subjects. Their finding suggested an enhanced sympathetic activity in those children with OSAS (Baharav et al., 1999). Conversely, Lauren C. Nisbet et al. have shown evidence of increased power in the high frequency band of HRV and a lower sympathovagal balance in moderate to severe OSAS children during both events included and event-free sleep. In that study, a lower sympathovagal balance was calculated using the power ratio of between HRV low-frequency bands and high-frequency bands (Nisbet et al., 2013).

Pulse Wave Amplitude

PWA provides alternative non-invasive measures of cardiovascular response to cortical and subcortical activation (Nisbet et al., 2014, Catcheside et al., 2001, Allen, 2007). Pulse wave amplitude measures the amplitude difference between the peak and the nadir of each pulse from PPG signal. Activation of the sympathetic nervous system causes peripheral vasoconstriction changes after body experience subcortical arousal, which reflects in attenuated PWA (Nisbet et al., 2014, Alian and Shelley, 2014). Partial upper airway obstructions would create stress in the system, autonomic reaction kicks in increases heart rate and blood pressure, blood vessel contracted cause less amount but fast of blood flow to the finger, and hence heart period and PWA decreases (Grote et al., 2003). The body responds differently to different stressors, even HP and PWA all have a consistent response to arousal (Catcheside et al., 2001). For example, after either normoxic or hypoxic type of events, PWA drops below the baseline and then recovers itself gradually. However, normoxic events followed by an oscillatory type of pattern is observed in heart rate during its recovering, but not the same for hypoxic events. Studies have shown the benefit of using PWA to be the marker of respiratory related autonomic activation and as a cheap and accessible alternative of PSG (Delessert et al., 2010, Janssens et al., 2011, Grote et al., 2003, Ramirez et al., 2013), but not much data exist on children.

Pulse Transient Time

Another alternative non-invasive measurement that extracted from PPG signal is pulse transient time (PTT). It measures the estimated time delay for a pulse travels from the aortic valve to the peripheral site (Mukkamala et al., 2015). Also, studies suggest that PTT can be used as a surrogate indicator of measuring blood pressure (BP) and has an inverse relation with BP (Smith et al., 2018). While PTT was shown a sensitive indicator of OSAS events and

arousals in children, it was still limited to use to distinguishing mild SDB from primary snoring (Smith et al., 2018).

From the previous literature review, it could be established that there are no well-established methods/rules for scoring more general breathing abnormalities. The effect of the adenotonsillectomy treatment on pathophysiological changes in inspiratory effort and autonomic activation in children with SDB are unclear. It is necessary to create more effective and reliable physiological markers that are applicable to children for detecting and monitoring a subtler version of abnormal breathing events, using non-invasive signals.

1.3 Open Questions to Address

- Does adenotonsillectomy normalise thoracoabdominal asynchrony children with OSAS?
- Does upper airway obstruction affect autonomic activation in children with sleep disordered breathing compared with normal children?
- Do children benefit from adenotonsillectomy by reducing the OSAS caused autonomic activation?
- Are thoracoabdominal asynchrony and autonomic activation similar in different sleep stages?
- Instead of only using AHI, can it combine with multiple other non-invasive measurements (thoracoabdominal signals or pulse signal) use for a more accurate SDB diagnose?

1.4 Data

Two clinical research study datasets were used for all the analyses in this thesis.

The CHAT study dataset

The Childhood Adenotonsillectomy Trial (CHAT) (Marcus et al., 2013) data will be used for the studies presented in this thesis. CHAT study is a randomized controlled trial for evaluating the childhood adenotonsillectomy treatment for childhood OSAS by randomly assigned the participants into early adenotonsillectomy group or a strategy of the watchful waiting group, then followed up after seven months as a comparison. Total of 453 children successful participate in CHAT study and provides 453 baseline PSG recordings and 407 follow up PSG recordings. Manual scoring results for each of the recordings using the Profusion system from CHAT study will use as a reference for developing new algorithms in this thesis. Besides of PSG recordings, the following neurophysiological outcomes that measured as part of the CHAT study were included in the analysis:

1) Behaviour, by the parent rating on the *Conners' Parent Rating Scale-Revised: Long version Global Index* (CGI T score), a two-factor score comprising the Restless Impulsive and Emotional-Lability factor sets, and by the *Behaviour Rating Inventory of Executive Function (BRIEF) Global Executive Composite (GEC)* T score, comprising summary measures of behavioural regulation and metacognition. Teacher ratings from parallel instruments (the CGI short version and BRIEF Teacher Report Form) were also evaluated.

2) Symptoms of OSAS, by the total score of the *Paediatric Sleep Questionnaire (PSQ), Sleep-Related Breathing Disorder Scale (SRBD)*.

3) Sleepiness, the *Epworth Sleepiness Scale* modified for children.

4) Global quality of life, by the parental total score from the *Paediatric Quality of Life Inventory (PedsQL)*, and disease-specific quality of life, assessed by the total score of the *OSA-18*, a composite of OSAS-related symptoms and quality of life.

5. The *Differential Ability Scales II (DAS)*, a measure of generalised intellectual functioning.

Adelaide Women's and Children's Hospital Study Dataset

The additional existing dataset is provided by Adelaide Women's and Children's Hospital in Australia is also used for validation. The detail of the dataset can be found in a previously published study (Immanuel et al., 2014). Briefly, there is a total of 80 children participated in the study, which includes a group of 40 children with a history of frequent snoring and a matched group of 40 non-snoring healthy children. The frequent snoring children were suspected of having upper airway obstruction and waiting for adenotonsillectomy. Overnight PSGs were recorded before and six months after AT. The healthy control group also underwent sleep studies at similar time points. Participants were screened to ensure they had not previously undergone ear, nose, throat or craniofacial surgery, or had a medical condition (other than upper airway obstruction) associated with hypoxia or sleep fragmentation or were taking medication known to affect sleep or cardiorespiratory physiology.

1.5 Statement of Original Contribution

A total of five academic peer-reviewed papers were prepared from the studies conducted towards this thesis, which are four original journal articles in Chapters 3 to 6 and one conference paper in Appendices A. The engineering methods and frameworks employed in each study were developed solely by the author using MATLAB. Additionally, formulated

the hypothesis, developed appropriate research methodology and analysis to test the hypothesis in each study were the original contributions of the author.

Chapter 2
Biomedical Signal Processing Methods

This chapter gives descriptions of all signal processing methods that have been developed and applied to the clinical research studies present in this thesis. This chapter contains four main sections, including: (1) measuring of thoraco-abdominal asynchrony; (2) measuring of pulse wave amplitude; and (3) physiological signal dynamic analysis

2.1 Measuring of thoraco-abdominal asynchrony

In this section, the detail of TAA estimation using the Hilbert Transform and related framework are described. Pre and post processing are required before applying the Hilbert transform for the TAA estimation to obtain reliable TAA.

2.1.1 TAA estimation using Hilbert Transform

The Hilbert transform creates analytic signals of the ribcage and abdominal ($\zeta_1(t), \zeta_2(t)$) that allow calculating of the instantaneous phase. The analytic signal of $x(t)$ is

$$\zeta(t) = x(t) + j\tilde{x}(t) = Ae^{i\varphi(t)}, \tag{1}$$

where $\tilde{x}(t)$ is the Hilbert transform of $x(t)$, which is $x(t)$ with a 90° phase shift, A and φ are the instantaneous amplitude and phase of the analytic signal.

The phase of the analytic signal is:

$$\varphi(t) = \arctan\left(\frac{\tilde{x}(t)}{x(t)}\right) \tag{2}$$

Hence, the relative phase difference between two signals is obtained as follows:

$$\varphi_1(t) - \varphi_2(t) = \arctan\left[\frac{x_1(t)\,\tilde{x}_2(t) - x_2(t)\,\tilde{x}_1(t)}{x_1(t)\,x_2(t) + \tilde{x}_1(t)\,\tilde{x}_2(t)}\right]. \tag{3}$$

In my study the Matlab "hilbter.m" from signal processing toolbox is used to produce the analytic signal of the discrete time signal $x[n]$. An example of outcomes of estimated TAA are shown below in Figure 4.

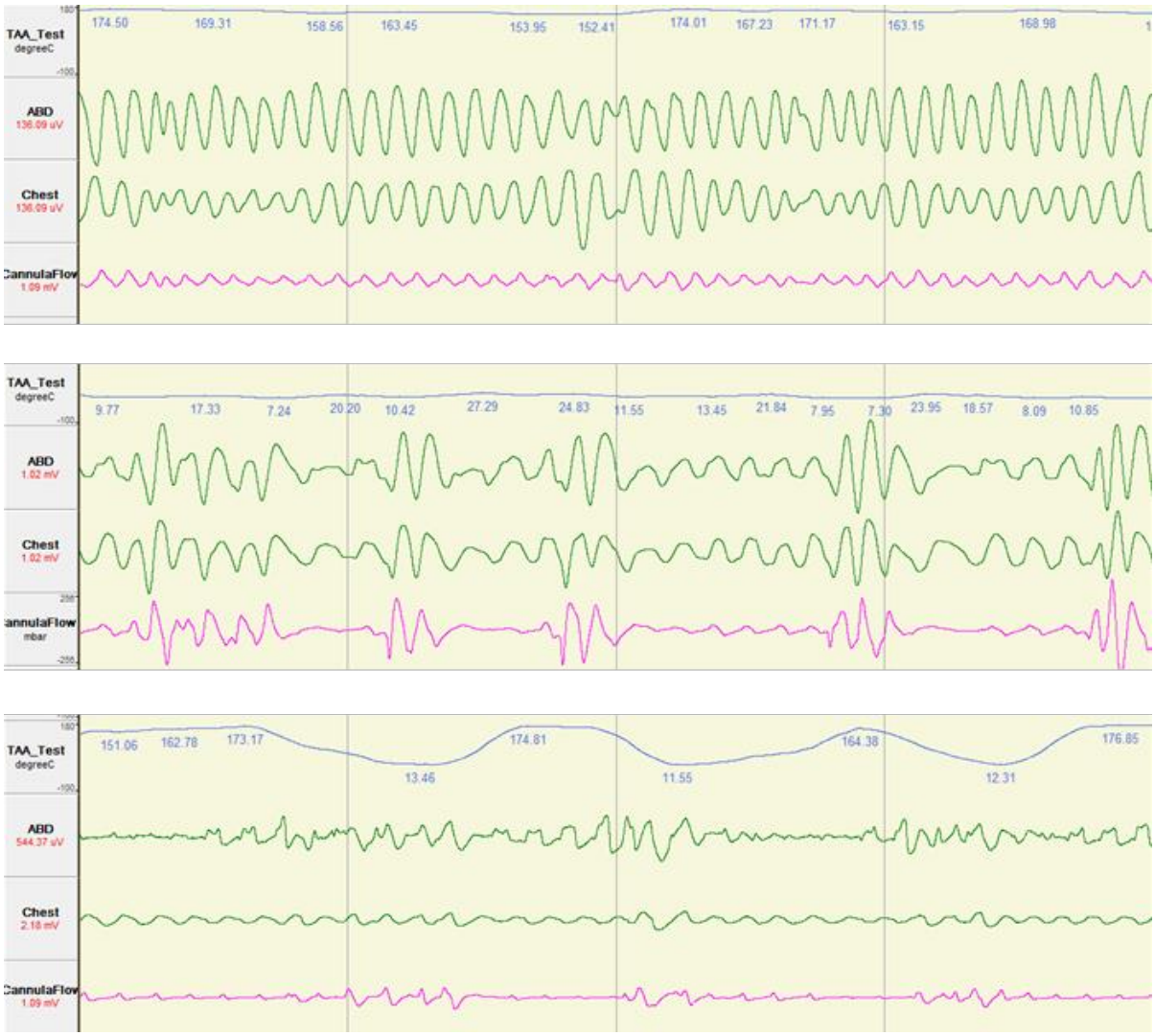

Figure 4. Illustration of TAA estimation plots for four epochs (30 seconds/epoch) in three different cases: normal breathing (top), central disordered breathing (centre), and obstructive disordered breathing (bottom). Measurement colour representation: blue – TAA estimation in degree; green – abdominal and chest movement signals in mV; and magenta – cannular flow signal in mV

2.1.2 Framework for TAA estimation

The framework flow chart for applying above method for discrete TAA estimation is shown in Appendix B.

PSG recordings of ribcage (RC) abdominal (ABD) inductance belts were considered for analysis in this study. In the pre-processing stage, both signals are filtered with a finite impulse response bandpass filter (0.1 - 5 Hz) with a filter length *M* that is 5 times the average human breathing period (average of 10 and 60 breaths per minute), and filter order as *M* if the *M* is odd or *M*-1 if *M* is even. Instantaneous TAA was computed within a window slide throughout the recording. The length of the sliding window was set to 3 times the average respiratory period, which was calculated from the fundamental frequencies of the RC and ABD signals that were estimated from the entire recordings using the Welch power spectral density estimation method with 50% of window overlap. The step size of the sliding window was set to a quarter of the average respiratory period.

TAA was calculated by applying the Hilbert transform to the RC and ABD signals $(x_1(t), x_2(t))$ contained in the sliding window, after subjecting both signals to a frequency selective filter that was set to the fundamental frequency. The fundamental frequencies from both RC and ABD window signals are estimated using the Welch power spectral density estimation method. Due to technical recording issues, some recording signal segments contain high energy at its second harmonic frequency. To accurately estimate the fundamental frequency for the signal, the algorithm classifies each window signal into different cases at frequency per-defining stage. If any signal has high energy at its second harmonic frequency, it is necessary to compare between the first two harmonics of two signals and define the most meaningful frequencies pair, since the signal frequencies of two signals are expected to be same/similar (defined as ± 20% difference in frequency).

Each calculated TAA value was subsequently automatically checked for validity and excluded if:

1) Signals were noisy (defined as the ratio of spectral power within the frequency band of interest to total power < 0.65),
2) Breathing frequencies lie outside the physiological range for children (i.e. 0.12 - 0.585 Hz or, respectively, 7.2 - 35.1 breaths/min),
3) Disparity between RC and ABD fundamental frequencies (defined by a difference > 20%)

Importantly, episodes of discretely scored respiratory events (e.g. apnea and hypopnea) were also excluded from the clinical research study shown in Chapter 3. All TAA results, therefore, represent periods of breathing that were free of frank respiratory events.

2.2 Measuring of Pulse Wave Amplitude

In this section, two methods are developed for measuring PWA. The first method introduced below is a conventional approach, which is a beat-to-beat PWA measurement. Every PWA is measured between every two consecutive heartbeats. The second method is a simplified way to estimate a continuous PWA using an envelope extraction of the finger photoplethysmogram.

2.2.1 Beat to beat pulse wave amplitude measurement

The PWA was measured for each cardiac cycle as the amplitude difference between the systolic peak and the preceding diastolic valley of the PPG signal. PWA values were calculated only if a valid pulse waveform could be identified within the time frame defined by concurrent QRS complexes in ECG.

Systolic peaks and diastolic valleys were located after filtering the photoplethysmogram (500^{th} order FIR bandpass filter from 1 to 10 Hz). A systolic peak was considered valid, if (a) it occurred > 50 ms after a detected diastolic valley and (b) had an amplitude difference between systolic peak and diastolic valley > 50% of the difference between maximum and minimum value of the photoplethysmogram segment defined by two consecutive R peaks in ECG (Figure 5).

Occasionally, the systolic peak or diastolic valley were not detectable within segment spanned by two consecutive R peaks, because the R peak occurred at, or slightly after, the diastolic valley, or the subsequent R peak was located slightly before the systolic peak. To maximise available pulse data for PWA calculation in those instances, systolic peaks or diastolic valleys were estimated based on the gradient of the filtered photoplethysmogram

segment. More specifically, the diastolic valley was estimated as the minimum gradient obtained between the start of the segment and the maximum gradient found before the systolic peak. To be valid, the minimum gradient had to be ≤ 0.1 % of the difference between the max and min of the filtered plethysmography signal segment. Likewise, systolic peaks were estimated at the minimum gradient from the maximum gradient found after the diastolic valley to the end of the segment.

Once both peak and valley were identified and met the criteria for a valid pulse, the pulse wave amplitude was calculated using the original, unfiltered plethysmography signal. In the event no valid pulse waveform could be detected the corresponding PWA was blanked. As PPG was recorded in arbitrary units, PWA time series were normalized to zero mean and unit variance prior to further analysis. Additionally, PWA time series were smoothed using a moving averaging window with a length of 11 heartbeats, to reduce the effect of respiratory modulation of PWA while maintaining the effect of autonomic vasomotor tone variations.

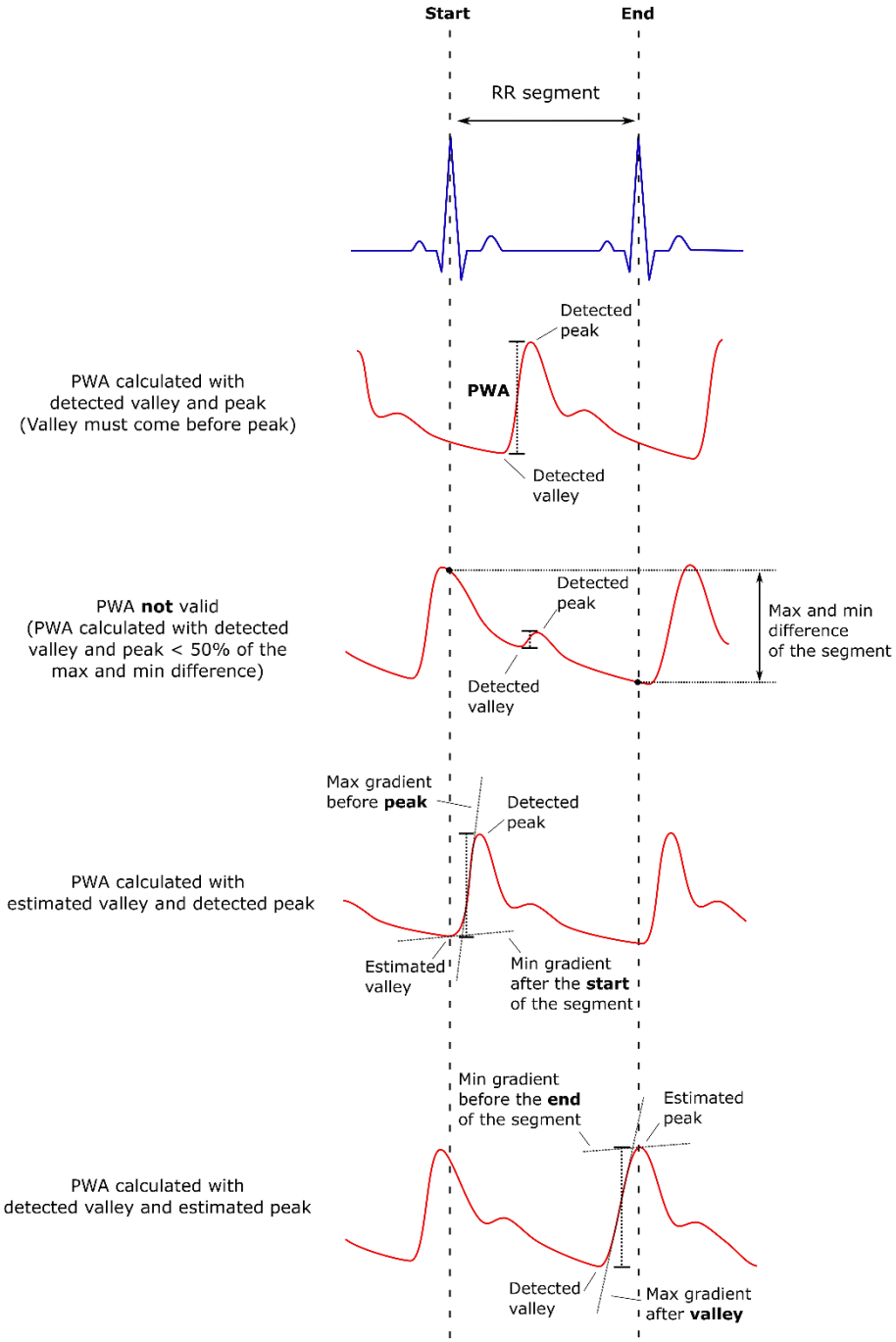

Figure 5: Schematic illustration of the Pulse wave amplitude detection algorithm.

2.2.2 Continuous PWA estimation using a simple envelope method

As PWA was defined as the pulse amplitude difference between a systolic peak to its following diastolic valley in each cardiac cycle, PWA is extracted from a figure PPG signal. To extract PWA, PPG can be filtered with a 500th order bandpass FIR filter with cut-off from 1 to 10 Hz. If the PPG sampling rate is too high, the PPG signal can be down sampled to 100 Hz to reduce the computational time. Since the PWA is a discrete measurement with one value per heartbeat, continuous PWA measurement can be obtained by applying interpolation. A simple method to estimate continuous PWA involves estimating the difference between the upper and lower peak envelopes of the pulse signal, an example shown in Figure 6. The envelope function of Matlab® 2018b is used for this estimation. The envelope is determined using spline, interpolation over local peaks separated by at least 50 samples, which are half of the signal sampling rate. The estimated PWA signal is filtered with a 0.1 Hz (about 6 breath/min) low pass FIR filter, to remove the respiratory modulation. All results are normalized by removing the mean and then divided by its standard deviation.

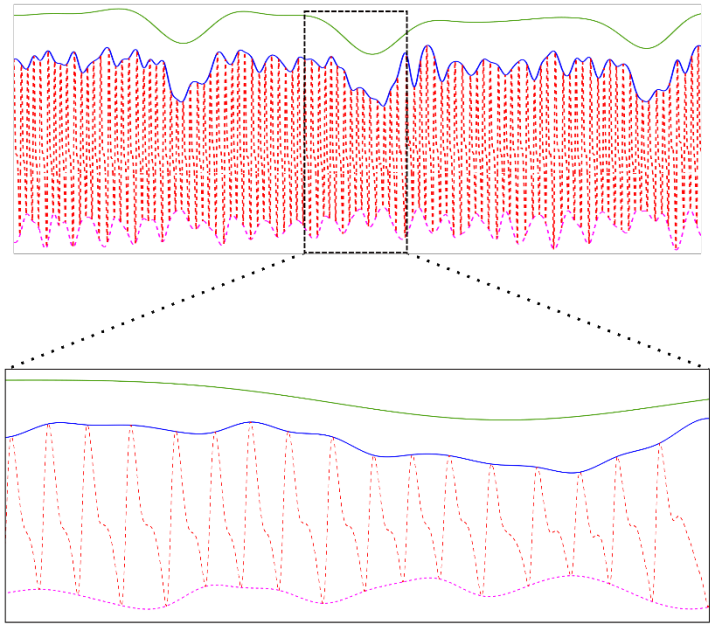

Figure 6. Illustration of PWA estimation and a zoomed in section. Measurement colour representation: green – estimated normalised PWA; blue – upper envelope of PPG; red – PPG; and magenta – lower envelope of PPG

2.3 Analysis of Physiological Signal Dynamics

In nature, a complex physiological system is often affected by many factors or variables that might be unknown, so the system is most likely nonlinear, nonstationary and noisy. As the system may seem chaotic, it is usually challenging to characterise it with linear models. Even though some systems can be described with nonlinear models, they are still difficult to solve most of the time. This section describes two main developed methods for analysing the dynamics of the cardiac system. One of which is symbolic dynamic analysis, which is a model-free approach to understand the behaviours and structure of a complex system (Porta et al., 2015). Instead of predicting the actual output of the system, the symbolic approach provides a way to predict system states and their relationships that are associated with system behaviours. By defining some conditions/thresholds, the system outcomes can be divided into a fixed number of states, which can be represented by a group of abstract symbols. The symbolic analysis merely encodes every sample into one of the defined abstract symbols and disregards unessential detailed information, which minimises the effect of the noise in the system. For an ordinary dynamic system, the system would produce symbolic trajectories that consist of symbol sequences with a fixed length from one symbol to another. A frequently appearing trajectory is considered a symbolic pattern, which likely indicates a particular state of the system. A state of the system could be closely linked with a particular system behaviour, which can be identified by analysing the pattern rate of a particular symbolic sequence. Hence, by observing the system change from one symbolic pattern to another, changes in the dynamics/behaviour of a complex nonlinear system can be understood without a model. However, since the symbolic dynamics cannot capture detailed information, the intensity level of the changes in the extracted patterns is unknown. Alternatively, a more

extensive method has been developed to capture the entire dynamic in terms of both depth and duration in my study.

2.3.1 Symbolic dynamic analysis

Symbolic dynamic analysis on Heart period

Heartbeat locations were extracted from ECG. The temporal distance between heartbeat locations yields a beat-to-beat time series of heart period (HP). Heart period changes were transformed into a sequence of symbols {0, 1 and 2} that represent coarse-grained heart rate dynamics (Figure 7). We used a symbolization scheme that proved effective in earlier studies (Baumert et al., 2015), where symbols are assigned based on the following rules:

$$s_n = \begin{cases} 0 : (x_n - x_{n-1}) > l_x \\ 1 : \ (x_n - x_{n-1}) < -l_x \\ 2 : Otherwise \end{cases}, \quad (1)$$

Where s_n is the n^{th} symbol in the beat to beat time series, x_n represents the n^{th} heart period in the beat to beat time series, x_{n-1} the preceding heart period, and l_x is a pre-defined non-negative threshold. In other words, symbol 0 represents an increase in heart period between consecutive beats beyond the threshold, while symbol 1 indicates a decrease in heart period and symbol 2 represents changes less or equal to the threshold. From the resulting symbols sequences series, 'words' comprising three consecutive symbols were constructed using a sliding window approach (the window slides only by one symbol to the right at each step).

The relative frequency of word types 000 and 111 was considered for further analysis, indicating the steady increase and decrease in heart period, respectively over four consecutive heartbeats.

Based on the results of a previous study investigating its ability for differentiating heart rate dynamics in children with sleep disordered breathing and normal children, we set l_x = 0 ms (Liu et al., 2018). This threshold showed the best performance when using either entire PSG data as well as PSG segments free from discretely scored respiratory or motor events (e.g. apnoea, hypopnoea, arousal, limb movement, etc.).

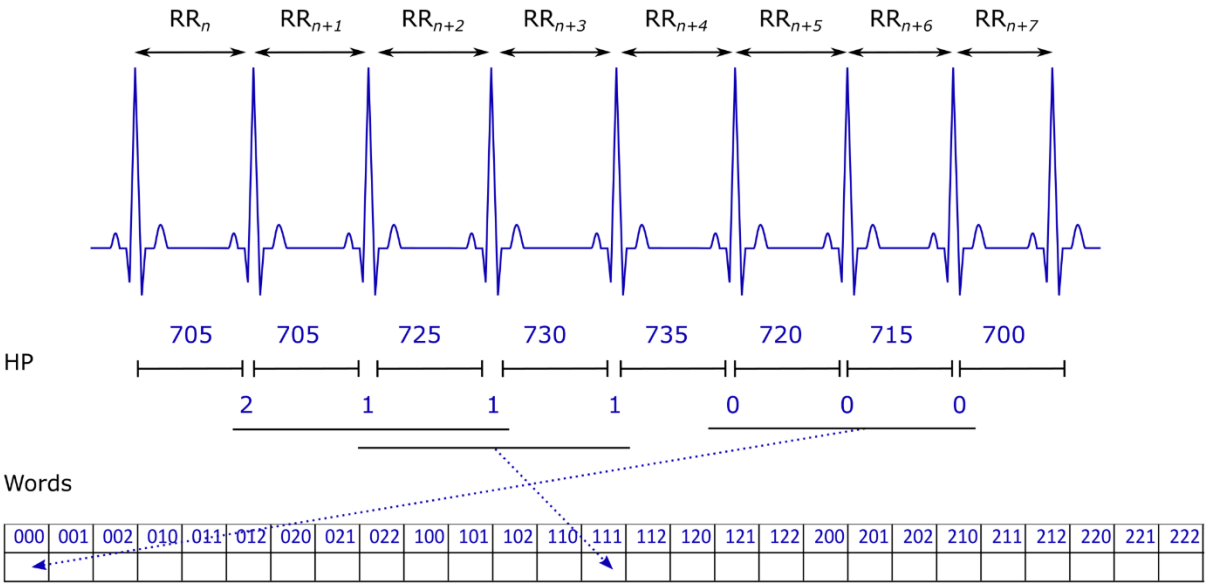

Figure 7. Schematic illustration of symbolic analysis of heart period (RR) patterns.

Joint Symbolic dynamic analysis on pulse wave amplitude and heart period

When observed in HP, these symbolic patterns may capture cyclic bradycardia-tachycardia sequences associated with obstructive apnea (Guilleminault et al., 1984). While in PWA, they capture tonic vasoconstrictions mediated by sympathetic activation due to cortical and/or subcortical arousal (Grote et al., 2003). We also considered the joint occurrence of these patterns in both PWA and HP as an additional marker of monotonic changes. By applying the same method to both PWA and HP to find out their joint dynamics. Since the word length is 3 and each symbol is taken from an alphabet of three the total number of possible word types (e.g. 020, 001, 201, …) is 27 ($3^3 = 27$), shown in Figure 8. The relative frequency of words 000 and 111, quantifying the presence of monotonous increase and decrease of PWA or HP, was used as a novel marker of autonomic activation during sleep.

Suitable values for the threshold l_x were identified by systematically investigating its ability for differentiating HP and PWA dynamics in children with upper airway obstruction (UAO) and non-snoring children, yielding suitable values of 0 milliseconds for HP and 0 normalise units for PWA respectively.

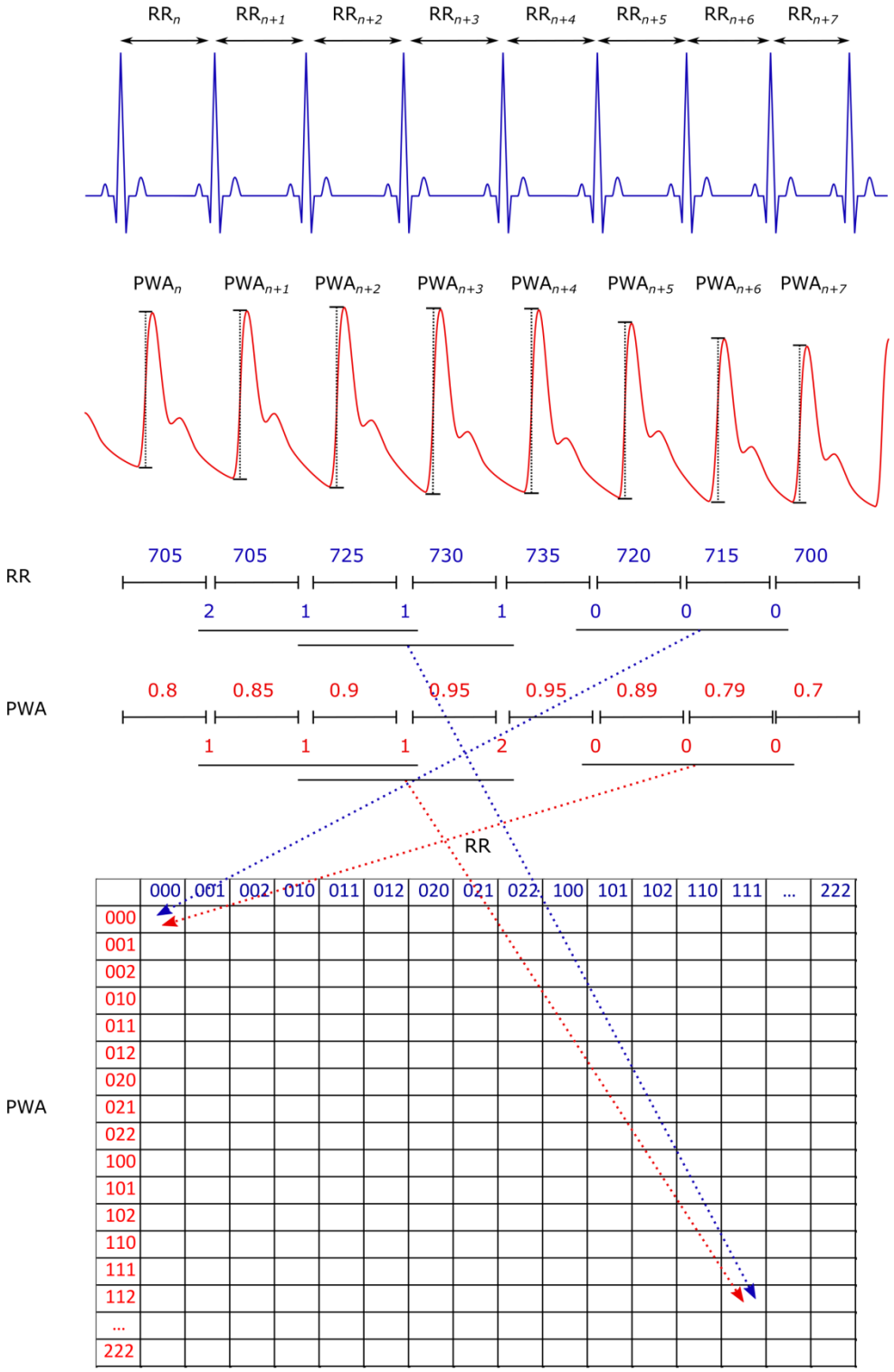

Figure 8. Schematic illustrating the analysis of symbolic dynamics of heart period (RR) and pulse wave amplitude (PWA). Joint symbolic dynamics are captured in the diagonals of the word type distribution matrix.

2.3.2 Extensive dynamic analysis

In order to capture all the detailed information in the system, an extensive dynamic analysis has been developed. The continuously dropping or rising PWA trends were detected based on slopes between every two samples. Continuous series of non-positive slopes were considered as a dropping trend, vice versa, continuous series of non-negative slops were considered as a rising trend. For every detected trend, the depth and duration of the trend were recorded. Dropping and rising trends have negative and positive depths in the normalized unit respectively. The duration of each trend was recorded in seconds. PWA dynamics were assessed by capturing the depth and duration of each drop and rise in this measurement. A PWA histogram matrix of dropping and rising trends was created for this analysis (Figure **9**). The matrix was 121 in depths by 201 in durations and created for visualizing the distribution of depths and durations of the trends. The bin width of the depths was set as 0.05 in normalized amplitude from the range -3 to 3, and the bin width of the durations were set to be 0.1 seconds from 0 to 20 seconds.

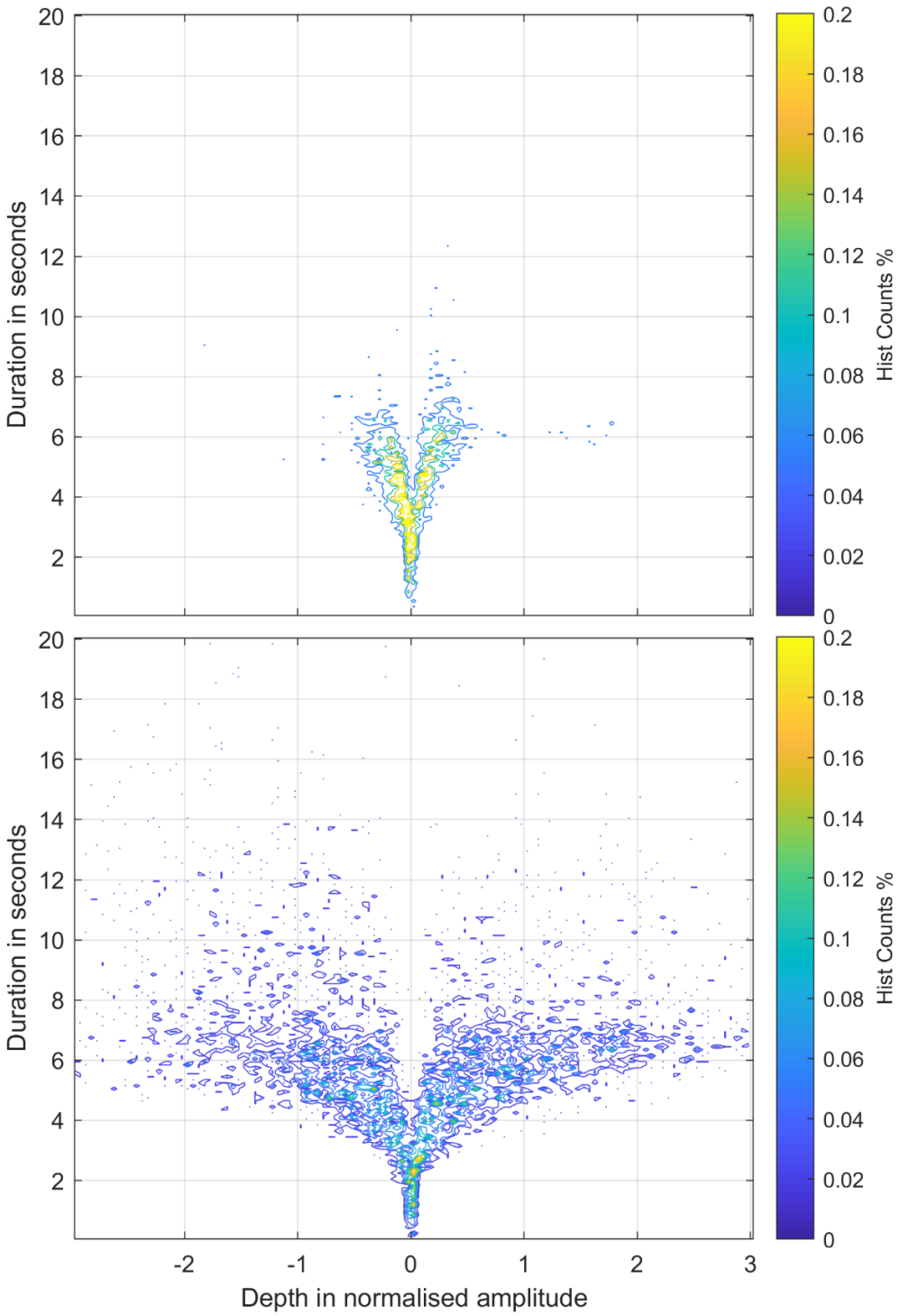

Figure 9. PWA dynamics – examples of dropping and rising trends distribution in contour plots of one normal child (top) and one child with SDB (bottom). Positive depth refers to rising trends, vice versa, negative refers to dropping trends. The colour bar indicates the percentage of the counts out of all trends in a particular range of depth and duration combination

Chapter 3

Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea–hypopnoea index normalisation does not

LIU, X., IMMANUEL, S., PAMULA, Y., KENNEDY, D., MARTIN, J. & BAUMERT, M. 2017. Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea−hypopnoea index normalisation does not. European Respiratory Journal, 49. DOI: 10.1183/13993003.01177-2016

Statement of Authorship

Title of Paper	Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea–hypopnoea index normalisation does not
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	LIU, X., IMMANUEL, S., PAMULA, Y., KENNEDY, D., MARTIN, J. & BAUMERT, M. 2017. Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea–hypopnoea index normalisation does not. European Respiratory Journal, 49. DOI: 10.1183/13993003.01177-2016

Principal Author

Name of Principal Author (Candidate)	Xiao LIU		
Contribution to the Paper	Conception, design, analysis and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	31/05/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Data Analysis, interpretation of results and version of the manuscript.		
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Contribution to the Paper	Interpretation of results and critical revision of the manuscript.		
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Contribution to the Paper	Conception, design and interpretation of results, preparation and critical revision of the manuscript.		
Signature		Date	31/5/19

Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea–hypopnoea index normalisation does not

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Adenotonsillectomy for childhood obstructive sleep apnoea reduces respiratory effort during sleep
http://ow.ly/TJcx304lKdm

Cite this article as: Liu X, Immanuel S, Pamula Y, *et al*. Adenotonsillectomy for childhood obstructive sleep apnoea reduces thoraco-abdominal asynchrony but spontaneous apnoea–hypopnoea index normalisation does not. *Eur Respir J* 2017; 49: 1601177 [https://doi.org/10.1183/13993003.01177-2016].

ABSTRACT The efficacy of adenotonsillectomy for treating obstructive sleep apnoea syndrome (OSAS) in children has been established, but its precise effects on inspiratory effort are not well documented.

In 353 children enrolled in the Childhood Adenotonsillectomy Trial, randomised to undergo either early adenotonsillectomy (n=182) or a strategy of watchful waiting with supportive care (WWSC) (n=171), thoraco-abdominal asynchrony (TAA) was analysed during quiet, non-apnoeic and non-hypopnoeic breathing during sleep at baseline and at 7 months using overnight polysomnography.

Children who underwent early adenotonsillectomy demonstrated a reduction in TAA post-surgery while the WWSC arm showed no change. On assessing TAA with regard to normalisation of clinical polysomnography findings at follow-up, TAA was reduced in children who had surgical resolution of OSAS (based on apnoea–hypopnoea index), but not in children who displayed spontaneous normalisation of apnoea–hypopnoea index. In the latter group, TAA was inversely correlated with quality of life.

We conclude that adenotonsillectomy reduces TAA during quiet sleep. Monitoring of instantaneous TAA may yield additional insight in the dynamic changes of inspiratory effort. In combination with traditional indices of obstruction, TAA may more accurately characterise the degree of sleep-disordered breathing in children.

This article has supplementary material available from erj.ersjournals.com

Received: June 14 2016 | Accepted after revision: Sept 14 2016

This study was registered at clinicaltrials.gov with identifier number NCT00560859.
Support statement: This project was partly supported by grant ARC DP 110102049. This CHAT study was supported by grants (HL083075, HL083129, UL1-RR-024134, UL1 RR024989) from the National Institutes of Health. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: None declared.

Introduction

Upper airway obstruction during sleep is relatively common during childhood, with a reported prevalence between 3 and 15% [1]. Its severity ranges from primary snoring to obstructive sleep apnoea syndrome (OSAS), with the majority of children showing symptoms at the milder end of the spectrum. While clinical concerns have focused largely on the associated behavioural and cognitive deficits, mounting evidence suggests that OSAS during childhood also affects the cardiovascular system, which if untreated may develop into cardiovascular disease later in life [2, 3].

In otherwise normal children, OSAS is most frequently observed when the tonsils and adenoids are enlarged and a family history of OSAS exists. It is characterised by increased upper airway collapsibility and upper airway loading. Consequently, adenotonsillectomy (AT) is commonly the first line of treatment. The efficacy of AT in treating the range of adverse health outcomes reported in children with OSAS, particularly for milder OSAS, has remained largely untested. Additional concerns pertain to post-surgical complications and the healthcare costs of performing large numbers of ATs [4–6].

Clinically, the severity of OSAS is assessed by using overnight polysomnography (PSG) and observing the rate of respiratory events (apnoea and hypopnoea). Although the limitations of simple indices derived from discretely scored events, such as the apnoea–hypopnoea index (AHI), have been debated within the sleep community, they are considered useful in current clinical practice [7, 8]. However, since the frequency of respiratory events is low in children with mild OSAS, the AHI may not reflect the overall impact on respiratory loading. Thus, other PSG measures that quantify inspiratory effort might add a useful dimension to the assessment of breathing disturbance. While AT has been shown to effectively reduce the number of incidents of apnoea and hypopnoea, it is less clear cut whether it also reduces inspiratory effort during respiratory-event-free periods of sleep [9].

The aim of this study was to investigate the effects of AT for treatment of OSAS on an indirect marker of inspiratory effort, namely the phase shift between thoracic and abdominal movements (thoraco-abdominal asynchrony (TAA)), by utilising data from the Childhood Adenotonsillectomy Trial (CHAT). The CHAT study is a landmark multicentre controlled trial evaluating health and behavioural outcomes in children with OSAS randomised into early AT (eAT) or watchful waiting with supportive care (WWSC) [10, 11]. We hypothesised that AT reduces inspiratory effort throughout respiratory-event-free sleep and thereby reduces TAA.

Methods

Study sample

Detailed particulars of the CHAT protocol have been published [11]. Data are publicly available at https://sleepdata.org/datasets/chat. Children between 5.0 and 9.9 years of age with PSG-confirmed OSAS (*i.e.* obstructive AHI $\geqslant$2 events·h^{-1} or an obstructive apnoea index (OAI) $\geqslant$1 events·h^{-1}), a history of snoring and considered to be surgical candidates for AT were recruited from paediatric sleep centres/sleep laboratories, paediatric otolaryngology clinics, general paediatric clinics and the general community from six clinical centres. Exclusion criteria included comorbidities, medications for psychiatric or behavioural disorders, recurrent tonsillitis, extreme obesity and severe OSAS (AHI $\geqslant$30 events·h^{-1}, OAI $\geqslant$20 events·h^{-1} or oxyhaemoglobin saturation <90% for >2% of total sleep time). The study was approved by the Institutional Review Board of each institution. Informed consent was obtained from caregivers, and assent from children $\geqslant$7 years of age. The study was registered at Clinicaltrials.gov (#NCT00560859).

CHAT interventions

Children were randomly assigned to either eAT (surgery within 4 weeks after randomisation) or a strategy of WWSC with reassessment of all the study variables at approximately 7 months. Complete bilateral tonsillectomy and removal of obstructing adenoid tissue was performed using standard surgical techniques.

Overnight polysomnography

Each child underwent in-laboratory baseline and follow-up PSG carried out by study-certified technicians, following American Academy of Sleep Medicine paediatric guidelines for both acquisition and scoring [12]. The PSGs were centrally scored by registered sleep technicians. Overnight PSG was repeated approximately 7 months after randomisation [11, 13].

Analysis of thoraco-abdominal asynchrony

PSG recordings of ribcage and abdominal inductance belts were utilised to measure the instantaneous phase difference between thoracic and abdominal excursions (TAA). For details, see supplementary material. Only portions of PSG that were free from discretely scored events (*e.g.* arousal, apnoea, hypopnoea, limb movement) and artefacts were included in the analysis. Instantaneous TAA values were averaged within each sleep stage. The mean±SD portion of sleep included in TAA analysis of the eAT arm

was 76.8±12.9% at baseline and 86.5±7.68% at follow-up. In the WWSC arm, the sleep portions were 77.8±11.9% and 80.4±12.3%, respectively (supplementary table S1). The TAA values for each recording can be obtained at https://sleepdata.org/datasets/chat

Neurophysiological tests and surveys

Neurophysiological tests and surveys were performed as part of the original CHAT study to assess behaviour, OSAS symptoms, sleepiness, quality of life and generalised intellectual functioning (supplementary material).

Statistical analysis

Anthropometric data were compared using t-tests and Chi-squared tests as appropriate. TAA values were log-transformed to achieve normal distribution and analysed for stages 2 (N2) and 3 (N3) in non-rapid eye movement (NREM) sleep as well as rapid eye movement (REM) sleep (R). One-way repeated measures ANOVA was performed to investigate the effect of sleep stage on TAA, followed by a Bonferroni test based on the t-statistic for *post hoc* comparison. Two-way ANCOVA was carried out to test the effect of surgery and time point (baseline *versus* follow-up; repeated measure) on TAA. Anthropometric variables that were likely to confound statistical analysis (body mass index (BMI) z-score, BMI z-score change between follow-up and baseline, age, sex and race) were included in the model as covariates. Subsequently, three-way ANCOVA was conducted to investigate the effects of AHI normalisation, study arm and time point on TAA. Spearman correlation analysis was performed to explore the relationship between AHI, the extent of oxygen desaturation, peak end-tidal carbon dioxide and TAA. To explore whether TAA has potential clinical value in stratifying OSAS diagnostics, we performed Spearman correlation analysis between TAA and previously reported measures of behaviour, OSAS symptom indicators, sleepiness, global quality of life and intellectual functioning [10] in those children whose AHI was normal during follow-up and hence OSAS was considered resolved.

Results

Subject demographics

In total, 353 children of the original CHAT study who underwent both baseline and follow-up PSG and whose respiratory inductance signals met the technical criteria were included in this study. Of these, 182 children underwent eAT and 171 children joined the WWSC group (figure 1). Both groups had comparable demographic profiles (table 1). The mean age of the participants at baseline was 6.6 years and 49% were male. Approximately half (54%) of the sample were African American and 34% were obese. Around 5% of children were treated with montelukast and ∼22% received glucocorticoids for rhinitis or asthma at the time of the baseline PSG. At follow-up, 83% of children in the eAT arm no longer had AHI-defined OSAS, *i.e.* values of AHI $\leqslant$2 and OAI $\leqslant$1, while 40% of children in the WWSC arm had spontaneous normalisation of AHI scores. Approximately 7% of children in the eAT arm and 8% in the WWSC arm were on montelukast, and 24% (eAT) and 26% (WWSC) were on glucocorticoids at the time of the follow-up PSG, representing a small but statistically nonsignificant increase compared with baseline.

Effect of sleep stage on TAA

Sleep stage had a significant effect on TAA (reported and analysed as log-transformed values in degrees) (N2: 3.20±0.72 log°, N3: 3.24±0.81 log°, R: 3.56±0.67 log°; p<0.001; measured on baseline PSG). *Post hoc* analysis showed significantly higher TAA in REM sleep compared with both NREM sleep stages (R *versus* N2: p<0.001, R *versus* N3: p<0.001), but no significant difference between NREM sleep stages (N2 *versus* N3: p=0.448).

Due to the effect of sleep stage on TAA, all subsequent data analyses were performed separately for each sleep stage.

Correlation between TAA and clinical measures of hypoxia and hypoventilation

Using TAA values obtained from baseline and follow-up PSG, statistically significant but weak positive correlations with the extent of oxygen desaturation were observed (percentage of sleep time spent at oxygen saturation $\leqslant$90%, N2: r=0.179, p<0.001; N3: r=0.135, p<0.001; R: r=0.172, p<0.001). A weak yet statistically significant positive correlation between TAA and the percentage of sleep time at a partial carbon dioxide pressure above 50 mmHg (log-transformed) was observed in REM sleep (r=0.082, p<0.048). TAA also showed a statistically significant but weak positive correlation with AHI across all three sleep stages (N2: r=0.281, p<0.001; N3: r=0.251, p<0.001; R: r=0.238, p<0.001).

Effect of surgery on TAA

No significant difference in TAA between baseline and follow-up PSG was observed in any sleep stage (table 2). Significant study arm effects were observed in sleep stages N2 and N3. Time point×study arm interaction effects were significant across all stages of sleep, consistently pointing towards a reduction in

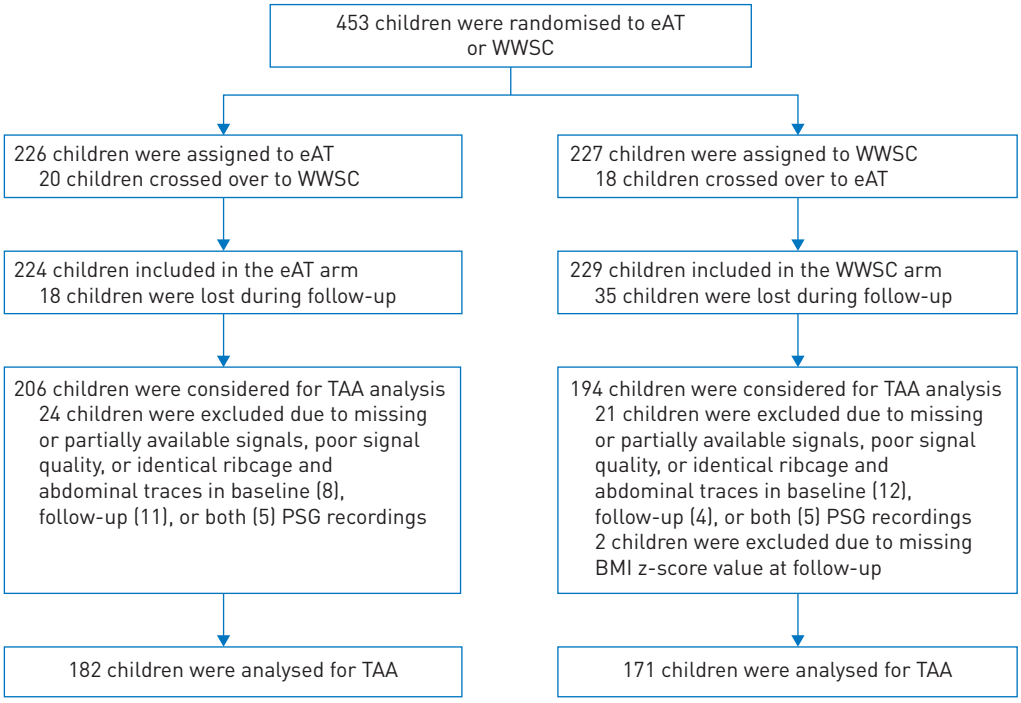

FIGURE 1 Summary of Childhood Adenotonsillectomy Trial study participants included in the thoraco-abdominal asynchrony (TAA) analysis. BMI: body mass index; eAT: early adenotonsillectomy; PSG: polysomnography; WWSC: watchful waiting with supportive care.

TAA in the eAT arm following AT. *Post hoc* comparison showed significantly lower TAA during follow-up PSG compared with baseline in the eAT arm only across all sleep stages (N2: p<0.0001; N3: p<0.0001; R: p<0.0001). The eAT arm displayed significantly lower TAA than the WWSC arm during follow-up PSG throughout all sleep stages (N2: p<0.0001; N3: p<0.0001; R: p=0.031). Of the covariates included in the model, increase in age was associated with a significant TAA reduction in REM sleep (F=8.73, p=0.003). Sex showed a weak but significant association with TAA in sleep stage N2 (F=3.99, p=0.046), where boys had lower TAA than girls.

TABLE 1 Baseline characteristics of subjects grouped according to study arm and apnoea–hypopnoea index (AHI) normalisation at 7 months

Characteristic	Study arm		AHI at 7 months	
	eAT	WWSC	Normalised	Not normalised
Subjects	182	171	219	134
Age years	6.64±1.46	6.60±1.40	7.10±1.46	7.31±1.43
Male n (%)	83 (45.6%)	89 (52%)	102 (46.6%)	70 (52.2%)
Race n (%)[#]				
African American	95 (52.2%)	97 (56.7%)	105 (47.9%)	87 (64.9%)
Caucasian	67 (36.8%)	59 (34.5%)	90 (41.1%)	36 (26.9%)
Other	20 (11%)	15 (8.8%)	24 (11%)	11 (8.2%)
BMI z-score	0.91±1.36	0.86±1.26	0.94±1.20	1.38±1.25
Weight class n (%)[¶]				
Overweight	92 (50.5%)	79 (46.2%)	104 (47.5%)	86 (64.2%)
Obese	63 (34.6%)	58 (33.9%)	70 (32%)	68 (50.7%)
Montelukast n (%)	8 (4.4%)	9 (5.3%)	12 (5.5%)	15 (11.2%)
Glucocorticoids n (%)	40 (22%)	37 (21.6%)	52 (23.7%)	37 (27.6%)

Data are presented as mean±SD unless otherwise stated. eAT: early adenotonsillectomy; WWSC: watchful waiting and supportive care; BMI: body mass index. [#]: reported by caregivers; [¶]: overweight was defined as BMI ⩾85th percentile, obese as BMI ⩾95th percentile.

TABLE 2 Comparison of thoraco-abdominal asynchrony (TAA) between time points and study arm across sleep stages

Parameter	eAT (n=182)		WWSC (n=171)		p-value		
	Baseline	Follow-up	Baseline	Follow-up	Time point	Study arm	Study arm×time point
N2 TAA# (degree)	3.23±0.72	2.89±0.72	3.17±0.72	3.21±0.73	0.326	0.025	<0.0001
N3 TAA# (degree)	3.26±0.83	2.92±0.86	3.21±0.78	3.29±0.83	0.175	0.019	<0.0001
R TAA# (degree)	3.62±0.70	3.29±0.67	3.49±0.63	3.44±0.67	0.687	0.739	0.0019

Data are presented as group mean±SD. p-values were obtained by using two-way ANCOVA adjusted for likely confounding factors of age (5–9 years), race (black, white, other), body mass index (BMI) z-score, BMI z-score change and sex. eAT: early adenotonsillectomy; WWSC: watchful waiting with supportive care; N2: stage 2 non-rapid eye movement sleep; N3: stage 3 non-rapid eye movement sleep; R: rapid eye movement sleep. #: reported and analysed as log-transformed values.

Effect of AHI normalisation and surgery on TAA

No significant TAA differences between baseline and follow-up, between eAT and WWSC groups, or study arm×AHI normalisation interactions were observed in any of the sleep stages (table 3). AHI normalisation and time point×study arm×AHI normalisation interactions were significant in stages N2 and N3. Study×AHI normalisation interaction effects were significant across all sleep stages, consistently pointing towards a reduction in TAA in the normalised group post-AT. However, the time point×study arm interaction effect was significant only within stage N2. Of the covariates included in the model, increase in age was associated with a significant TAA reduction in REM sleep ($F=8.99$, $p=0.003$). Sex showed a weak but significant association with TAA in sleep stage N2 ($F=4.96$, $p=0.027$), where boys had lower TAA than girls.

When comparing baseline TAA with follow-up TAA for both arms (figure 2), significant differences were found only in the subgroup of children in the eAT arm whose AHI normalised during follow-up. This was consistent across all sleep stages (N2: $p<0.00001$; N3: $p<0.00001$; R: $p<0.00001$).

Post hoc comparisons of the follow-up data showed a significant TAA decrease in children whose AHI normalised compared with children whose AHI remained abnormal (figure 3). This was observed within the WWSC and eAT arms across all sleep stages (WWSC: N2: $p=0.0078$; N3: $p=0.0044$; REM: $p=0.0254$; eAT: N2: $p=0.0007$; N3: $p=0.0023$; R: $p=0.0200$) (figure 3). The TAA reduction was more pronounced in children of the eAT arm compared with the WWSC arm (N2: $p=0.028$).

Correlation between TAA and cognitive, behavioural and OSAS symptom indicators in children with normal AHI

Among those children that were classified as normal on clinical PSG score during follow-up, statistically significant negative correlations were observed between the parent total scale score of the Paediatric Quality of Life Inventory and TAA during NREM sleep (N2: $r=-0.183$, $p<0.01$; N3: $r=-0.147$, $p<0.05$), but not with AHI. In addition, the total obstructive sleep apnoea-18 (OSA-18) survey score was positively correlated with TAA during NREM sleep (N2: $r=0.151$, $p<0.05$; N3: $r=0.149$, $p<0.05$), but not with AHI. No correlations were found between TAA and behaviour, OSAS symptom measures or sleepiness. When analysing the eAT and WWSC arms separately, correlations between the parent total scale score of the Paediatric Quality of Life Inventory and TAA were evident in the WWSC arm (N2: $r=-0.360$, $p<0.005$; N3: $r=-0.314$, $p<0.01$; R: $r=-0.246$, $p<0.05$) (figure 4), but not in the eAT arm. Correlations between OSA-18 score and TAA were no longer significant.

Discussion

Our main finding is a reduction in TAA during quiet, event-free sleep in children with OSAS following AT, indicating an overall reduction in inspiratory effort. However, this was not observed in children whose OSAS resolved spontaneously (as measured by the clinical diagnostic marker, *i.e.* AHI). Outcome-specific analysis suggests that normalisation of AHI, in particular in those children who underwent AT, is associated with TAA reduction at 7-month follow-up. In children whose AHI normalised without surgical intervention and hence were clinically diagnosed as OSAS free at follow-up, high TAA values were associated with poorer quality of life. This indicates that increased inspiratory effort, even in the absence of frank apnoea or hypopnoea, has adverse health outcomes.

TAA measures the phase angle between thoracic and abdominal excursions and is considered a noninvasive measure of inspiratory effort [9]. We have recently devised a robust, fully automated method of TAA measurement that can be easily implemented in PSG analysis [14]. Although TAA cannot provide

TABLE 3 Comparison of thoraco-abdominal asynchrony (TAA) between time points, study arm and apnoea–hypopnoea index (AHI) normalisation across sleep stages

Parameter	eAT (n=182)		WWSC (n=171)		p-value						
	AHI normalised (n=151)	AHI not normalised (n=31)	AHI normalised (n=68)	AHI not normalised (n=103)	Time point	Study arm	Normalisation	Time point×study arm	Study arm×AHI normalisation	Time point×AHI normalisation	Study arm×time point×AHI normalisation
N2 TAA[#] (degree)											
Baseline	3.25±0.72	3.15±0.71	3.06±0.71	3.25±0.73	0.743	0.633	0.001	0.043	0.924	0.005	0.050
Follow-up	2.81±0.69	3.26±0.75	3.04±0.73	3.33±0.72							
N3 TAA[#] (degree)											
Baseline	3.31±0.79	3.02±0.97	3.09±0.74	3.28±0.80	0.595	0.305	0.011	0.169	0.388	<0.001	0.016
Follow-up	2.84±0.81	3.35±0.97	3.06±0.81	3.44±0.82							
R TAA[#] (degree)											
Baseline	3.65±0.71	3.47±0.66	3.47±0.65	3.50±0.62	0.337	0.701	0.110	0.306	0.789	0.002	0.272
Follow-up	3.25±0.68	3.47±0.61	3.31±0.67	3.53±0.67							

Data are presented as group mean±SD, unless otherwise stated. p-values were obtained using three-way ANCOVA adjusted for likely confounding factors of age (5–9 years), race (black, white, other), body mass index (BMI) z-score, BMI z-score change and sex. eAT: early adenotonsillectomy; WWSC: watchful waiting with supportive care; N2: stage 2 non-rapid eye movement sleep; N3: stage 3 non-rapid eye movement sleep; R: rapid eye movement sleep. [#]: reported and analysed as log-transformed values.

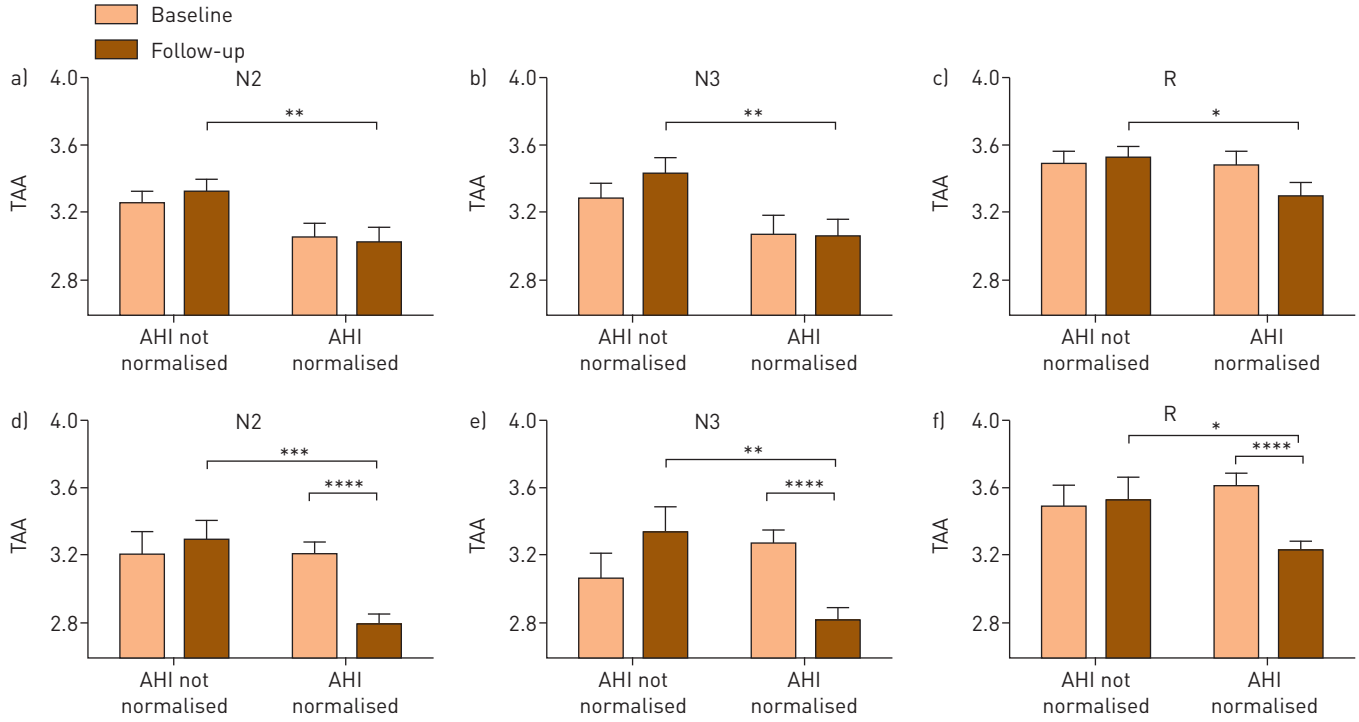

FIGURE 2 Thoraco-abdominal asynchrony (TAA) across sleep stages in children who underwent early adenotonsillectomy (eAT) (d–f) *versus* watchful waiting with supportive care (WWSC) (a–c) at baseline and follow-up polysomnography grouped by apnoea–hypopnoea index (AHI) normalisation. TAA values are reported and analysed as log-transformed values (degrees). Data are presented as mean±SEM. N2: stage 2 non-rapid eye movement sleep; N3: stage 3 non-rapid eye movement sleep; R: rapid eye movement sleep. *: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001.

a direct measure of increase in workload in terms of energy expenditure, it reflects changes in inspiratory effort due to airway obstruction [9]. Upper airway obstruction leads to increased inspiratory effort in order to maintain airway patency; this manifests as asynchronous or paradoxical inward motion of the ribcage [15–17] and hence increased TAA. TAA has been demonstrated in children with increased inspiratory effort due to upper airway obstruction and OSAS [18, 19].

Our study suggests that TAA adds important information towards the diagnosis of OSAS by quantifying overall inspiratory effort. In children with mild symptoms, in whom frank apnoeic events are rare, measuring the rate of events may not represent the full extent of respiratory disturbance during sleep. Children who snore have to overcome an increased respiratory load, but may not necessarily display frank respiratory events, desaturation or cortical arousals [20, 21]. TAA was also associated with standard PSG measures of hypoxia (percentage of sleep time spent at <90% oxygen desaturation) and with increased AHI throughout all stages of sleep. Presumably, children with more frequent/severe respiratory events also experience higher

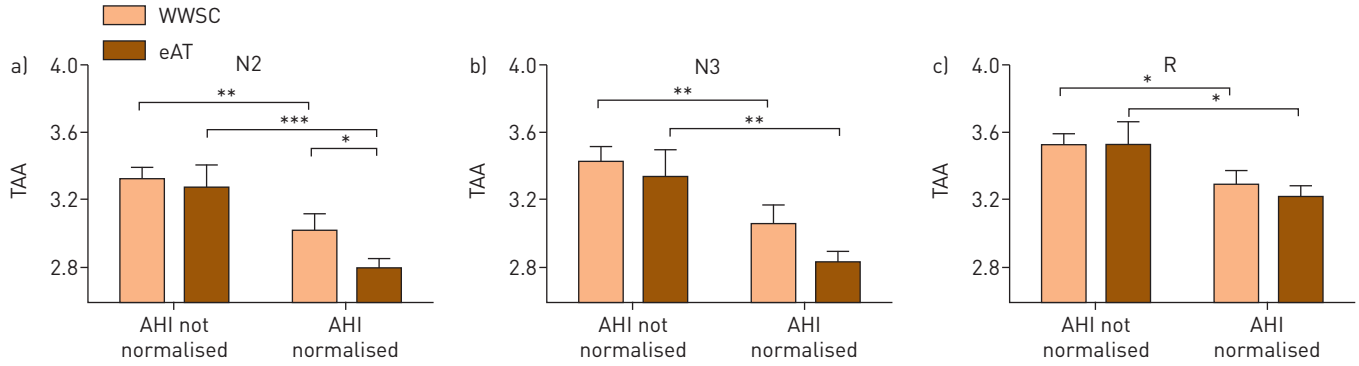

FIGURE 3 Thoraco-abdominal asynchrony (TAA) during follow-up polysomnography across sleep stages a) N2, b) N3, c) R in children who underwent early adenotonsillectomy (eAT) *versus* watchful waiting with supportive care (WWSC) grouped by apnoea–hypopnoea index (AHI) normalisation. TAA values are reported and analysed as log-transformed values (degrees). Data are presented as mean±SEM. N2: stage 2 non-rapid eye movement sleep; N3: stage 3 non-rapid eye movement sleep; R: rapid eye movement sleep. *: p<0.05; **: p<0.01; ***: p<0.001.

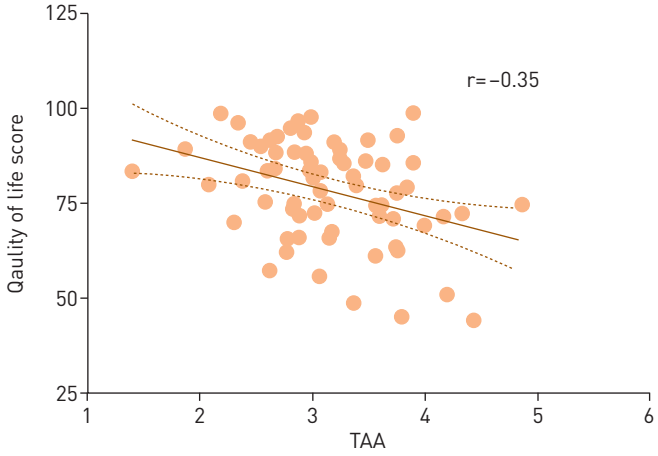

FIGURE 4 Relationship between thoraco-abdominal asynchrony (TAA) averaged across all sleep stages and Paediatric Quality of Life Inventory Parent Total Scale Score. TAA values are reported and analysed as log-transformed values (degrees). Lines indicate the linear regression function (solid) and 95% confidence intervals (dashed).

inspiratory loads during event-free periods of sleep. While the detailed effects of increased TAA in the absence of frank apnoea or hypopnoea and underlying mechanisms have not been fully elucidated, studies in children with primary snoring have shown elevated blood pressure and reduced arterial distensibility [22, 23], subtle dysregulation of glycaemic homeostasis [24] and neurocognitive impairments [25]. Pre-pubescent rats subjected to increased upper airway loading (without hypoxia) demonstrated reduced production of growth hormone and insulin-like growth factor I and impaired longitudinal growth [26].

As has been shown previously, AT is effective at resolving clinical PSG markers of OSAS (83% of the children in the eAT arm had AHI normalisation). However, 40% of the children in the WWSC arm, primarily those with mild OSAS, had AHI values below the clinical cut-off during follow-up, raising important questions about whom to treat and when. Our analyses show that children who underwent surgery and subsequently normalised their AHI values also demonstrated reduced TAA. This suggests a benefit of AT on inspiratory effort by enlarging the upper airway (figure 2), as the decrease in upper airway volume is related to the increase in respiratory effort during sleep [27]. Within the WWSC arm, spontaneous AHI normalisation did not coincide with TAA reduction, but children who had normal AHI values at follow-up demonstrated lower TAA at baseline, possibly because their OSAS was milder [28]. Interestingly, in children whose AHI normalised spontaneously during follow-up, TAA was inversely correlated with quality of life, suggesting that increased inspiratory effort persists in some of these children and has adverse effects on their well-being.

We have previously measured TAA during quiet, event-free sleep in children with sleep-disordered breathing undergoing AT in comparison to normal children, and observed increased TAA levels at baseline that were no longer different from TAA of normal children 6 months post AT [29], providing further evidence for the beneficial effect of AT on inspiratory effort. Our study also confirms that TAA values are higher in REM sleep than in NREM sleep [29]. This difference is possibly caused by the reduction in intercostal muscle activity, contributing to distorted ribcage movement [30] and/or decreased pharyngeal muscle activity associated with upper airway obstruction [31]. Interestingly, we observed an inverse association between TAA and age during REM sleep. Paradoxical inward ribcage motion in REM sleep and its lessening with age has been well documented in infants and toddlers [32]. Although the chest wall and ribcage are fully developed at the age of 5 years, neural respiratory control may still undergo maturation, explaining our observation [33]. Our analysis also demonstrated sex differences in TAA; to our knowledge this has not been reported previously in pre-pubescent children.

Our study has several limitations. Children in this study had only mild to moderate OSAS as defined by AHI, and the follow-up time was relatively short. More severe OSAS is likely to result in higher inspiratory effort. Although our results are based on a large randomised control trial with racially diverse groups, and included standardised measurements and high follow-up rates, there are limitations with respect to their interpretation. Several of the recordings from the original study were omitted due to poor signal quality and the per-protocol design. Sleep position is known to affect TAA [29]. We were not able to retrieve reliable information on body position from the PSG database. In addition, anti-inflammatory medication may have affected TAA in some children.

We conclude that, in addition to its well-established effectiveness for resolving frank respiratory events in children with OSAS, AT also reduces inspiratory effort throughout quiet respiratory-event-free sleep. Surgery may therefore have an additional, previously unrecognised benefit. TAA appears to be a sensitive marker of increased inspiratory effort that is inversely associated with quality of life in children with symptomatic OSAS. Monitoring TAA over time may yield additional insight into the dynamic changes of inspiratory effort during sleep and, in combination with traditional indices of obstruction, more accurately characterise the degree of sleep-disordered breathing in children. Furthermore, our findings demonstrate that spontaneous AHI normalisation does not necessarily indicate that OSAS has resolved, highlighting the need for more sensitive measures.

Acknowledgements

We would like to thank Michael Rueschman, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA, USA for support with handling and interpreting the CHAT dataset.

Xiao Liu, Sarah Immanuel and Mathias Baumert had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Yvonne Pamula, James Martin and Declan Kennedy contributed substantially to the interpretation and the writing of the manuscript.

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Chapter 4

Effect of adenotonsillectomy for childhood obstructive sleep apnea on nocturnal heart rate patterns

LIU, X., IMMANUEL, S., KENNEDY, D., MARTIN, J., PAMULA, Y. & BAUMERT, M. 2018. Effect of adenotonsillectomy for childhood obstructive sleep apnea on nocturnal heart rate patterns. Sleep, zsy171-zsy171. DOI: 10.1093/sleep/zsy171

Statement of Authorship

Title of Paper	Effect of adenotonsillectomy for childhood obstructive sleep apnea on nocturnal heart rate patterns
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	LIU, X., IMMANUEL, S., KENNEDY, D., MARTIN, J., PAMULA, Y. & BAUMERT, M. 2018. Effect of adenotonsillectomy for childhood obstructive sleep apnea on nocturnal heart rate patterns. Sleep, zsy171-zsy171. DOI: 10.1093/sleep/zsy171

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Name of Principal Author (Candidate)	Xiao LIU		
Contribution to the Paper	Design, analysis and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Conception, design and interpretation of results, preparation and critical revision of the manuscript.		
Signature		Date	31/05/19

SLEEPJ, 2018, 1–8

doi: 10.1093/sleep/zsy171
Advance Access publication Date: 24 August 2018
Original Article

ORIGINAL ARTICLE

Effect of adenotonsillectomy for childhood obstructive sleep apnea on nocturnal heart rate patterns

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Abstract

Study Objectives: To assess the effect of adenotonsillectomy for relieving obstructive sleep apnea syndrome (OSAS) symptoms in children on cardiac autonomic modulation.

Methods: In 354 children enrolled in the Childhood Adenotonsillectomy Trial, randomized to undergo either early adenotonsillectomy (eAT; N = 181) or a strategy of watchful waiting with supportive care (WWSC; N = 173), nocturnal heart rate control was analyzed during quiet, event-free sleep at baseline and at 7 months using overnight polysomnography (PSG). The relative frequency of patterns indicating monotonous changes in heart rate was quantified.

Results: Children who underwent eAT demonstrated a significantly greater reduction in heart rate patterns postsurgery than the WWSC group. On assessing those heart rate patterns regarding normalization of clinical PSG, heart patterns were reduced to a similar level in both groups. In children whose AHI normalized spontaneously, heart rate patterns were already significantly less frequent at baseline, suggesting that upper airway obstruction was milder in this group at the outset.

Conclusions: Adenotonsillectomy reduces monotonous heart rate patterns throughout quiet event-free sleep, reflecting a reduction in cardiac autonomic modulation. Heart rate pattern analysis may help quantifying the effect of OSAS on autonomic nervous system activity in children.

Clinical Trial Registration: The study was registered at Clinicaltrials.gov (#NCT00560859).

Statement of Significance

This study shows that adenotonsillectomy for obstructive sleep apnea syndrome affects cardiac autonomic modulation during sleep. We identified a previously unreported baseline difference in heart rate dynamics in children who normalize spontaneously. Analysis of heart rate pattern may therefore help identify children with mild–moderate symptoms who do not require surgery.

Key Words: sleep apnea; children; adenotonsillectomy; autonomic control

Submitted: 23 April, 2018; **Revised:** 28 June, 2018

Introduction

Between 3 and 15 per cent of children experience some level of upper airway obstruction (UAO) during sleep [1], ranging from primary snoring to obstructive sleep apnea syndrome (OSAS). Most children are at the milder end of this spectrum. UAO has often been associated with impairment of neurocognitive and behavioral function, but increasing evidence suggests that it also affects autonomic cardiovascular control [2–5]. Importantly, OSAS is a key driver of change in the cardiovascular system [6–8] and may increase the risk of developing cardiovascular disease later in life [4, 5, 9].

As the most common etiology for childhood OSAS is enlarged tonsils and adenoids, the recommended first-line of treatment is adenotonsillectomy (AT). Although the efficacy of AT for children with UAO has been widely confirmed, residual symptoms and parental concerns are known to persist after surgery [10–14]. Additionally, current clinical diagnostic markers of UAO derived from overnight polysomnography (PSG), such as apnea–hypopnea index (AHI), are less discriminative in identifying children with mild OSAS who despite their lower AHI may benefit from AT. The effect of mild UAO on children's health remains debatable. Postsurgical complications and the healthcare costs associated with performing large numbers of AT have become further concerns [11–13].

Heart rate variability (HRV) is commonly used to noninvasively measure cardiac autonomic activation. But findings on the effect of UAO on HRV in children are inconclusive [2, 15–19]. Absolute HRV values may vary significantly between and within individuals, hampering its diagnostic potential. Symbolic analysis of heart rate patterns provides an alternative way to quantify autonomic control. It allows detecting particular heart rate patterns of interest, e.g. sequences of monotonously increasing or decreasing heart rates. Several studies have shown that symbolic analysis can capture diagnostically useful features of cardiac control [20–23].

The aim of this study was to investigate the effects of AT for OSAS on cardiac autonomic modulation by measuring the relative frequency of monotonously increasing/decreasing heart rate patterns. We hypothesized that AT reduces cardiac autonomic modulation throughout quiet, scored event-free sleep, observable through a reduction of monotonously increasing/decreasing heart rate patterns on standard overnight PSG.

Methods

Study sample

We utilized data from the Childhood Adenotonsillectomy Trial (CHAT), a landmark multicenter randomized controlled trial, evaluating health and behavioral outcomes in children with OSAS who underwent early AT (eAT) versus watchful waiting with supportive care (WWSC) [24, 25]. Detailed particulars of the CHAT protocol have been previously published [25]. All data are publicly available at https://sleepdata.org/datasets/chat. In brief, children between 5.0 and 9.9 years of age with PSG-confirmed OSAS (obstructive AHI ≥ 2 events/hr or an obstructive apnea index [OAI] ≥ 1 events/hr), a history of snoring and considered to be surgical candidates for AT were recruited from pediatric sleep centers/sleep laboratories, pediatric otolaryngology clinics, general pediatric clinics, and the general community from six clinical centers. Exclusion criteria included comorbidities, medications for psychiatric or behavioral disorders, recurrent tonsillitis, extreme obesity (body mass index > 2.99 for age group and sex-z-score) and severe OSAS (AHI ≥ 30 events/hr, OAI ≥ 20 events/hr or oxyhemoglobin saturation < 90 per cent for >2 per cent of total sleep time). The study was approved by the Institutional Review Board of each institution. Informed consent was obtained from caregivers, and assent from children ≥7 years of age.

CHAT interventions

Children were randomly assigned to either eAT (surgery within 4 weeks after randomization) or a strategy of WWSC with reassessment of all the study variables at approximately 7 months. Complete bilateral tonsillectomy and removal of obstructing adenoid tissue was performed using standard surgical techniques.

Overnight polysomnography

Each child underwent in-laboratory baseline and follow-up PSG carried out by study-certified technicians, following American Academy of Sleep Medicine pediatric guidelines for both acquisition and scoring [26]. The PSGs were centrally scored by registered sleep technicians. Overnight PSG was repeated approximately 7 months after randomization [25, 27].

Symbolic analysis of heart rate patterns

Heart beat locations were extracted from ECG as detailed in Supplementary Material. The temporal distance between heartbeat locations yields a beat-to-beat time series of heart period (HP). HP changes were transformed into a sequence of symbols {0, 1, and 2} that represent coarse-grained heart rate dynamics (Supplementary Figure S1). We used a symbolization scheme that proved effective in earlier studies [20], where symbols are assigned based on the following rules:

$$s_n = \begin{cases} 0 : (x_n - x_{n-1}) > l_x \\ 1 : (x_n - x_{n-1}) < -l_x \\ 2 : Otherwise, \end{cases} \quad (1)$$

where s_n is the nth symbol in the beat to beat time series, x_n represents the nth HP in the beat to beat time series, x_{n-1} the preceding HP, and l_x is a predefined nonnegative threshold. In other words, symbol 0 represents an increase in HP between consecutive beats beyond the threshold, whereas symbol 1 indicates a decrease in HP; symbol 2 represents changes less or equal to the threshold. From the resulting symbols sequences series, "words" comprising three consecutive symbols were constructed using a sliding window approach (the window slides only by one symbol to the right at each step).

The relative frequency of word types 000 and 111 was considered for further analysis, indicating the steady increase and decrease in HP, respectively, over four consecutive heartbeats.

Based on the results of a previous study investigating its ability for differentiating heart rate dynamics in children with sleep-disordered breathing and normal children, we set l_x = 0 ms [28]. This threshold showed the best performance when using either entire PSG data as well as PSG segments free from discretely scored respiratory or motor events (e.g. apnea, hypopnea, arousal, and limb movement).

Statistical analysis

Statistical analysis were conducted using IBM SPSS 25 (Chicago, United States). Anthropometric data [28] were compared by using *t*-tests and X^2 tests as appropriate. One-way repeated measures ANOVA was carried out to investigate the effect of sleep stage on heart rate patterns, followed by a Bonferroni test based on Student's *t* statistic for post hoc comparisons. A two-way analysis of covariance (ANCOVA) was carried out to look at the effect of surgery on heart rate patterns with study (baseline vs. follow-up) and study arm (eAT vs. WWSC) in three different sleep stages. Also, a three-way analysis of covariance (ANCOVA) was carried out to test for the effect of AHI-normalization and study arm (eAT vs. WWSC) with study (baseline vs. follow-up) as the repeated measure on heart rate patterns in three different sleep stages. Anthropometric variables that were likely to confound statistical analysis (BMI z-score, BMI z-score change between follow-up and baseline, age, gender, and race) were included in the model as covariates. Spearman correlation analysis was conducted to explore the relationship between AHI, the extent of oxygen desaturation, peak-end tidal CO_2, and heart rate patterns across all available PSG.

Results

Participant demographics

A total of 354 children of the original CHAT study who underwent both baseline and follow-up PSG and who had ECG signals meeting technical criteria were included in this study. The dataset comprised 181 children who underwent eAT and 173 children who were assigned to the WWSC group and participated in both the baseline and follow-up sleep studies and had PSG that met the technical requirements (Figure 1). Baseline anthropomorphic characteristics are summarized in Table 1. Both groups had comparable demographic profiles. Overall, the mean age of the participants at baseline was 6.55 years and 48 per cent were male. Approximately half (54.5 per cent) of the sample were African American and 33.9 per cent were obese.

At follow-up, 82.3 per cent of participants in the eAT group no longer had AHI-defined OSAS, i.e. values of AHI ≤ 2 and OAI ≤ 1, whereas in the WWSC group, 43.4 per cent of children had spontaneous normalization of AHI scores. Children in the WWSC group who AHI-normalized spontaneously had an AHI of 3.42 ± 2.99 at baseline and 0.58 ± 0.47 at follow-up ($p < 0.00001$). Children who did not normalize had a baseline AHI of 6.81 ± 5.84 at baseline that increased to 9.18 ± 11.61 at follow-up ($p = 0.07$). In the eAT group, children who normalized had a baseline and follow-up of 5.20 ± 5.49 and 0.50 ± 0.44 ($p < 0.00001$), respectively. Children who did not normalize following surgery had baseline and follow-up AHIs of 7.37 ± 5.32 and 3.63 ± 3.38 ($p = 0.0014$), respectively, i.e. were more severely affected.

Spontaneously AHI-normalized children had significantly lower BMI z-score at baseline compared with children in the WWSC arm who did not normalize (0.63 ± 1.15 vs. 1.08 ± 1.23, $p = 0.018$). The change in BMI z-score at follow-up was significantly larger in children who did not normalize spontaneously (–0.007 ± 0.40 vs. 0.11 ± 0.33, $p = 0.038$). There was no significant relationship between race and spontaneous AHI normalization.

Around 5.4 per cent of children were treated with Montelukast and approximately 21.2 per cent received nasal glucocorticoids for rhinitis or asthma at the time of the baseline PSG. Approximately 7.7 per cent of children in the eAT arm and 9.2 per cent in the WWSC arm were on Montelukast, and 23.8 and 26 per cent of children in the eAT arm and WWSC arm,

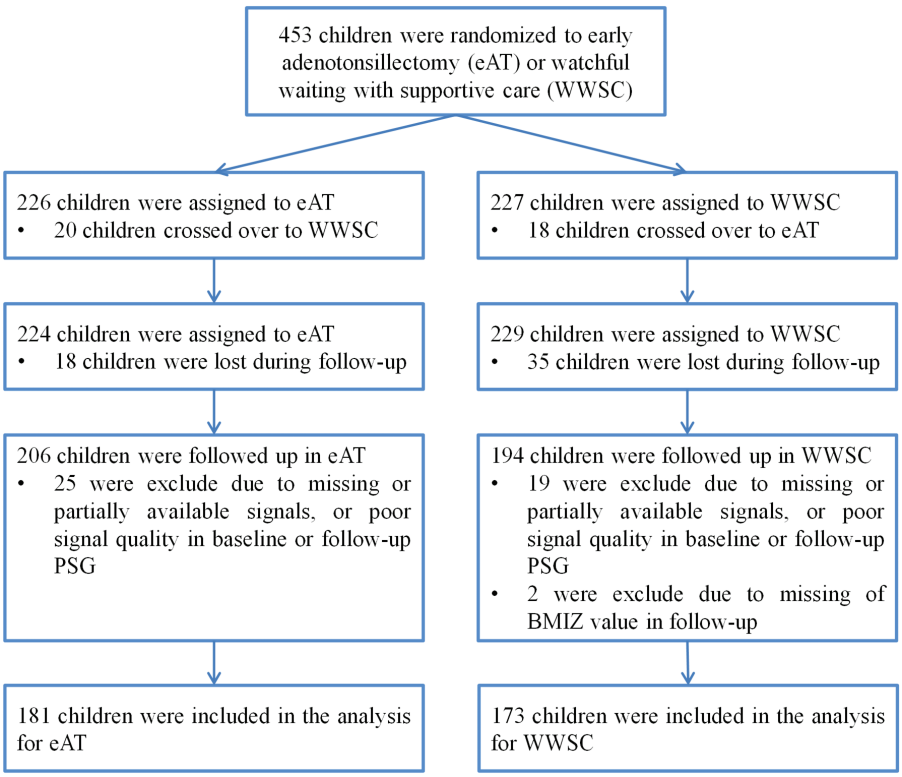

Figure 1. Summary of CHAT study participants included in the heart rate pattern analysis.

Table 1. Baseline characteristics of participants grouped according to study arm and AHI normalization at 7 months, respectively

	Study arm		AHI at 7 months	
Characteristic	Early adenotonsillectomy (*N* =181)	Watchful waiting (*N* =173)	Normalized (*N* = 224)	Not normalized (*N* =130)
Age^ (years)	6.57 ± 1.438	6.53 ± 1.38	6.98 ± 1.43	7.25 ± 1.43
Male sex—*N* (%)	81 (44.8%)	89 (51.4%)	105 (46.9%)	65 (50%)
Race—*N* (%)[†]				
African American	96 (53%)	97 (56.1%)	106 (47.3%)	87 (66.9%)
Caucasian	65 (35.9%)	59 (34.1%)	91 (40.6%)	33 (25.4%)
Other	20 (11%)	17 (9.8%)	27 (12.1%)	10 (7.7%)
BMI z score[‡]	0.88 ± 1.35	0.88 ± 1.22	0.92 ± 1.19	1.40 ± 1.23
Weight class—*N* (%)[§]				
Obese (BMI ≥ 95th percentile)—*N* (%)	62 (34.3%)	58 (33.5%)	70 (31.3%)	67 (51.5%)
Montelukast—*N* (%)	9 (5%)	10 (5.8%)	14 (6.3%)	16 (12.3%)
Glucocorticoids[‖]—*N* (%)	38 (21%)	37 (21.4%)	53 (23.7%)	35 (26.9%)
OAHI	5.58 ± 5.51	5.34 ± 5.09	0.53 ± 0.45	7.82 ± 10.48

[†]Race reported by caregivers.
[‡]Data are presented as mean ± *SD*.
[§]Overweight was defined as a body mass index in the 85th percentile or higher, obese as a BMI in the 95th percentile or higher.
[‖]Topical application.

respectively, were on nasal glucocorticoids at the time of the follow-up PSG, representing a small but statistically nonsignificant increase compared with the baseline sample. Comparing children in the WWSC arm who did not spontaneously normalize versus those who did, no significant differences were found in the use of Montelukast (10.20 vs 8.70 per cent) or glucocorticoids (29.59 vs 21.33 per cent).

Effect of sleep stage on heart rate patterns

During baseline PSG the percentage of heart rate patterns observed, during different sleep stages, were 18.64 ± 6.65 per cent (N2), 16.52 ± 6.92 per cent (N3), and 16.57 ± 5.12 per cent (R), respectively, showing a significant sleep stage effect ($p < 0.00001$). Post hoc testing showed more frequent patterns in N2 sleep compared with both N3 and rapid eye movement (REM) sleep stages (N2 vs N3: $p < 0.00001$; N2 vs REM: $p < 0.00001$). Consequently, all subsequent data analyses were carried out for individual sleep stages.

Correlation between heart rate patterns and polysomnographic measures of hypoxia and hypoventilation

Statistically significant, but small positive correlations between the relative frequency of heart rate patterns and the extent of oxygen desaturation (percentage of sleep time spent at oxygen saturation T < 90 per cent: N2: $r = 0.139$, $p < 0.001$; N3: $r = 0.134$, $p < 0.001$; REM: $r = 0.081$, $p < 0.032$) were observed. A small, yet statistically significant positive correlation between heart rate pattern frequency and the percentage of sleep time at a partial CO_2 pressure above 50 mm Hg (log-transformed; 0 replaced with 0.00001): (N2: $r = 0.202$, $p < 0.00001$; N3: $r = 0.220$, $p < 0.00001$; REM: $r = 0.172$, $p < 0.0001$) was observed. Heart rate pattern frequency also showed a statistically significant, but weak positive correlation in all three sleep stages with AHI calculated as the total number of obstructive apneas and hypopneas associated with all desaturations per hour of sleep (N2: $r = 0.319$, $p < 0.00001$; N3: $r = 0.313$, $p < 0.00001$; REM: $r = 0.239$, $p < 0.00001$) and also with the central apnea index based on all desaturations (N2: $r = 0.196$, $p < 0.00001$; N3: $r = 0.152$, $p < 0.00005$; REM: $r = 0.180$, $p < 0.00001$).

Effect of surgery on heart rate patterns

A significant reduction in the percentage of heart rate patterns was observed at follow-up PSG in all three sleep stages (N2: $p < 0.00001$; N3: $p < 0.00001$; REM: $p < 0.0001$; Table 2). Significant study arm differences were observed in non-REM sleep stages (N2: $p = 0.019$; N3: $p = 0.011$). Study x study arm interaction effects were significant in all stages of sleep (N2: $p = 0.0006$; N3: $p = 0.0026$; REM: $p = 0.0046$), consistently pointing towards a reduction in heart rate patterns in the eAT group post-AT. Post hoc results demonstrate significantly less frequent patterns during follow-up compared with baseline PSG in all three sleep stages in the eAT group only (N2: $p < 0.00001$; N3: $p < 0.00001$; REM: $p < 0.00001$). The eAT group displayed significantly fewer heart rate patterns than the WWSC group during follow-up PSG throughout all sleep stages (N2: $p < 0.00005$; N3: $p < 0.0001$; REM: $p = 0.011$).

Of the covariates included in the models, increase in age was associated with a significant reduction in heart rate patterns in all three sleep stages (N2: $F = 14.60$; $p = 0.00015$; N3: $F = 14.78$; $p = 0.00013$; REM: $F = 7.54$; $p = 0.0062$). Gender showed a small yet significant association with heart rate pattern frequency in sleep stage N3 ($F = 4.92$; $p = 0.027$), where boys had fewer patterns than girls. BMI z-score change between follow-up and baseline was also significantly, but weakly associated with heart rate patterns in all the sleep stages (N2: $F = 4.85$; $p = 0.028$; N3: $F = 7.71$; $p = 0.0056$; REM: $F = 4.76$; $p = 0.030$), where a greater BMI z-score increase was associated with a higher the percentage of heart rate patterns.

Effect of AHI normalization and surgery on heart rate patterns

To explore the effect of AHI normalization on heart rate patterns, we performed three-way ANCOVA. No significant differences in heart rate pattern frequency were observed between

Table 2. Comparison of heart rate patterns between study, study arm for three sleep stages N2, N3, and R

Heart rate patterns [%]	Early adenotonsillectomy (N = 181)		Watchful waiting (N = 173)		P		
	Baseline	Follow-up	Baseline	Follow-up	Study	Study Arm	Study Arm x Study
N2	18.98 ± 6.75	14.34 ± 5.79	18.30 ± 6.54	16.88 ± 6.16	<0.00001	0.019	0.0006
N3	16.74 ± 7.14	12.41 ± 6.01	16.29 ± 6.69	14.9 ± 6.50	<0.00001	0.011	0.0026
R	16.98 ± 5.23	14.27 ± 4.64	16.13 ± 4.99	15.47 ± 4.39	<0.0001	n.s.	0.0046

All *p* values have been obtained using two-way ANCOVA adjusted for likely confounding factors of age (5 to 10 years of age), race (black, white, and other), BMI z-score, BMI z-score change, and gender.
n.s. = not statistically significant.

Table 3. Per-protocol comparison of heart rate patterns between sleep study, study arm and AHI normalization for three sleep stages

Heart rate patterns [%]		Early adenotonsillectomy (N = 181)		Watchful waiting (N = 173)		P						
		Normalised AHI (N = 149)	AHI not normalised (N = 32)	Normalised AHI (N = 75)	AHI not normalised (N = 98)	Study	Study Arm	Normalised	Study x Study arm	Study Arm x AHI normalization	Study x AHI normalization	Study Arm x Study x AHI normalization
N2	Baseline	19.39 ± 6.76	17.05 ± 6.43	16.93 ± 6.92	19.34 ± 6.07	0.007	0.082	n.s.	0.0001	0.009	n.s.	n.s.
	Follow-up	14.48 ± 5.51	13.69 ± 7	15.2 ± 6.07	18.17 ± 5.94							
N3	Baseline	17.28 ± 7.1	14.24 ± 6.88	14.98 ± 7.33	17.3 ± 5.99	0.005	0.035	n.s.	0.001	0.006	n.s.	n.s.
	Follow-up	12.64 ± 5.74	11.33 ± 7.11	13.33 ± 6.24	16.11 ± 6.48							
R	Baseline	17.36 ± 5.18	15.23 ± 5.18	15.1 ± 4.92	16.91 ± 4.93	n.s.	n.s.	n.s.	0.003	0.010	n.s.	n.s.
	Follow-up	14.44 ± 4.35	13.51 ± 5.83	14.6 ± 4.23	16.14 ± 4.41							

All *p* values have been obtained using three-way ANCOVA adjusted for likely confounding factors age (5 to 10 years of age), race (black, white, and other), BMI z-score, BMI z-score change, and gender.
n.s. = not statistically significant.

normalized and not normalized, or study x AHI-normalization interaction, or study x study arm x AHI normalization interactions were observed in any of the sleep stages (Table 3).

Significant differences in heart rate patterns between baseline and follow-up were observed in nonrapid eye movement (NREM) sleep stages, consistent with the two-way analysis. Comparing the eAT and WWSC arms, heart rate patterns in the eAT arm are slightly but statistically significantly less frequent than in the WWSC arm in N3. Study x study arm interaction effects and study arm x AHI-normalization interaction effects were significant in all stages of sleep, consistently pointing towards a bigger reduction in heart rate patterns post-AT in both AHI-normalized and not normalized children.

Of the covariates included in the models, increase in age was associated with a reduction in heart rate patterns in non-REM sleep (N2: $F = 7.211$; p=0.008, N3: $F = 87.386$; p=0.007). Study x BMI z-score change interaction showed a weak yet significant association with heart rate patterns in sleep stage N2 ($F = 4.117$; p=0.043). The percentage of patterns increases as the BMI z-score increases.

Post hoc comparison of children who did not AHI-normalize spontaneously at follow-up (Figure 2) showed significantly more frequent heart rate patterns in all three sleep stages than children who underwent surgery, but did not normalize (N2: $p = 0.0005$ [Figure 2, A and D]; N3: $p = 0.0004$ [Figure 2, B and E]; REM: $p = 0.0126$ [Figure 2, C and F]).

Considering baseline PSG in the WWSC arm, children whose AHI normalized spontaneously showed significantly lower frequencies of heart rate patterns than children in whom AHI did not normalize (N2: $p = 0.027$; N3: $p = 0.037$; REM: $p = 0.016$) These differences persisted at follow-up (N2: $p = 0.001$; N3: $p = 0.005$; REM: $p = 0.013$). Children who had spontaneously AHI-normalized also showed significant less frequent heart rate patterns at baseline compared with children in the eAT arm in N2 ($p = 0.0341$, Figure 2, A and D) and REM sleep ($p = 0.0053$, Figure 2, C and F).

In the WWSC arm, heart rate patterns were significantly less frequent during follow-up PSG than during baseline PSG in both the AHI-normalized and not normalized subgroup in NREM sleep stages (AHI-normalized: N2: $p = 0.002$; N3: $p = 0.007$, AHI not normalized: N2: $p = 0.024$; N3: $p = 0.026$).

Similar results were also found in the eAT arm where the difference was even more significant. Heart rate patterns reduced even more dramatically at follow-up than in the WWSC arm in both AHI-normalized and not normalized subgroups in all sleep stages (AHI-normalized: N2: $p < 0.00001$; N3: $p < 0.00001$; REM: $p < 0.00001$, AHI-not normalized: N2: $p = 0.0002$; N3: $p = 0.0015$; REM: $p = 0.020$).

Discussion

Our study demonstrates that AT for childhood obstructive sleep apnea affects autonomic cardiac modulation. By employing a nonlinear signal processing technique originating from the mathematical framework of symbolic dynamics, we observed a significant reduction in the relative frequency of steadily increasing and decreasing heart rate patterns post AT; this effect was independent of the AHI-normalization.

Considering the WWSC arm, the AHI normalized spontaneously in 43.35 per cent of children. A reduction in steadily

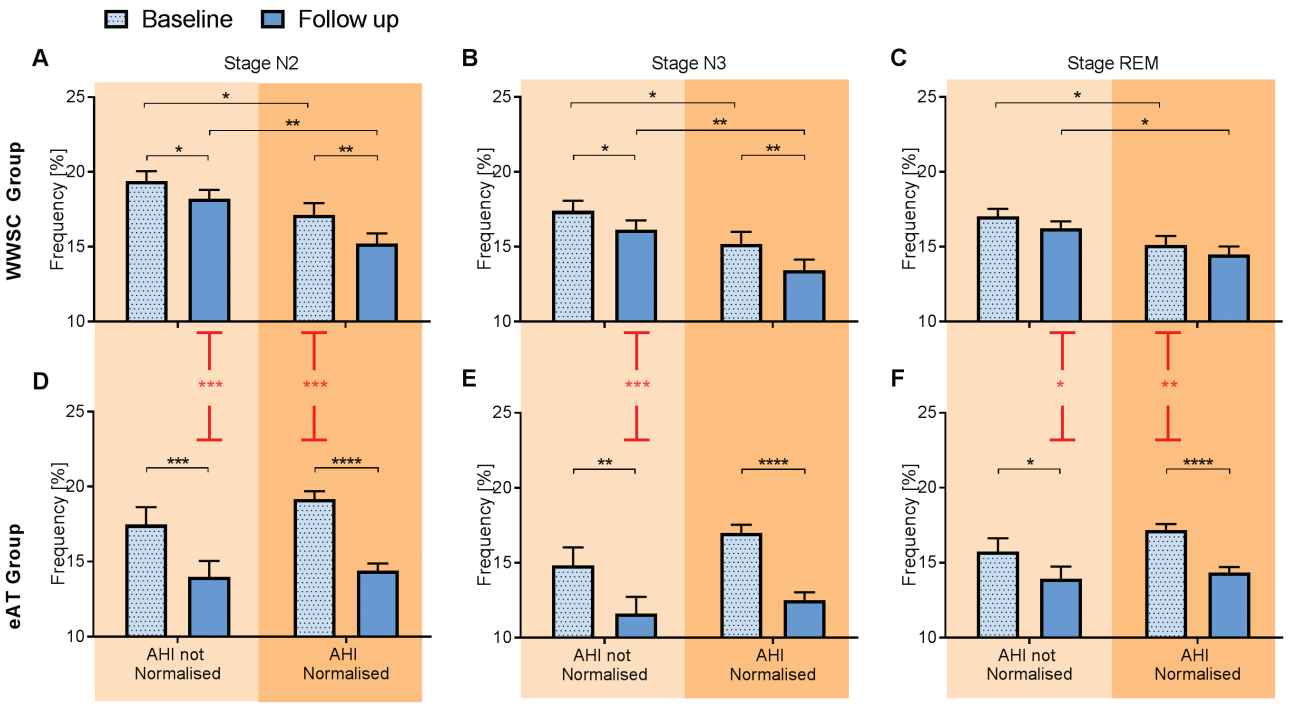

Figure 2. Heart rate patterns in sleep stages in children who underwent eAT versus WWSC at baseline and follow-up PSG grouped by AHI normalization. Data are presented as mean and SEM. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$.

increasing/decreasing heart rate patterns was evident in NREM sleep, possibly due to the effect of aging [29]. Importantly, children whose AHI normalized spontaneously already had fewer heart rate patterns at baseline PSG and also lower AHI values, demonstrating that their OSAS was milder to begin with, challenging the notion of spontaneous OSAS resolution. Quantification of heart rate patterns may help stratifying children who may not require AT.

It is conceivable, and indeed it has been frequently argued, that the diagnostic accuracy of PSG is poor in children with mild UAO based on AHI criteria, classifying them somewhat arbitrarily as either normal or having OSAS [10, 30]. The rate of spontaneous OSAS resolution, observed in the original CHAT report, exemplifies the bluntness of AHI as a much-described gold standard diagnostic tool and predictor of outcomes in the pediatric population. Considering those children that have been classified as not normalized based on their AHI regardless of the study arm, we observed the reduction in their increasing/decreasing heart rate patterns after 7 months, but the effect was significantly higher in children who underwent surgery compared with those in the WWSC arm. This further demonstrates the benefit of AT for reducing autonomic cardiac modulation in these children; pronounced autonomic cardiac modulation appears to persist if not treated.

The reduction in frequency of steadily increasing/decreasing heart rate patterns following surgery indicates a reduction in neural outflow to the heart. Although the (patho-) physiological source of those patterns cannot be clearly identified from this analysis, they likely reflect subcortical activation due to increased inspiratory load. We have previously shown slower breathing rate and increased thoraco-abdominal asynchrony in these children [31] and others [32] that might modulate cardiac rhythm via central mechanisms and baroreflex blood pressure control.

Importantly, we excluded any discrete respiratory events identified by experienced sleep technicians using current scoring conventions from the analysis; heart rate patterns quantified in this study are therefore not the secondary result of clinically scored obstructive events, but rather capture independent information that is currently not included in standard sleep assessment.

HRV has been previously studied in children with OSAS to quantify cardiac autonomic control, but findings reported in the literature are conflicting. In an early study on a small number of children with OSAS, typical heart rate patterns associated with respiratory events were observed in Poincare plots [15]. More recent studies have shown lower HRV in children with OSAS compared with controls, during wakefulness [2] and event-free sleep and argued that it indicates an increased sympathetic activity [16]. Other authors believe reduced HRV points towards an overall depression of autonomic tone [17]. Power spectrum analysis of HR during event-free period sleep in children with OSAS demonstrated increased power in lower frequency range in comparison to normal children, which has been interpreted as increased sympathetic activity [18]. Others have reported higher HRV in children with moderate to severe OSAS arguing for altered "sympathovagal balance" during sleep that was present when respiratory events are included and in event-free sleep [19].

Discrepancy in HRV analysis results can be partly explained by methodological differences (e.g. the somewhat arbitrary definitions of high frequency and low frequency bands in the power spectrum, neglecting the confounding effect of respiratory rate) and high interindividual differences that are common in the normal population and more so in patient cohorts, yielding low sensitivity and specificity. Previous analysis of CHAT data found a weak relationship between OSAS and heart rate

[33], but no differences in respiratory sinus arrhythmia [4]. Here, we employed a technique that overcomes some of these issues; symbolic analysis is robust to noise, captures nonlinear as well as linear characteristics, and often yields superior performance. Unlike conventional HRV analysis, it does not quantify the magnitude of HRV, but its dynamics (patterns). Results are therefore unaffected by high interindividual differences in the magnitude HRV.

Our study suggests that heart rate pattern analysis may add additional information towards diagnosis of OSAS by quantifying the level of autonomic modulation in children at the mild–moderate range of the OSAS spectrum. Frank apneic events rarely occur in that part of the spectrum in children; therefore, counting the frequency the discrete respiratory events may not capture the full extent of respiratory disturbance. For example, subtle UAOs may cause children to snore when working against increased inspiratory load, and those characteristics are not identified in the OAHI index [34, 35].

Our analysis shows that heart rate pattern frequency was positively correlated with standard PSG measures of hypoxia and hypercapnia, suggesting that children with more serve OSAS also have higher levels of respiratory load during respiratory event-free sleep, as reported previously [31].

Our study has several limitations: the children studied here were only in the mild to moderate range of the OSAS spectrum, and only been followed for a short period of 7 months. The heart rate patterns described here may likely be more frequent in more severe OSAS cases. We did not observe an overall effect of AHI-normalization on heart rate pattern frequency; this illustrates limited ability of the AHI to capture autonomic activation related to mild OSAS. Several recordings were excluded from the analysis due to the poor quality of the signal. Anti-inflammatory medication, such as Montelukast, might have some effect on autonomic heart rate modulation in some patients. Interestingly, many children in both groups were receiving nasal steroids, which did not seem to influence AHI normalization.

In conclusion, children with OSAS benefit from AT that reduces cardiac autonomic modulation during sleep, regardless of whether the child was considered cured as measured by AHI. We identified a previously unreported baseline difference in heart rate dynamics in children who normalize AHI spontaneously. Symbolic analysis of heart rate pattern is a robust tool for measuring the cardiac autonomic modulation and may therefore help identify children with mild–moderate OSAS who do not require surgery.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Acknowledgments

We would like to thank Michael Rueschman, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston for support with handling and interpreting the CHAT dataset. X.L., S.I., and M.B. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Y.P., J.M., and D.K. contributed substantially to the interpretation and the writing of the manuscript.

Funding

This CHAT study was supported by grants (HL083075, HL083129, UL1-RR-024134, and UL1 RR024989) from the National Institutes of Health. This study was partly funded by the Australian Research Council (DP 110102049). This project was partly supported by the interdisciplinary research fund of the University of Adelaide.

Conflict of interest statement. None declared.

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Chapter 5

Pulse wave amplitude and heart period variability in children with upper airway obstruction

LIU, X., IMMANUEL, S. A., PAMULA, Y., MARTIN, J., KENNEDY, D., KOHLER, M. & BAUMERT, M. 2018. Pulse wave amplitude and heart period variability in children with upper airway obstruction. Sleep Medicine, 50, 55-62. DOI: 10.1016/j.sleep.2018.05.020

Statement of Authorship

Title of Paper	Pulse wave amplitude and heart period variability in children with upper airway obstruction. Sleep Medicine
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	LIU, X., IMMANUEL, S. A., PAMULA, Y., MARTIN, J., KENNEDY, D., KOHLER, M. & BAUMERT, M. 2018. Pulse wave amplitude and heart period variability in children with upper airway obstruction. Sleep Medicine, 50, 55-62. DOI: 10.1016/j.sleep.2018.05.020

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Name of Principal Author (Candidate)	Xiao LIU		
Contribution to the Paper	Design, analysis and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	31/05/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	6/6/19

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Contribution to the Paper	Conception, design and interpretation of results, preparation and critical revision of the manuscript.		
Signature		Date	31/05/19

Sleep Medicine 50 (2018) 55–62

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Pulse wave amplitude and heart period variability in children with upper airway obstruction

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ARTICLE INFO

Article history:
Received 19 December 2017
Received in revised form
25 May 2018
Accepted 25 May 2018
Available online 1 June 2018

Keywords:
Upper airway obstruction
Cardiovascular control
Autonomic activation
Heart rate
Pulse wave amplitude
Adenotonsillectomy

ABSTRACT

Objective: The aim of this study was to assess cardiovascular autonomic modulation in children with upper airway obstruction (UAO), to compare this modulation to that of non-snoring children and to investigate the effect of adenotonsillectomy (AT).
Methods: ECG and finger photoplethysmographic signals obtained from overnight polysomnographic (PSG) recordings of 31 children with mild-to-moderate UAO and 34 non-snoring children were analysed. The extent of autonomic modulation was assessed by symbolic analysis of heart period (HP), pulse wave amplitude (PWA), and their joint dynamics during non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.
Results: Children with UAO showed more frequent patterns of monotonically increasing and decreasing HP in NREM sleep and monotonically increasing and decreasing joint PWA-HP patterns in REM and NREM sleep at baseline compared to controls, even when considering only periods of sleep free of discrete respiratory events. Following AT, HP, and joint PWA-HP dynamics significantly altered towards levels observed in the control group.
Conclusions: In children with mild-to-moderate UAO, cardiovascular autonomic modulation is more prevalent, even during quiet, event-free sleep. AT appears to reverse this pattern.

1. Introduction

Upper airway obstruction (UAO) is common in children and ranges from primary snoring to obstructive sleep apnoea. While UAO has been commonly associated with neurocognitive and behavioural impairment, increasing evidence suggests that it may also be associated with functional or structural cardiac changes and increased risk of cardiovascular disease later in life [1,2].

Because enlarged tonsils and adenoids are often the underlying cause of UAO in children, adenotonsillectomy (AT) is often recommended as the first line of treatment. The efficacy of AT for children with UAO is well established, but residual obstruction and parental concerns may persist post-surgery [3–7].

While severe levels of UAO can be easily identified by overnight polysomnography (PSG) using the apnoea–hypopnoea index (AHI), mild-to-moderate obstruction is less easily delineated based on AHI because it does not capture the subtle changes in breathing associated with increased inspiratory load that do not qualify as hypopnoea. Given that even children at the milder end of UAO appear to develop cognitive and cardiovascular changes, the effectiveness of AHI as a measure of paediatric UAO has become an increasing concern [3,8,9].

Chronic autonomic activation has been identified as a key driver for structural and functional cardiovascular changes in children with UAO [10–14]. Studies have shown autonomic system dysfunction in children with UAO during both sleep [15–18] and daytime wake [19]. Autonomic activation can be observed on ECG and finger photoplethysmogram (PPG) by measuring the variability in heart period (HP), pulse wave amplitude (PWA) or pulse transit time (PTT) [2,20–23]. During sleep, sympathetic overactivity and

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https://doi.org/10.1016/j.sleep.2018.05.020
1389-9457/

weaker parasympathetic modulation have been shown in children with UAO [13]. During wakefulness, magnitude of sympathetic discharge-induced attenuation of pulse arterial tonometry signal was found to be significantly increased in children with UAO [15]. Blood pressure regulation has also been explored to quantify autonomic dysfunction in children during sleep [11,14].

The aim of this study was to probe autonomic nervous system (ANS) activation in the context of UAO by measuring PWA and HP during sleep and to quantify the following: (i) the frequency of monotonic increase or decrease in beat-to-beat PWA and HP and (ii) concurrent monotonic beat-to-beat changes in both PWA and HP by using the concept of joint symbolic dynamics [24–27]. Symbolic dynamics is an effective approach to characterise the dynamics of time series. It involves coarse graining of the observed time series into a few symbols and subsequent quantification of sequences of symbols ('words'). Symbolic dynamics has been extensively explored to characterise dynamics in RR interval time series in health and disease, and its relevance in the field of heart rate variability (HRV) research has been firmly established [28]. Rather than quantifying the magnitude of HRV, the occurrence of specific patterns is quantified. Considering that the finger plethysmogram is uncalibrated and hence its variance difficult to interpret, symbolic analysis may be useful for identifying patterns of amplitude reduction typical of vasoconstriction associated with autonomic arousal. PWA changes may be more sensitive to subcortical arousal than to PTT shortening [29].

We hypothesised that autonomic activation during sleep is augmented in children with UAO compared to that in non-snoring children, and this can be captured by symbolic analysis of HP and PWA. Surgical treatment will restore the cardiac autonomic control to normal levels.

2. Material and methods

2.1. Study participants

We analysed overnight polysomnographic (PSG) recordings of 40 children with parental reports of frequent snoring (UAO) and 40 non-snoring children matched for age and gender; details of study protocols can be found in a previously published study [30]. In brief, children with UAO underwent PSG before AT and six months after the procedure. Non-snoring children underwent sleep studies at similar time points. Children were excluded if they had undergone previous ENT or craniofacial surgery; had a medical or psychological condition associated with hypoxaemia, sleep fragmentation, cognitive and/or behavioural problems and were currently taking medications known to affect sleep, respiration or neuropsychological performance. This study was approved by the Women's and Children's Health Network Human Research Ethics Committee, South Australia, with parental consent and child assent obtained from all participants.

2.2. Overnight PSG and sleep scoring

Each child was well on the night of the sleep study and free of sedation, sleep deprivation or any recent illness including respiratory infection. Overnight PSG began close to each child's usual bedtime, and a parent was present throughout the procedure. Using the S-Series Sleepwatch System (Compumedics, Australia), the following signals were continuously recorded: electroencephalogram (C3-A2 and C4-A1), left and right electrooculogram (EOG), heart rate by ECG, submental and diaphragmatic electromyogram (EMG) with skin surface electrodes, piezoelectric motion detection for leg movement, thermistor and nasal pressure to measure oronasal airflow, respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography, arterial oxygen saturation (SpO_2) by pulse oximetry (Nellcor N-595, Covidien, Ireland; with a 3-s averaging time), and transcutaneous carbon dioxide, using a heated (43 °C) transcutaneous electrode (TINA, Radiometer Pacific, Australia). Each child was monitored continuously overnight using an infrared camera and by a paediatric sleep technician who also documented observations of sleep behaviour including the presence or absence of snoring. A repeat PSG was performed on average 29.4 ± 5.9 weeks later (range 19–55 weeks), after AT for the UAO group and without any intervention for the control group.

Sleep stages were scored visually in 30-s epochs according to the standardised EEG, EOG, and EMG criteria of Rechtschaffen and Kales [31]. Movement time (>50% of an epoch obscured by movement artefact) was scored as a separate category and was not included in either sleep or wake time. Respiratory variables were scored according to standard guidelines recommended for paediatric sleep studies [32]. All respiratory events were scored if ≥2 respiratory cycles in duration and associated with a minimum 3% SaO_2 desaturation and/or an arousal within two breaths of event termination. Obstructive apnoeas were defined as the absence of airflow associated with continued chest and abdominal wall movement. Obstructive hypopnoeas were defined as a ≥50% reduction in the amplitude of RIP and/or airflow signal associated with paradoxical chest/abdominal wall movement. The presence of any other supportive data such as increased diaphragmatic or submental EMG activity was further used to distinguish obstructive from central hypopnoeas. Central apnoeas were scored if there was an absence of respiratory effort as determined by RIP and diaphragmatic EMG in association with an absence of airflow. Central apnoeas were also scored if the event lasted for ≥20 s. Central hypopnoeas were defined as a ≥50% reduction in airflow from the baseline in association with a ≥50% reduction in respiratory effort from the baseline. Apnoea events that included both central and obstructive components were scored as a mixed apnoea. The obstructive apnoea–hypopnoea index (OAHI) was calculated as the total number of obstructive apnoeas, mixed apnoeas, and obstructive hypopnoeas per hour of total sleep time. The total number of obstructive apnoeas, mixed apnoeas, and obstructive hypopnoeas divided by the total sleep time and expressed as the number of events/h of sleep yielded the OAHI. The SpO_2 desaturation index represents the number of ≥3% O_2 desaturations/h of sleep. The BMI z-scores were calculated using the height and weight of the children measured on the night of PSG along with established growth charts corrected for age and gender [33].

2.3. PWA and HP measurement

In this study, finger PPG and ECG signals were analysed. Both signals were sampled at 500 Hz and used to extract PWA and HP, respectively.

HP was measured on the basis of QRS locations in ECG that were automatically detected using a template matching algorithm and subsequently visually checked for errors, which were manually corrected.

The PWA was measured for each cardiac cycle as the amplitude difference between the systolic peak and the preceding diastolic valley of the PPG signal. PWA values were calculated only if a valid pulse waveform could be identified within the time frame defined by concurrent QRS complexes in ECG. For details, see online supplement.

2.4. Joint symbolic dynamics of PWA and HP

Beat-to-beat values of PWA and HP were transformed into a sequence of symbols {0, 1 and 2} based on the tertiary

symbolisation scheme proposed by Baumert et al. [24], where symbols are assigned on the basis of the following rules:

$$s_n = \begin{cases} 0 : (x_n - x_{n-1}) > l_x \\ 1 : (x_n - x_{n-1}) < -l_x \\ 2 : Otherwise \end{cases} \quad (1)$$

where s_n is the nth symbol in the beat-to-beat time series, x_n is the nth PWA or HP in the beat-to-beat time series, x_{n-1} is the preceding PWA or HP in the beat-to-beat time series and l_x is a pre-defined non-negative threshold set for PWA or HP time series. In other words, symbol 0 represents that the value difference between current PWA or HP value and the previous one is greater than the defined threshold l_x, symbol 1 for the value difference less than the negative value of the defined threshold l_x and symbol 2 is for anywhere else. From the resulting symbolic sequences, a series of 'words' of length three were constructed using a sliding window approach, ie the window slides only by one symbol to the right at the time. Because the word length is three and each symbol is taken from an alphabet of three, the total number of possible word types (eg, 020, 001, 201, …) is 27 ($3^3 = 27$) (see Fig. 1).

The relative frequency of words 000 and 111, quantifying the presence of monotonic increase and decrease of PWA or HP, was used as a novel marker of autonomic activation during sleep. When observed in HP, these symbolic patterns may capture cyclic bradycardia–tachycardia sequences associated with obstructive apnoeas [34], whereas in PWA, these patterns capture tonic vasoconstrictions mediated by sympathetic activation owing to cortical and/or subcortical arousal [35]. We also considered the joint occurrence of these patterns in both PWA and HP as an additional marker of monotonic changes.

Suitable values for the threshold l_x were identified by systematically investigating its ability for differentiating HP and PWA dynamics in children with UAO and non-snoring children, thereby yielding suitable values of 0 ms for HP and 0 normalised units for PWA, respectively. For details, see online supplement.

2.5. Statistical analysis

Anthropometric data were compared using one-way ANOVA. PWA, HP and joint HP-PWA patterns were analysed separately for NREM and REM sleep stages. The pairwise t-test was used to examine the effect of sleep stage on PWA, HP and joint HP-PWA patterns. Two-way ANCOVA was carried out to test the effects of study (baseline versus follow-up; repeated measure) and group on PWA, HP and joint HP-PWA patterns across, followed by post-hoc comparison using the Bonferroni test. In the initial analysis, we included the entire PSG to quantify the full extent of autonomic modulation in the presence of respiratory perturbation. Subsequently, we reanalysed scored event-free sections of the PSG to investigate whether autonomic activity is generally altered in the absence of events triggering autonomic cardiovascular response.

Anthropometric variables that were likely to confound statistical analysis (body mass index (BMI) z-score at baseline, BMI z-score at follow-up, age at baseline and gender) were included in the model as covariates. Spearman correlation analysis was performed to explore the relationship with AHI at baseline and follow-up.

3. Results

3.1. Anthropometric data

In total, 65 of original study participants, who underwent both baseline and follow-up PSG and whose plethysmography and ECG signals met the technical criteria, were included in our study. Fourteen children were excluded because of a missing pulse signal in either one of the baseline or follow-up PSG. One child was excluded because of a missing BMI z-score. Of the remaining participants, 34 children were non-snoring and 31 children had UAO. Both groups had comparable demographic profiles (Table 1). The mean age of the participants at baseline was 7.6 years, and 56.9% were male. There was no significant age difference between the two groups at both baseline and follow-up. No significant difference in BMI z-score was found at baseline, but a slightly increased BMI z-score was observed in the UAO group compared to controls at follow-up. The average OAHI was significantly higher in children with UAO than in controls at baseline. In the control group, all children had a normal OAHI (ie, <1), whereas 20 children in the UAO group had an OAHI <5 (ie, mild-to-moderate severity). After AT, the UAO group still had a small but significantly higher average OAHI, but no child had an OAHI >5.

3.2. Sleep stage and cardiovascular dynamics

To investigate the effect of sleep stage on symbolic and joint symbolic dynamics of interest derived from PWA and HP, we considered baseline PSG data from non-snoring children and children with UAO (Table 2). Pairwise t-tests showed significantly higher values in REM than in NREM sleep for all the measures in both groups, when considering both event-free sleep and the entire PSG, except for HP, which did not show significant group differences when the entire PSG was analysed. Because of the significant sleep stage differences in PWA, HP, and joint HP-PWA patterns, all subsequent data analyses were performed separately for these sleep stages.

3.3. UAO and cardiovascular dynamics during the entire sleep period

The results of two-way ANCOVA analysis based on symbolic and joint symbolic dynamics of interest derived from HP and PWA during the entire night sleep are summarised in Table 3. Although no significant overall group differences between UAO and controls or overall time effects between baseline and follow-up were observed for PWA, HP and their joint patterns in either REM or NREM sleep, we identified significant study × group interaction effects in HP and joint HP-PWA patterns across both NREM and REM sleep as well as in PWA patterns during REM sleep. The results are consistent with a higher relative frequency of symbolic patterns associated with monotonic increases and decreases in HP and PWA in children with UAO at baseline. Post-hoc comparison (Fig. 2) confirmed significantly higher relative frequencies of HP and joint HP-PWA patterns measures in children with UAO than in non-snoring children in NREM sleep at baseline only (HP: $p = 0.018$; joint HP-PWA: $p = 0.011$). Following AT, children with UAO showed significantly lower relative frequencies of HP and joint HP-PWA measures than those at baseline in NREM sleep (HP: $p < 0.0001$; joint HP-PWA: $p < 0.0001$) and significantly lower relative frequencies of all three dynamics measures at follow-up than those at baseline in REM sleep (PWA: $p = 0.015$; HP: $p = 0.0004$; joint HP-PWA: $p = 0.0002$).

3.4. UAO and cardiovascular dynamics during event-free sleep

Similar to the results reported in the previous section, no significant overall group effects or overall time effects on HP, PWA, and joint HP-PWA dynamics were observed during analysis of scored event-free periods of sleep (Table 4). Study × group interaction effects were significantly different for HP and joint HP-PWA patterns across both NREM and REM sleep and were significantly

Table 1
Subject demographics of non-snoring children (Control) and children with upper airway obstruction (UAO) at baseline and follow-up.

Variables	Baseline			Follow-up		
	Control (n = 34)	UAO (n = 31)	p	Control (n = 34)	UAO (n = 31)	P
Age, years	7.9 ± 2.7	7.1 ± 2.6	ns	8.3 ± 2.7	7.8 ± 2.6	ns
BMI z-score	0.35 ± 0.88	0.67 ± 1.35	ns	0.34 ± 0.85	0.89 ± 1.18[a]	0.032
OAHI (median, range)	0.32 ± 1.21	6.19 ± 10.06[a]	0.0015	0.26 ± 0.35	0.90 ± 0.97[a]	0.0006
	0.00 (0–7)	2.75 (0–49.64)		0.16 (0–1.69)	0.58 (0–3.17)	
CAHI (median, range)	0.70 ± 0.84	1.38 ± 2.22	ns	0.49 ± 0.58	0.90 ± 0.74[a]	0.017
	0.41 (0–4.42)	0.65 (0–10.28)		0.33 (0–2.76)	0.95 (0–2.79)	
Gender, n	17 males, 17 females	20 males, 11 females		17 males, 17 females	20 males, 11 females	

Data are presented as mean ± SD.
[a] Significant difference between UAO OAHI at baseline and follow-up and BMI z-score at follow-up.

different in REM for PWA dynamics, all showing higher relative frequencies in children with UAO group before AT (Table 4). Post-hoc comparison (Fig. 2) at baseline confirmed that, compared to the controls, the UAO groups showed significantly higher relative frequencies of HP and joint HP-PWA dynamics measures during NREM sleep (HP: $p = 0.033$; joint HP-PWA: $p = 0.023$), whereas joint HP-PWA dynamics were more frequent during REM sleep ($p = 0.026$). Following AT, the UAO group showed significantly reduced relative frequencies of HP and joint dynamics measures in NREM sleep (HP: $p < 0.0001$; joint HP-PWA: $p = 0.00028$) and all three measures of symbolic dynamics in REM sleep compared to baseline (PWA: $p = 0.0091$; HP: $p = 0.00024$; joint HP-PWA: $p < 0.0001$).

3.5. Correlation between PWA, HP and their joint dynamics and clinical measures of UAO

Significant positive correlations were found between PWA, HP, and joint HP-PWA dynamics measures with OAHI in baseline PSG during both NREM sleep (PWA: $r = 0.309$, $p = 0.012$; HP: $r = 0.287$, $p = 0.020$; joint HP-PWA: $r = 0.343$, $p = 0.005$) and REM sleep of overnight sleep (HP: $r = 0.256$, $p = 0.040$; joint HP-PWA: $r = 0.245$, $p = 0.049$). Similar results were observed when considering only the event-free periods of NREM sleep (PWA: $r = 0.283$, $p = 0.022$; HP: $r = 0.272$, $p = 0.028$; joint HP-PWA: $r = 0.297$, $p = 0.016$) and REM sleep (HP: $r = 0.256$, $p = 0.039$) during baseline PSG.

4. Discussion

The main finding of our study is significantly altered dynamics of HP as well as joint patterns of HP and PWA during sleep in children with UAO compared to age- and sex-matched non-snoring children. This was observed in sleep that included discrete respiratory events, but notably, this was also observed during quiet, event-free segments of NREM sleep. Joint HP-PWA patterns were also significantly more pronounced during event-free REM sleep, thus indicative of more frequent ANS activation in children with UAO. Following AT, these cardiovascular activations significantly reduced compared to baseline and appeared to normalise and were no longer different from those of non-snoring children. In addition, PWA patterns normalised in REM sleep but not in NREM sleep.

Both HP and PWA provide non-invasive measures of cardiovascular oscillations and response to cortical and subcortical activation [2,21,22]. PWA has been shown to attenuate as part of the sympathetic nervous system activation because of subcortical arousal, which results in peripheral vasoconstriction [2,20]. Partial UAO, which is not clinically scored according to current guidelines, could still trigger increase in heart rate and blood pressure. Contraction of peripheral arterial blood vessels increases blood flow velocity and reduces PWA. Although both HP and PWA show a consistent response to arousal, they still react somewhat differently when the body is exposed to different stressors [22]. An oscillatory pattern in heart rate is observed as it recovers to baseline after a normoxic event, but not after a hypoxic event. However, this phenomenon has not been observed in PWA. Our results support the differentiated HP and PWA response as illustrated by a frequency of joint HP-PWA patterns which is much lower than that the frequency of PWA and HP patterns (Fig. 2).

Comparing NREM sleep with REM sleep, monotonic HP and PWA patterns as well as their joint occurrence were generally more frequent in the latter, thus reflecting higher levels of ANS activation. In children with UAO, there was no statistical difference in HP patterns when respiratory events were included in the analysis, possibly reflecting the cumulative effect of heart rate response to obstruction.

Our study suggests that all three measures add information towards quantifying the level of autonomic activation in children with predominately, mild-to-moderate UAO, even in the absence of discrete respiratory events. Because complete obstructions are rare in children at the milder end of the UAO spectrum, the OAHI cannot characterise the full extent of symptoms and sequelae of UAO such as those during subtler version of obstructed breathing not

Table 2
Comparison of pulse wave amplitude (PWA), heart period (HP) and their joint symbolic dynamics between REM and NREM sleep in each group at baseline PSG.

Parameter	Control (N = 34)		*p* value	UAO (N = 31)		*p* value
	NREM	REM		NREM	REM	
Entire PSG						
PWA [%]	31.1 ± 8.01	36.2 ± 7.47	<0.0001	35.4 ± 7.84	39.5 ± 6.68	<0.0001
HP [%]	14.9 ± 5.71	18.1 ± 5.15	<0.0001	19.8 ± 7.09	20.8 ± 5.11	0.151
Joint HP-PWA [%]	3.35 ± 1.87	4.75 ± 2.18	<0.0001	5.15 ± 2.66	6.24 ± 2.54	<0.001
Event-free						
PWA [%]	30.1 ± 8.30	35.6 ± 7.71	<0.0001	34.1 ± 8.53	38.9 ± 7.37	<0.0001
HP [%]	13.8 ± 5.87	16.9 ± 5.31	<0.0001	18.5 ± 7.59	20.1 ± 5.56	0.023
Joint HP-PWA [%]	2.69 ± 1.76	4.11 ± 2.13	<0.0001	4.29 ± 2.67	5.70 ± 2.52	<0.0001

All *p* values have been obtained using paired *t*-tests.

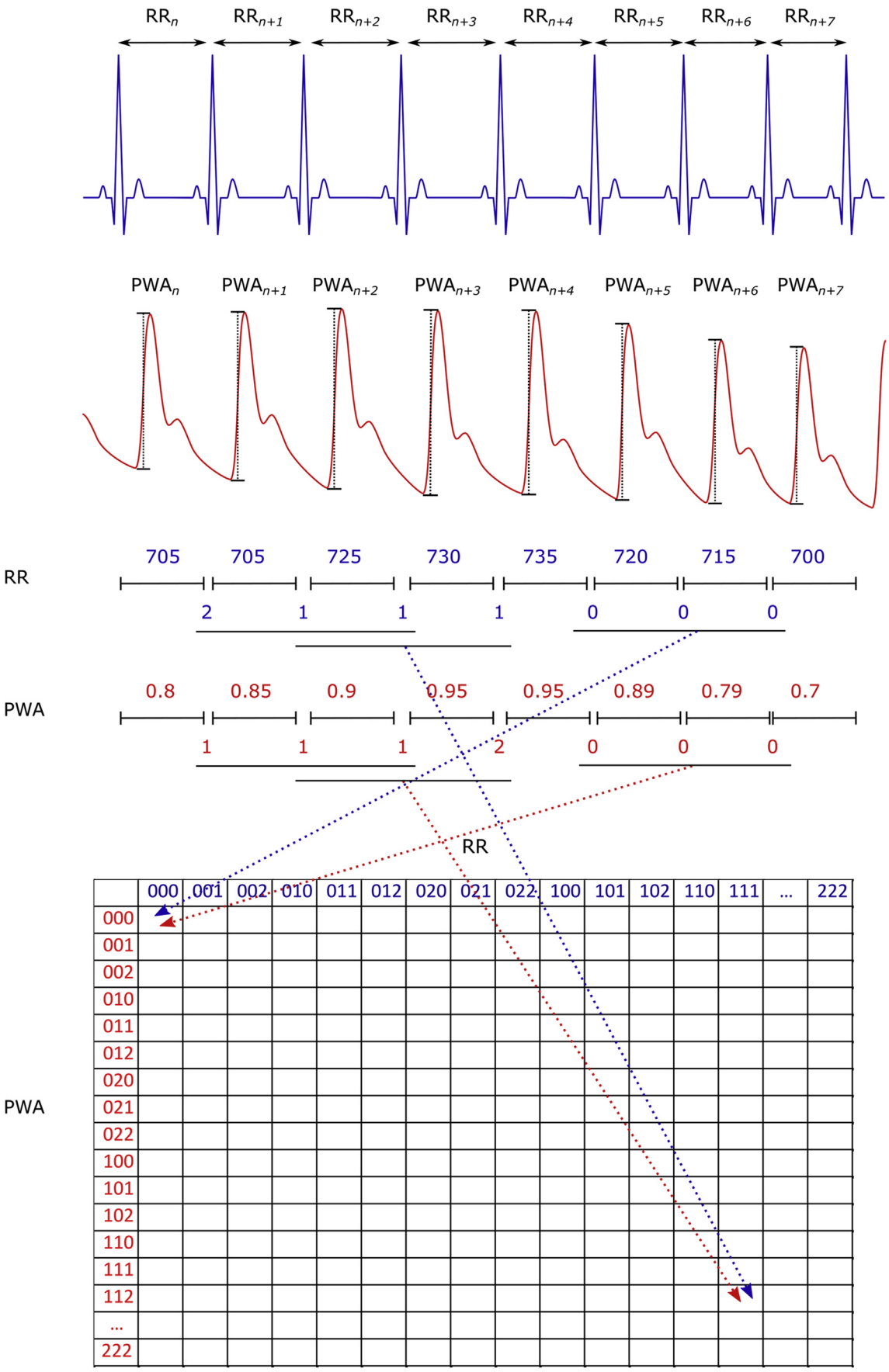

Fig. 1. Schematic illustrating the analysis of symbolic dynamics of heart period (RR) and pulse wave amplitude (PWA). Joint symbolic dynamics are captured in the diagonals of the Word-type distribution matrix.

Table 3
Comparison of pulse wave amplitude (PWA), heart period (HP) and their joint symbolic dynamics obtained from REM and NREM sleep periods of overnight PSG.

Parameter	Control (N = 34)		UAO (N = 31)		*p* value		
	Baseline	Follow-up	Baseline	Follow-up	Study	Group	Study x Group
PWA NREM [%]	31.1 ± 8.01	30.7 ± 8.60	35.4 ± 7.84	32.1 ± 8.01	0.385	0.254	0.116
PWA REM [%]	36.2 ± 7.47	36.6 ± 7.84	39.5 ± 6.68	36.8 ± 7.10	0.704	0.767	0.027
HP NREM [%]	14.9 ± 5.71	15.2 ± 6.08	19.8 ± 7.09	14.9 ± 5.63	0.823	0.298	<0.0001
HP REM [%]	18.1 ± 5.15	17.9 ± 4.64	20.8 ± 5.11	17.9 ± 4.46	0.501	0.487	0.025
Joint HP-PWA NREM [%]	3.35 ± 1.87	3.34 ± 2.09	5.15 ± 2.66	3.61 ± 1.88	0.586	0.105	0.0040
Joint HP-PWA REM [%]	4.75 ± 2.18	4.81 ± 2.26	6.24 ± 2.54	4.88 ± 1.89	0.382	0.434	0.0037

All *p* values have been obtained using two-way ANCOVA adjusted for likely confounding factors of age at baseline (3.25–12.87 years of age), BMI z-score at baseline, BMI z-score at follow-up and gender.

identified as an apnoeic event [36,37]. All three measures were positively associated with OAHI throughout NREM sleep, especially joint PWA-HP patterns. Possibly, the relative dormancy of the sympathetic nervous system during normal NREM sleep makes our novel measures more susceptive to ANS activation patterns. By contrast, baseline sympathetic activity is already high in REM sleep; the superimposed effect of UAO may be comparably lower.

Despite a relatively low incidence of monotonic increases and decreases, more robust information on cardiovascular activation related to UAO may be obtained by analysing HP and PWA patterns jointly. Although PWA patterns were not discriminatory, joint analysis of PWA-HP patterns yielded bigger differences than HP patterns alone, in the ability to distinguish between groups. Presumably, a higher AHI is also associated with a more frequent subcortical arousal even in the absence of obstructive apnoeas or hypopnoeas.

Previous studies have demonstrated that AT is effective in reducing the number of apnoeic events in children with UAO, but some of the UAO symptoms remain post AT [4–6,38], such as non-specific impaired breathing. However, we have previously shown in these data that AT also normalises overall increased inspiratory effort caused by UAO, as indicated by lower thoracoabdominal asynchrony after surgery [39], which we subsequently confirmed in a secondary analysis of the childhood AT trial [40]. Notably, thoracoabdominal asynchrony was inversely related to quality of life. This raises the question whether AHI, the current clinical diagnostic marker that quantifies UAO in children, is effective. This study suggests that children with primarily mild-to-moderate UAO also benefit from AT, which resulted in normalised PWA, HP, and joint PWA-HP patterns in REM sleep as well as HP and joint PWA-HP patterns in NREM sleep (Fig. 2).

PPG is non-invasive and a commonly used physiological signal for probing cardiac pulse waves. It is readily available in most PSG systems, and it can be used to extract simple non-invasive measures of autonomic activity such as PTT in addition to PWA [22]. While PWA measures the amplitude of each pulse, PTT measures the time taken for a pulse to propagate through the arterial tree. Both PWA and PTT react in a similar way to autonomic arousal, but it remains to be established which measure is more sensitive. In our previous study of HP and PTT that utilised a similar symbolic

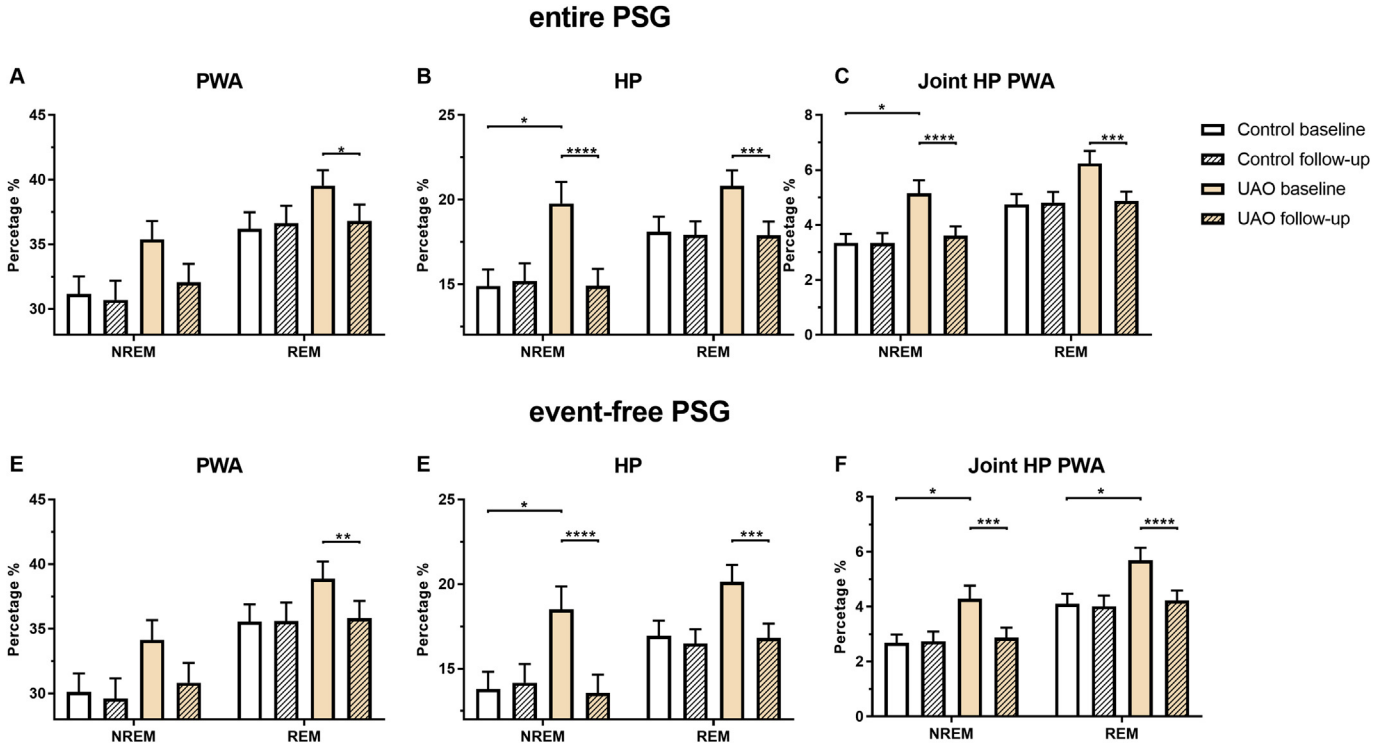

Fig. 2. Bar plots of univariate PWA, HP and joint HP-PWA dynamics throughout the entire sleep recordings (A–C) and during event-free sleep (D–F) at baseline and follow-up for both non-snoring children (control), and children with upper airway obstruction (UAO). Data are presented as mean ± SEM. NREM: non–rapid eye movement sleep; REM: rapid eye movement sleep. *: p < 0.05; **: p < 0.01; ***: p < 0.001; ****: p < 0.0001.

Table 4
Comparison of pulse wave amplitude (PWA), heart period (HP) and their joint symbolic dynamics in event-free periods between study as well as groups for non-REM and REM sleep stages.

Parameter	Control (N = 34)		UAO (N = 31)		*p* value		
	Baseline	Follow-up	Baseline	Follow-up	Study	Group	Study x Group
PWA NREM [%]	30.1 ± 8.30	29.6 ± 9.10	34.1 ± 8.53	30.8 ± 8.59	0.414	0.308	0.145
PWA REM [%]	35.6 ± 7.71	35.6 ± 8.31	38.9 ± 7.37	35.8 ± 7.40	0.755	0.659	0.028
HP NREM [%]	13.8 ± 5.87	14.2 ± 6.36	18.5 ± 7.59	13.6 ± 6.01	0.884	0.417	<0.0001
HP REM [%]	16.9 ± 5.31	16.5 ± 4.90	20.1 ± 5.56	16.8 ± 4.70	0.389	0.308	0.030
Joint HP-PWA NREM [%]	2.69 ± 1.76	2.74 ± 2.08	4.29 ± 2.67	2.88 ± 1.98	0.561	0.186	0.0065
Joint HP-PWA REM [%]	4.11 ± 2.13	4.02 ± 2.30	5.70 ± 2.52	4.24 ± 1.95	0.555	0.228	0.005

All *p* values have been obtained using two-way ANCOVA adjusted for likely confounding factors of age at baseline (3.25–12.87 years of age), BMI z-score at baseline, BMI z-score at follow-up and gender.

dynamics approach, no significant improvement was found in children with UAO [41], whereas multivariate autoregressive modelling of HP and PWA dynamics identified improvement in cardiovascular control following AT in these children [42].

Consistent with previous findings [43,44], BMI increased following AT. Although it is beyond the scope of this study to determine why this occurs, it is important to consider the impact of disproportionate growth on PWA and HP.

Our study has several limitations. The age of the children varied across a wide range, which might have affected the results. Younger children are more likely to have ANS activation than older children because of the development of the ANS [45]. The severity of UAO varied broadly, although most children had mild-to-moderate UAO levels, which, together with the small sample size, prevented us from analysing the effect of severe UAO on ANS activation. Owing to the lack of calibration of finger plethysmograms, our analysis does not rely on absolute values of PWA. Therefore, the dynamic change of PWA only captures relative changes in peripheral vascular tone and sympathetic nervous system activation, respectively. Because the original study commenced before the release of the ASSM recommendations, Rechtschaffen and Kales criteria were used for scoring.

5. Conclusion

Symbolic analysis of joint PWA-HP dynamics suggests increased activation of ANS in children with UAO that persists throughout scored event-free sleep. This implies that AT not only resolves respiratory obstructions in children with UAO but also normalises the ANS activation during scored event-free sleep. Assessing joint PWA-HP patterns may provide additional information when assessing UAO when combined with current clinical criteria using overnight PSG. This study adds to a growing body of evidence that ANS dysfunction is evident even in children with mild-to-moderate UAO, which if left untreated may be the precursor to the development of cardiovascular disease in adulthood.

Acknowledgement

This study was partly supported by a grant from the Australian Research Council (DP0663345).

Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.05.020.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sleep.2018.05.020.

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Chapter 6

Utilisation of machine learning to predict surgical candidates for treatment of childhood upper airway obstruction

LIU, X., PAMULA, Y., IMMANUEL, S. A., MARTIN, J., KENNEDY, D. & BAUMERT, M. 2019. Utilisation of machine learning to predict surgical candidates for treatment of childhood upper airway obstruction. (Unsubmitted manuscripts)

Statement of Authorship

Title of Paper	Utilisation of machine learning to predict surgical candidates for treatment of childhood upper airway obstruction
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☑ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	**LIU, X.**, IMMANUEL, S. A., PAMULA, Y., MARTIN, J., KENNEDY, D. & BAUMERT, M. 2019. Utilisation of machine learning to predict surgical candidates for treatment of childhood upper airway obstruction.

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Contribution to the Paper	Conception, design, analysis and interpretation of the data; the drafting and revision of the manuscript and final approval of the version to be submitted		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	31/05/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Utilisation of machine learning to predict surgical candidates for treatment of childhood upper airway obstruction

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Abstract

Objective: To investigate the effect of adenotonsillectomy on OSAS symptoms based on a data-driven approach and thereby identify criteria that may help avoid unnecessary surgery in children with OSAS.

Methods: In 323 children enrolled in the Childhood Adenotonsillectomy Trial, randomized to undergo either early adenotonsillectomy (eAT; N=165) or a strategy of watchful waiting with supportive care (WWSC; N=158), the apnea-hypopnea index, heart period pattern dynamics and thoraco-abdominal asynchrony measurements from overnight polysomnography (PSG) were measured. Using machine learning, all children were classified into one of two different clusters based on those features. The cluster transitions between follow-up and baseline PSG were investigated for each to predict those children who recovered spontaneously, following surgery and those who did not benefit from surgery.

Results: The two clusters showed significant differences in OSAS symptoms, where children assigned in cluster A had fewer physiological and neurophysiological symptoms than cluster B. While the majority of children were assigned to cluster A, those children who underwent surgery were more likely to stay in cluster A after 7 months. Those children who were in cluster B at baseline PSG, were more likely to have their symptoms reversed via surgery. Children who were assigned to cluster B at both baseline and 7 months after surgery had significantly higher end-tidal carbon dioxide at baseline. Children who spontaneously changed from cluster B to A presented highly problematic ratings in behaviour and emotional regulation at baseline.

Conclusions: Data-driven analysis demonstrated that AT helps to reverse and to prevent the worsening of the pathophysiological symptoms in children with OSAS. Multiple pathophysiological markers used with machine learning can capture more complete information of childhood OSAS. Children with mild physiological and neurophysiological symptoms could avoid AT, and children who have UAO symptoms post AT may have sleep-related hypoventilation disease which requires further treatment. Furthermore, the findings may help surgeons more accurately predict who they should perform AT on.

Keywords: sleep apnea, children, adenotonsillectomy, machine learning, data-driven

Statement of significance

This study shows that machine learning can be used to demonstrate the efficacy of adenotonsillectomy for childhood obstructive sleep apnea syndrome. We identified previously unreported baseline differences in children who reversed their pathophysiological symptoms spontaneously and therefore could avoid surgery. The combination of OAHI3, N2 event free heart period pattern dynamics and N3 event free thoraco-abdominal asynchrony measurements may, help identify children with mild-moderate symptoms who do not require surgery.

Chapter 6

Introduction

Between 3 to 15% of children are reported as having upper airway obstruction (UAO) during sleep [1]. Although a wide spectrum of UAO from primary snoring to obstructive sleep apnea syndrome (OSAS) exists, the majority of children are at the milder end of the range. Children with UAO have demonstrated impaired neurocognitive and behavioural function [3-5] and increasing evidence suggests they also have altered cardiovascular function [6]. OSAS is considered a key driver of changes in the cardiovascular system [7-9] that may lead to cardiovascular disease later in life [10-13]. Early detection and treatment of UAO in childhood may therefore reduce cardiovascular morbidity in adulthood.

Contrary to adults, OSAS in otherwise normal healthy children stems most commonly from enlarged tonsils and adenoids. The first-line treatment is, therefore, adenotonsillectomy (AT), which reduces upper airway resistance by removing the enlarged tissue. Although AT has demonstrated positive health outcomes in children with significant OSAS, residual symptoms often exist in some children and related parental concerns also persist post-surgery [14-18].

In contrast, the benefits of AT in children with milder UAO remains largely untested. The landmark Childhood Adenotonsillectomy Trial (CHAT) reported around 46% of the children had their apnea-hypopnea index (AHI) spontaneously normalise without having AT treatment [19]. The AHI metric is obtained from overnight polysomnography (PSG) and is the current clinical measure of UAO severity and a major determinant in the decision to treat UAO. However, concerns have been raised about the limitations of the AHI as it over-simplifies the spectrum and severity of UAO and correlates poorly with numerous health endpoints [20-22]. This raises the question of how to identify individuals for whom surgery will be beneficial and those who may recover without surgery, thereby reducing the health care costs and risks of performing AT [15-17].

Children with mild UAO generally have a low AHI, and it is currently not known if they would benefit from AT as the AHI only measures the frequency of discrete respiratory events but not necessarily the severity. Furthermore, other markers of UAO such as increased respiratory load and other abnormal breathing patterns are not quantified in routine PSG [22]. Even though some children enrolled in the CHAT had spontaneously normalised AHI at follow-up without surgical intervention, our previous study found that those children had a relatively lower quality of life after 7 months compared to who AHI normalised via AT [23]. This illustrates one of the numerous limitations of relying on the AHI as the sole measure of UAO severity.

Our previous studies have found that those children whose AHI-normalised spontaneously in the CHAT had relatively lower cardiac autonomic activation and inspiratory load at baseline than children who's AHI did not resolve spontaneously [23, 24]. Similar findings were shown in studies on normal children in comparison with children with sleep-disordered breathing [25, 26]. Further analysis of the CHAT suggested that the Paediatric Sleep Questionnaire (PSQ) and snoring score could be used to identify children who do not need AT [27].

To overcome limitations of the current diagnostic criteria for childhood UAO, assessment should comprise multiple physiological variables rather than relying on the AHI alone. Using a data-driven approach, children with similar pathophysiological profiles should cluster into the same group and possibly help identify which children have fewer pathophysiological symptoms thereby possibly not requiring surgery. The emergence of large data sets in the medical field in recent years has seen machine learning increasingly being utilised to aid diagnosis, prognosis and treatment decisions across a range of clinical disciplines including sleep disorders [28-31]. The aim of this study therefore was to investigate the effects of AT for OSAS using a data-driven approach that combines cluster analysis and linear discriminant analysis. Using baseline and follow-up measurements of the CHAT dataset, we sought to create better diagnostic criteria for OSAS in children. By analysing the transition of children between clusters from baseline to follow-up data, it may be possible to predict when AT is needed.

Method

Study samples

Details of the CHAT protocol have been previously published [32]. All data are publicly available at https://sleepdata.org/datasets/chat. In brief, children between 5.0-9.9 years of age with PSG-confirmed OSAS (obstructive apnea-hypopnea index [AHI] ≥2 events/h or an obstructive apnea index [OAI] ≥1 events/h), a history of snoring and considered to be surgical candidates for AT were recruited from paediatric sleep centres/sleep laboratories, paediatric otolaryngology clinics, general paediatric clinics and the general community from six clinical centres. Exclusion criteria included comorbidities, medications for psychiatric or behavioural disorders, recurrent tonsillitis, extreme obesity (body mass index >2.99 for age group and sex-z-score) and severe OSAS (AHI ≥ 30 events/h, OAI ≥20 events/h or oxyhemoglobin saturation <90% for >2% of total sleep time). The study was approved by the Institutional Review Board of each institution. Informed consent was obtained from caregivers, and assent from children ≥7 years of age. The study was registered at Clinicaltrials.gov (#NCT00560859).

CHAT interventions

Children were randomly assigned to either early adenotonsillectomy (eAT; surgery within 4 weeks after randomization) or a strategy of watchful watching with supportive care (WWSC) with a reassessment of all the study variables at approximately 7 months. Complete bilateral tonsillectomy and removal of obstructing adenoid tissue were performed using standard surgical techniques.

Overnight polysomnography

Each child underwent in-laboratory baseline and follow-up PSG carried out by study-certified technicians, following the American Academy of Sleep Medicine paediatric guidelines for both acquisition and scoring [33]. The PSGs were scored centrally by registered sleep technicians. Overnight PSG was repeated approximately 7 months after randomization [32, 34].

Data-driven analysis

The goal of our data-driven analysis (Figure 2) was to assign all children to one of two clusters (named A and B) based on three variables that we have previously identified as potentially useful discriminators: (1) OAHI3 (as derived from the CHAT study), (2) heart period (HP) pattern dynamics in N2 and REM sleep, and (3) thoraco-abdominal asynchrony (TAA, log-transformed) during N3 sleep, (the latter two variables were discriminators calculated using original methods

[23, 24]). OAHI3 represents the number of apneas and hypopneas per hour of sleep associated with a > 3% oxygen desaturation. OAHI3 was transformed due to its nonlinearity using box-cox transformation with lambda at 0.2019. Heart period patterns quantify the degree of cardiac autonomic modulation related to OSAS and were demonstrated to help to identify children who spontaneously normalised their AHI without surgery at baseline [24]. We chose event-free N2 sleep for analysis because it provides more reliable and stable recordings than REM sleep. To measure inspiratory-effort changes due to upper airway obstruction we considered N3 sleep epochs free of respiratory events [23].

All features were normalised to zero mean and unit variance prior to further analysis. We used the CHAT follow-up PSG, including children from both arms (WWSC and eAT), for training the classifier, whereas baseline PSG was used as the predicating dataset.

Cluster definition

The characteristics of the two clusters were determined with the CHAT follow-up dataset using the K-mean clustering method, which is a frequently utilised unsupervised machine learning technique [35]. To separate the two clusters, two points are randomly chosen as the initial cluster centroid. Subsequently, each data point is assigned to its closest cluster, based on the shortest space representation distance to the cluster centroid compared the other cluster centroids. The cluster centroid is recalculated every time a data point was assigned to a cluster. This process is repeated until the centroid of each cluster no longer changes. We used the squared Euclidean distance to represent space, and the clustering was repeated 20 times to obtain the best clustering results, where a new set of initial centroids was used each time.

Classification using Linear Discriminant Analysis

Once the two reference clusters were defined on the follow-up dataset, linear discriminant analysis (LDA) was used to create a classifier model. The LDA is a supervised machine learning method frequently used to reduce the feature space dimension, maximizing the difference in means between classes while minimising the variance of each class to separate two or more classes by finding a linear combination of predictive features. The LDA model was used to validate the follow-up dataset and classify the baseline dataset.

Definition of cluster transition classes

Four transition classes were defined according to the cluster change from baseline to follow-up study, which are baseline cluster A to Follow-up cluster B (A→B), baseline cluster B to follow-

up cluster A (B→A), baseline cluster A to follow-up cluster A (A→A), and baseline cluster B to follow-up cluster B (B→B). The cluster transitions were used to identify children would not need AT surgery.

Statistical analysis

Anthropometric data were compared by using t-tests and X^2 tests as appropriate. One-way analysis of covariance (ANCOVA) was carried out to investigate the effect of clustering on key physiological and neurophysiological measurements on all available data. One-way analysis of covariance (ANCOVA) was also carried out to investigate the effect of cluster transition classes on key physiology and neurophysiological measurements for baseline watchful waiting and eAT groups respectively, followed by a Bonferroni test based on Student's t statistic for post-hoc comparisons. The key physiological and neurophysiological measurements included in the analysis were: obstructive apnea-hypopnea index (>=3% desaturation, OAHI3), central apnea index all desaturations (CAI0P), percentage of time < 90% oxygen saturation (SaO2) (PCTLT90), percentage of total sleep time (TST) where end-tidal carbon dioxide (ETCO2) > 50 mmHg (RPCTCO2G50), event free symbolic HP patterns, event free TAA, previously reported measures of behaviour, OSAS symptom indicators, pediatric sleep questionnaire scale, global quality of life and intellectual functioning (DAS-II GCA). Anthropometric variables that were likely to confound statistical analysis (BMI z-score, age, gender and race) were included in the statistical model as covariates.

Results

Subject Demographics

A total of 323 children of the original CHAT study who underwent both baseline and follow-up studies and who had all three physiological discriminators and PSG that met the technical requirements were included in this analysis. The dataset comprised 165 children who underwent eAT and 158 children in the WWSC group (**Figure 1**). Baseline anthropomorphic characteristics are summarized in Table 1. Both groups had comparable demographic profiles. Overall, the mean age of the participants at baseline was 6.6 years and 48% were male. Approximately half (54.5%) of the samples were African American and 34.4% were obese. Around 4.6% of children were treated with Montelukast and approximately 21.1% received nasal glucocorticoids for rhinitis or asthma at the time of the baseline PSG. At follow up, 83% of subjects in the eAT group no longer had AHI-defined OSAS, i.e. values of AHI $\leqslant$2 and OAI $\leqslant$1, while in the WWSC group 40.5% of children had spontaneous normalization of AHI scores. Approximately 6.7% of children in the eAT arm and 8.7% in the WWSC arm were on Montelukast and 23.6% (eAT) and 26.6% (WWSC) were on nasal glucocorticoids at the time of the follow-up PSG, representing a small but statistically non-significant increase compared to the baseline sample.

Chapter 6

Data-driven Analysis

Patient clustering using the K-mean clustering method

From the follow-up dataset (**Table 2**), 199 out of 323 children were assigned to cluster A, which has its centroid at OAHI3, HP patterns and TAA values of -0.484, -0.444 and -0.385, respectively. The remaining 124 children were assigned to cluster B whose centroid of OAHI3, HP patterns and TAA dimensions was located at 0.763, 0.705 and 0.603, respectively. Considering the positive effect of surgery, 132 children (80 %) in the intervention arm were assigned to cluster A and 33 children (20%) assigned to cluster B. Of the children in the WW arm, around 42.4% (67 children) were part of cluster A and the remaining 57.6% (91 children) were part of cluster B.

Classification of children using linear discriminate analysis of follow-up PSG

Considering the clustering results of the previous section, LDA was employed to create a function that separates both clusters. Defining the coefficients of classification equation as

$$Y = -2.2259 * OAHI3 - 2.8297 * HP - 2.3290 * TAA + 1.3966,$$

Where values of Y ≤ 0, result in a given child classified cluster A (otherwise cluster B), yields classification results shown in **Figure 3**.

The accuracy of the classification results for the follow-up dataset is:

$$Accuracy = \frac{TA + TB}{TA + FA + TB + FB} = \frac{199 + 122}{199 + 2 + 122 + 0} = 99.38\%$$

Where TA is the true classification of cluster A, FA is the false classification of cluster A, TB is the true classification of cluster B and FB is the false classification of cluster B. The results obtained for the follow-up study with LDA (**Table 3)** was in agreement with the K-means clustering results.

Eighty-one percent of children who underwent surgery (134 out of 165 children) were classified into cluster A and 19% (31 out of 165) into cluster B (**Tables 2 and 3**). Furthermore, comparing LDA results with the current clinical marker of OSAS using AHI normalisation, about 84% (168 out of 201) of normalised children were in cluster A and 73% (89 out of 122) of children were considered as not normalised were in cluster B.

Classification of the baseline PSG using linear discriminate analysis

The linear discriminate analysis was applied to the baseline dataset using the classification equation created by using follow-up dataset (**Figure 3**). Around 2/3 (208 out of 323) of children were classified as cluster A, while only about 1/3 (115 out of 323) were classified as cluster B (**Table 3**). Similar classified results were obtained in both watchful waiting and surgery groups, 106 children are considered as cluster A in WW group, and 102 children in the eAT group. For cluster B, 52 out of 158 were in the WW group, which is over 42% less than the follow-up result, and 63 out of 165 children were in the eAT group.

Effect of the clusters on physiology and neurophysiological measurements

To explore the physiological and the neuropsychological differences between the two clusters, one-way ANCOVA was applied to baseline and follow-up for the two clusters respectively (**Tables 4** & **5**). Of the 646 PSGs recorded, 514 PSG contained all of the interested physiological and neuropsychological measurements for analysis, 256 at baseline and 258 at follow-up.

At baseline (**Table 4**), significant differences were found between clusters in OAHI3, RPCTCO2G50, PCTLT90, symbolic heart rate patterns and TAA in all sleep stages (N2, N3 and REM). Of the covariates included in the models, age associated with symbolic heart rate pattern in N3 sleep; male gender showed a significant effect on TAA in N3 sleep; generalised intellectual functioning was significantly influenced by race and BMIZ; and moreover, BMIZ significantly affected OAHI3, PCTLT90, the total score of the paediatric sleep questionnaire, and TAA in N2 and N3 sleep.

Similar significant differences between clusters were found at follow-up (**Table 4**), expect TAA in REM sleep. Additionally, questionnaire-based OSAS symptom indicators and the total score of the paediatric sleep questionnaire showed significant differences between clusters, where cluster B has higher scores than cluster A. Of the covariates included in the models, age associated with symbolic heart rate pattern in all sleep stages (N2, N3 and REM) and TAA in REM sleep; both male gender and race showed a significant effect on the total score of the paediatric sleep questionnaire; male gender also had an impact on the central apnoea index (CAI0P); generalised intellectual functioning was significantly influenced by race and BMIZ.

Chapter 6

Cluster Transition Analysis

Cluster transition and the effect of surgery

The transition of children between the two clusters from baseline to follow-up study comprised 62 children from A→B, 55 children from B→A, 146 children from A→A and 60 children from B→B (**Table 5**). The relationships of the four transition classes with respect to whether children had surgery or OAHI normalisation were analysed. Comparing between the interventions, 47 children from WW and 15 from eAT was classified as A→B, 8 children from WW and 47 from eAT was classified as B→A, 59 children from WW and 87 from eAT was classified as A→A and 44 children from WW and 16 from eAT was classified as B→B.

Effect of cluster transition classes on physiology and neurophysiological measurements for baseline WW group

Considering the baseline characteristics of children in the control arm (**Table 6**), 118 out of 158 children had complete data on neurophysiological measurements (37 transitioning from A→B, 5 from B→A, 45 from A→A and 31 from B→B). Significant difference between all classes were observed in OAHI3, OMAHI3, the extent of oxygen desaturation, Conners' GI Restless - Impulsive T-Score, Conners' GI Emotional Liability T-Score, the Behavior Rating Inventory of Executive Function (BRIEF), symbolic heart rate pattern in all sleep stages (N2, N3 and REM), TAA in NREM sleep stages (N2 and N3). Of the covariates included in the statistical models, no covariance was significantly associated with any of the above measurements.

Post-hoc comparisons showed that children transitioned B→A had significantly higher values compared to other classes in Conners' GI Restless - Impulsive T-Score (B→A vs A→A: $p = 0.002$; B→A vs B→B: $p = 0.010$; B→A vs A→B: $p = 0.008$), Conners' GI Emotional Liability T-Score (B→A vs A→A: $p = 0.0004$; B→A vs B→B: $p = 0.0005$; B→A vs A→B: $p = 0.0005$), the Behavior Rating Inventory of Executive Function (BRIEF) (B→A vs A→A: $p = 0.0078$; B→A vs B→B: $p = 0.011$; B→A vs A→B: $p = 0.015$), TAA in sleep stage N2 (B→A vs A→A: $p < 0.0001$; B→A vs B→B: $p = 0.038$; B→A vs A→B: $p = 0.0005$) and TAA in sleep stage N3 (B→A vs A→A: $p < 0.0001$; B→A vs A→B: $p = 0.0004$).

Children who remained in A (A→A) had significant lower values compared to children who remained in B (B→B) in OAHI3 ($p < 0.0001$), TAA in sleep stage N2 ($p = 0.0025$) and N3 ($p < 0.0001$), heart rate pattern in all three sleep stages (N2: $p < 0.0001$; N3: $p < 0.0001$; REM: $p = 0.0004$).

Effect of cluster transition classes on physiology and neurophysiological measurements for baseline eAT group

Considering children who underwent surgery (**Table 7**), 138 out of 165 children had data on neurophysiological measurements (10 children transitioning from A→B, 39 children transitioning from B→A, 77 children transitioning from A→A and 12 children transitioning from B→B). Significant differences between all classes were observed in OAHI3, OMAHI3, the extent of oxygen desaturation, peak end-tidal carbon dioxide, symbolic heart rate pattern and TAA in all sleep stages (N2, N3 and REM). Of the covariates included in the models, no covariance was significantly associated with any of the above measurements. Of the covariates included in the models, age was associated with TAA in N3 stage, symbolic heart rate pattern in N2, N3 and REM sleep; TAA in N3 stage was significantly associated with race; and BMI z-score affected OAHI3, the extent of oxygen desaturation, and TAA in N2 and N3 sleep stages.

Post-hoc comparisons showed that children who remained in cluster B (B→B) had significant higher values of peak end-tidal carbon dioxide compared to all other children (B→B vs A→A: $p < 0.0001$; B→B vs B→A: $p = 0.0067$; B→B vs A→B: $p = 0.0086$). Additionally, those children had significantly higher OAHI3 values ($p < 0.022$), TAA in sleep stage N2 ($p = 0.0008$) and N3 ($p < 0.0038$), and monotonous heart rate pattern in all three sleep stages (N2: $p < 0.0001$; N3: $p < 0.0007$; REM: $p = 0.0023$) compared to children who remained in the A cluster (A→A).

Children who transitioned from B→A had a significant higher values in OAHI3 ($p < 0.0001$), OMAHI3 ($p < 0.0001$), the extent of oxygen desaturation ($p = 0.0011$), TAA in all three sleep stages (N2: $p < 0.0001$; N3: $p < 0.0001$; REM: $p = 0.010$), and heart rate pattern in all three sleep stages (N2: $p < 0.0001$; N3: $p < 0.0001$; REM: $p = 0.0001$) compared to children who transitioned from A→B.

Chapter 6

Discussion

Our data-driven analysis of the CHAT dataset confirms that children with OSAS can benefit from AT. By separating the entirety of follow-up study into 2 clusters (A, B) based on their AHI and respiratory effort and ANS activation, significant differences in OSAS clinical indicators and sleep quality measures were observed, where children in cluster A showed fewer physiological and neurophysiological deficits compared to those in cluster B. Additionally, we found that the majority of children were assigned to cluster A at baseline, despite being considered to have OSAS based on the current clinical diagnostic metric, the AHI. Analysis of cluster transitions from baseline to follow-up PSG demonstrated that surgery (**Table 5**) is able to reverse symptoms (47 out of 165 children) or preventing symptoms (87 out of 165 children) from worsening. Additionally, children who had residual UAO despite AT in terms of physiological and neurophysiological symptoms had significantly higher peak end-tidal carbon dioxide at baseline. Children who spontaneously reversed PSG indices of UAO (i.e., AHI) had high problematic ratings in behaviour and emotional at baseline.

Machine-learning can reveal novel patterns in alarge, complex datasets and uncover hidden relationships by anlaysing non-linear associations among multiple variables. A study has demostrated that the spectrum of children with sleep-disordered breathing can be classified into 6 unique classes using machine learning [2]. In our study, each follow-up PSG was assigned to one of two clusters, solely based on the three features. The three chosen features, i.e. OAHI, N2 sleep stage heart period dynamics and N3 sleep stage respiratory event-free TAA, may represent key pathophysiological domains affected by OSAS in children. These three discriminators are calculated from data that included respiratory events as well a segments that excluded respiratory events, providing apects levels ofOSAS related information [23-25]. Statistical comparison of all other clinical variables between the two clusters enabled a more comprehensive characterisation of the both groups of children and helped to define their pathophysiological profile.

Previous studies using the CHAT data have demonstrated the benefit of AT for children with OSAS. Children who had surgery demonstrated fewer pathophysiological symptoms compared to their baseline PSG and the PSG of children in the WWSC group (i.e. AHI [19], heart rate, heart rate variability [24, 36], respiratory rate [37], respiratory effort [23]). Therefore the follow-up PSG data provided an ideal training set for the machine learning to create our classification model, which may overcome the limitation of using AHI as the only marker for children having OSAS.

Our study showed that children in cluster A had fewer discrete OAH events during sleep, showed less respiratory effort and fewer autonomic activations during the respiratory-event free sleep period compared with children in cluster B. These findings may suggest children from cluster A have milder OSAS despite having clnically defined OSAS based on the AHI and may be more likely to show spontaneosu resolution of AHI [6, 25, 26].

Our previous studies reported fewer pathophysiological symptoms at baseline PSG in children who spontaneously normalised their AHI [23, 24]. This further questions the validity of the AHI as the current gold standard for defining clinically significant OSAS in children, which may over diagnose OSAS in paediatric populations due to the low cut-off that is typically applied. Since AHI was included in our data-driven analysis, we observed a positive correlation between AHI normalisation and data classification at follow-up (**Table 3**), where the majority of AHI-normalised children were assigned to cluster A. Cluster B in contrast contained most of the children who's AHI-did not normalise However, the approximately 20% of the children categorized into the other clusters reflect the additional information gained by heart rate patterns and TAA analysis. Furthermore, almost 2/3 of children were classed as A using baseline data (**Table 3**), demonstrating comparably fewer pathophysiological symptoms despite meeting the diagnostic (AHI) criteria for OSAS.

Considering the number of children classified into each cluster at baseline and follow-up, we found a similar ratio (2:1) of children in cluster A vs cluster B in the surgery and watchful waiting group at baseline (**Table 3**), reflecting the randomization of the trial. However, follow-up results (**Table 3**) showed an increased number of children classified into cluster A for children who underwent surgery, while most of the children in cluster B did not undergo surgery, which confirmed the beneficial effect on children from the intervention group as reported previously [6, 23-25].

By analysing the cluster transitions for each child separately for both study arms (**Table 5**), we found over half of the children who underwent surgery were assigned to cluster A at baseline and follow-up, while only 1/3 of children in the watchful waiting group were assigned to, and remained in cluster A. Considering the higher percentage for children who underwent surgery, surgery appears to improve the likelihood of children staying in cluster A. The presence of children of the watchful waiting arm in cluster A suggests that their condition was mild and did not worsen without undergoing surgery.

By contrast, our results suggest it is more likely for children in the watchful waiting arm, who were assigned to cluster B, to remain in B even after 7 months. Importantly, there were 16 children

who had surgery and remained in cluster B; our post hoc analysis showed that those children had extremely high peak end-tidal carbon dioxide measure during sleep at baseline PSG. This suggests the presence of sleep-related hypoventilation even in the absence of discrete respiratory events, and intimates these children still had significant UAO despite AT. Significant lung disease could lead to high peak end-tidal carbon dioxide in children. For example people with asthma [38] might show symptoms on PSG similar OSAS. Similarly, unresolved lung diseases might be a possible reason to explain why their UAO related physiological and neurophysiological symptoms still remain comparably high.

It was almost 6 times more likely for children in the surgery group who were in cluster B at baseline to transition to cluster A at follow-up than for children in the watchful waiting group. Children in the watchful waiting group were > 3 times more likely to transition from cluster A to B than those who underwent surgery. This further demonstrates that surgery can help reduce the OSAS related physiological symptoms. Moreover, those symptoms are more likely getting worse if children remain without treatment. Interestingly, 5 children in the watchful waiting group transitioned from cluster B to cluster A after 7 months. These children had higher pathophysiological symptoms at baseline PSG, and significantly more problematic behaviour and emotional issues than others, which has controversial with studies have presented in the current literature [39, 40].

Our study has several limitations. Children enrolled in CHAT were within the mild and moderate spectrum of OSAS and the follow-up duration was relatively short. Distinct clusters may form more clearly if more severe cases of OSAS are considered; possibly more than two clusters could be considered. Since the trial did not include an arm of healthy control children, we cannot verify if cluster A had similar symptoms as healthy subjects. Several children from the original trial had to be excluded due to poor signal quality. Some of the transition subclasses had very few children, which may have impacted the reliability of some results.

In conclusion, data-driven analysis shows that AT has a beneficial effect on children with OSAS by reversing and preventing the worsening of the syndrome. Multi-domain analysis of PSG markers and machine learning may provide a more complete picture of children with OSAS than AHI alone and may help predict which individuals do not need surgical intervention to recover.

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Figures

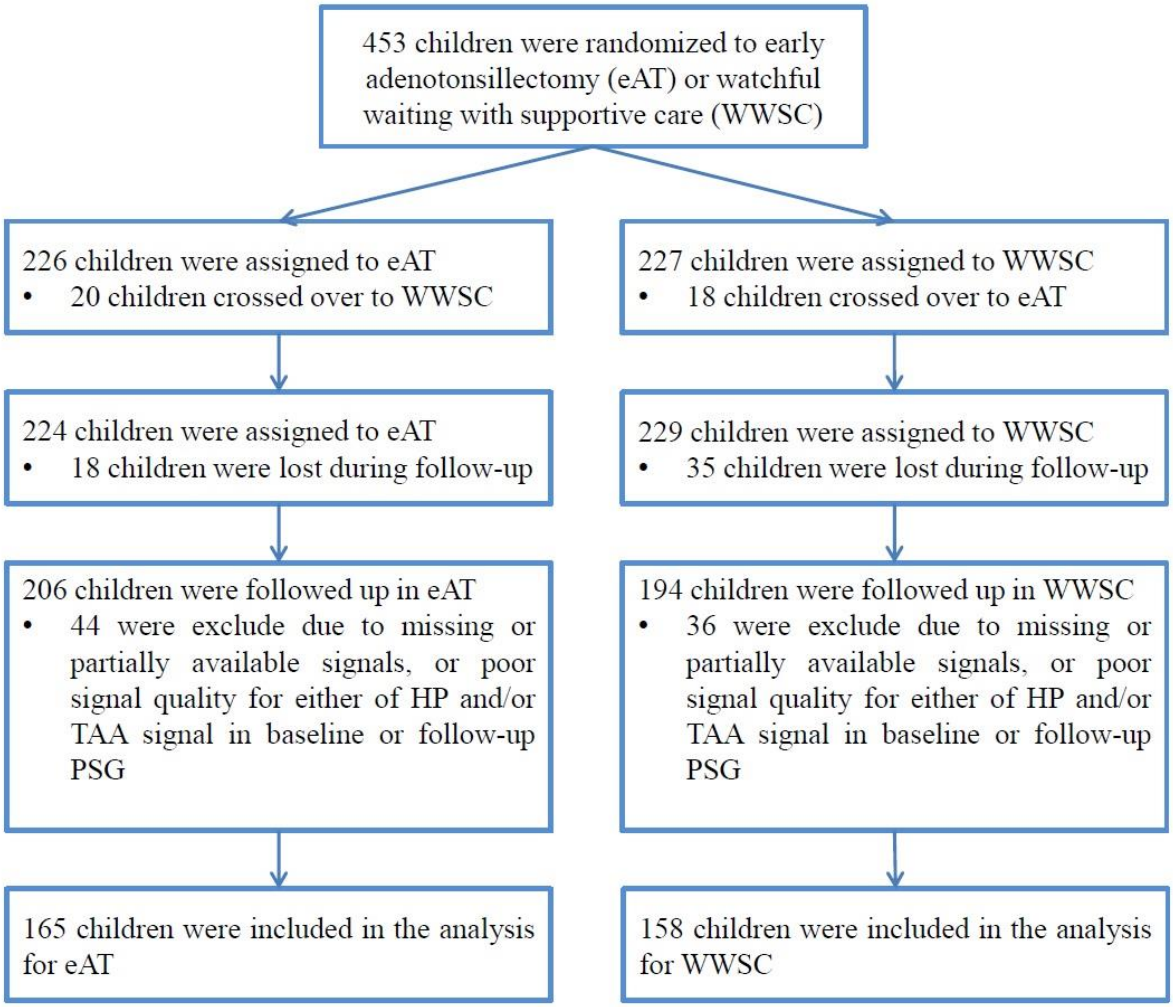

Figure 1 Summary of Childhood Adenotonsillectomy Trial study participants included in the data driving analysis. eAT: early adenotonsillectomy; WWSC: watchful waiting with supportive care; PSG: polysomnography; TAA: thoraco-abdominal asynchrony; HP: Heart rate patterns.

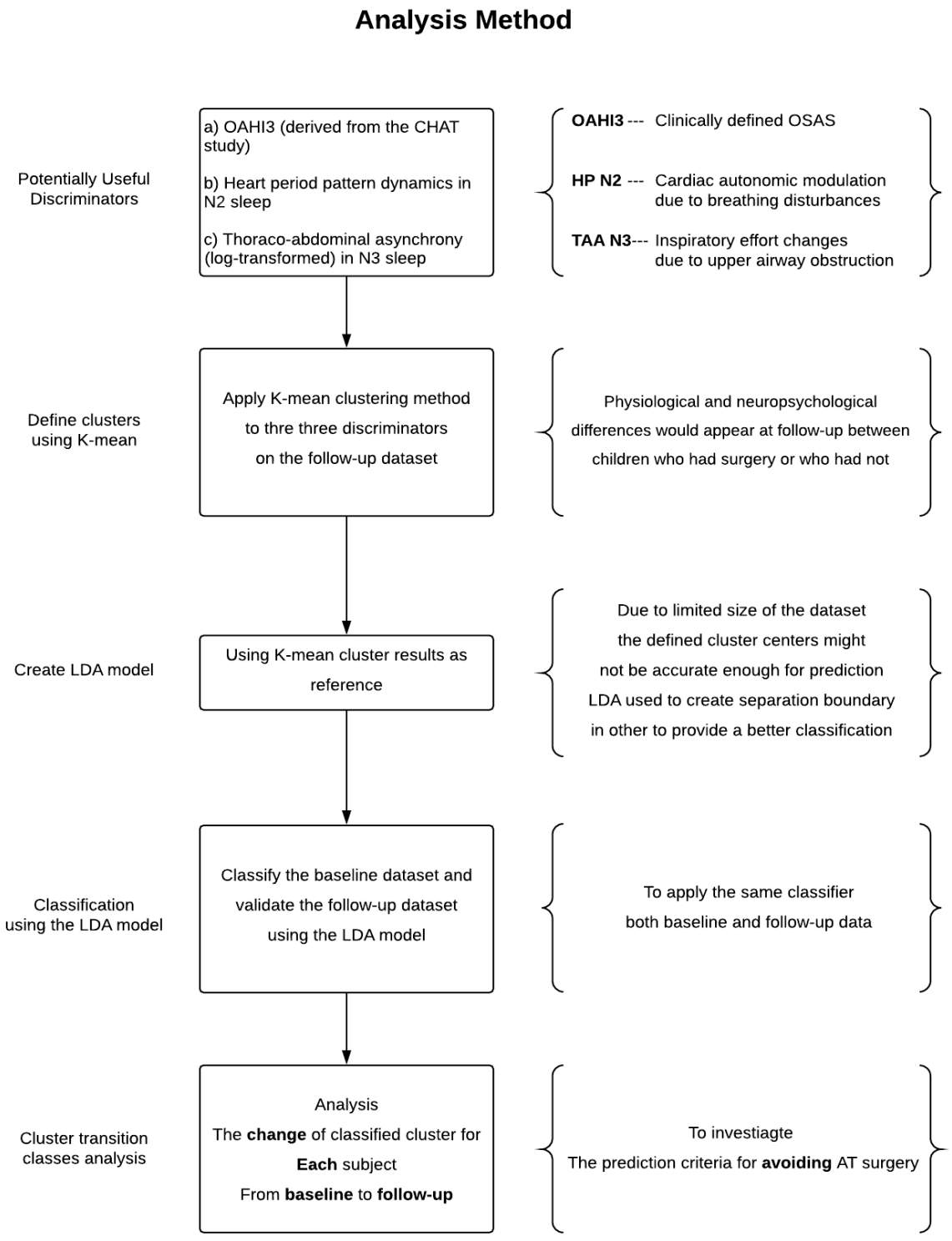

Figure 2 Data-driven analysis processes flowchart presented vertically; each process module was presented with the key description and purpose horizontally

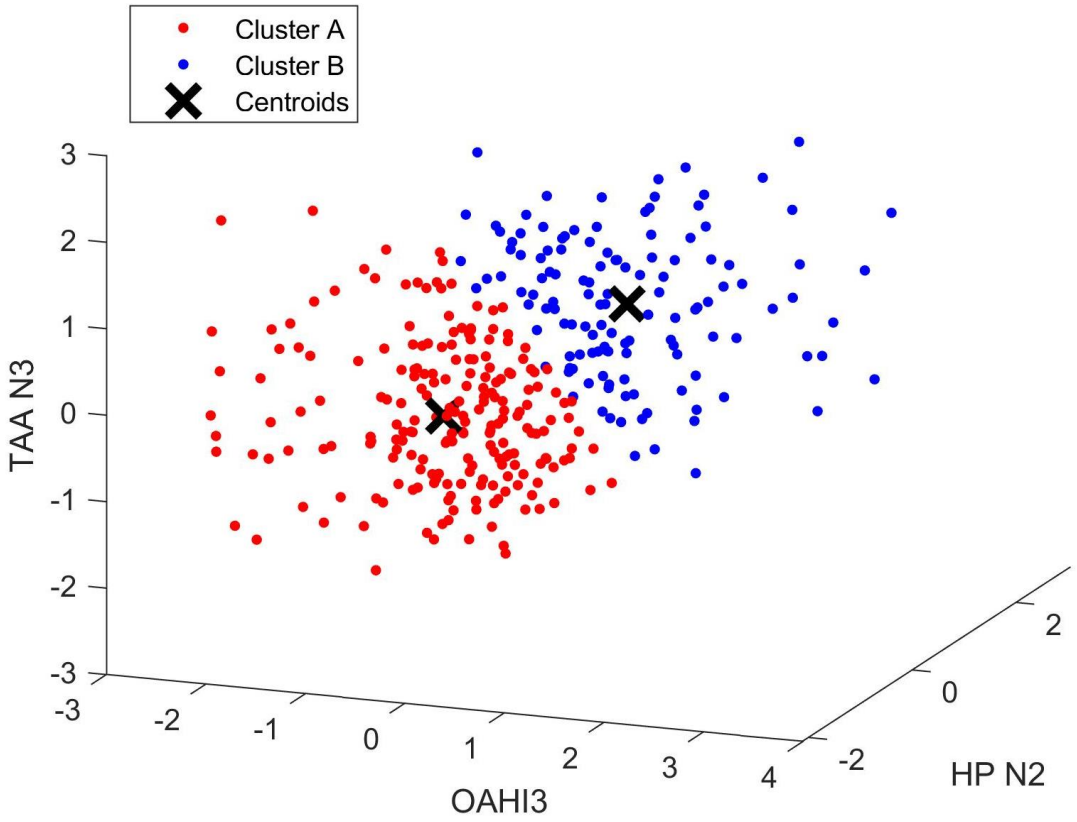

Figure 3 Clusters separation by the LDA model for follow-up dataset

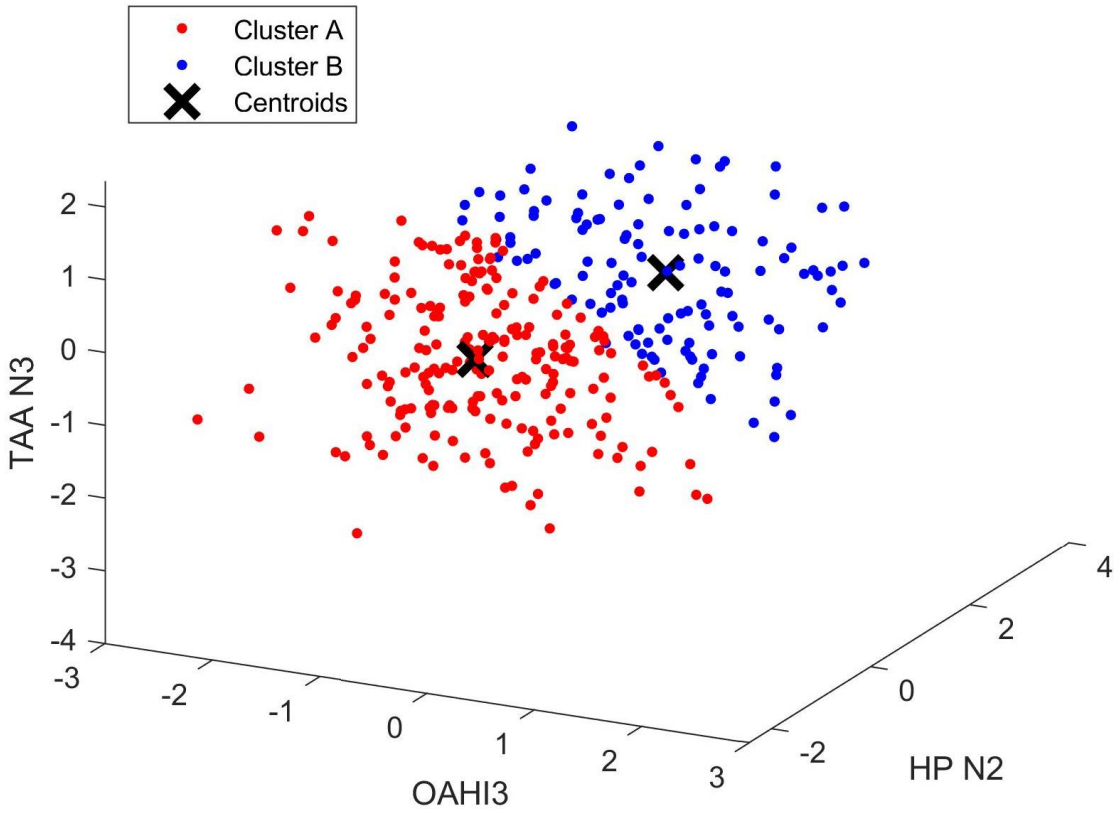

Figure 4 Clusters separation by the LDA model for baseline dataset

Tables

Table 1 Subject characteristics at baseline and 7 month follow-up grouped according to study arm.

characteristics	Early Adenotonsillectomy (N =165)		Watchful Waiting (N =158)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Age^ (years)	6.61 ± 1.46	7.16 ± 1.46	6.58 ± 1.40	7.13 ± 1.44
Male sex- N (%)	74 (44.8%)		81 (51.3%)	
Race - N (%)†				
African American	86 (52.1%)		90 (57.0%)	
Caucasian	60 (36.4%)		53 (33.5%)	
Other	19 (11.5%)		15 (9.5%)	
BMI z score^	0.91 ± 1.35	1.19 ± 1.21	0.88 ± 1.23	1.03 ± 1.26
Weight Class - N (%)‡				
Overweight (BMI ≥ 85th percentile) - N (%)	85 (51.5%)	93 (56.4%)	74 (46.8%)	85 (53.8%)
Obese (BMI ≥ 95th percentile) - N (%)	58 (35.2%)	69 (41.8%)	53 (33.5%)	58 (36.7%)
Montelukast - N (%)	6 (3.6%)	11 (6.7%)	9 (5.7%)	14 (8.7%)
Glucocorticoids - N (%)	34 (20.6%)	39 (23.6%)	34 (21.5%)	42 (26.6%)

^ Data are presented as mean ±SD.
† Race reported by caregivers.
‡ Overweight was defined as a body-mass index in the 85th percentile or higher, obese as a BMI in the 95th percentile or higher.

Table 2 Cross tabulation of classification result from K-mean cluster vs factor study arm at follow-up

Cluster	Study arm		Total
	WW	eAT	
A	67	132	199
B	91	33	124
Total	158	165	323

Table 3 Cross tabulation of classification result from LDA vs study arm at baseline and follow-up, and LDA vs factor Normalisation at follow-up

Cluster	Baseline		Follow-up			
	Study arm		Study arm		Normalisation	
	WW	eAT	WW	eAT	Not normalised	Normalised
A	106	102	67	134	33	168
B	52	63	91	31	89	33

Table 4 Comparison of interested physiology and neuropsychological measurements between LDA clusters on all baseline and follow-up data

	Baseline			Follow-up		
Measurements	**Cluster A (N =169)**	**Cluster B (N =87)**	**p-value**	**Cluster A (N =165)**	**Cluster B (N =93)**	**p-value**
OAHI3	3.46 ± 3.06	9.42 ± 6.50	**<0.00001**	0.79 ± 1.01	6.68 ± 9.57	**<0.00001**
CAI0P	0.91 ± 0.88	1.19 ± 1.82	0.1272	0.87 ± 0.93	0.81 ± 0.97	0.7547
RPCTCO2G50	5.82 ± 14.75	16.35 ± 22.89	**0.00003**	6.09 ± 13.35	13.82 ± 22.32	**0.0007**
PCTLT90	0.03 ± 0.20	0.20 ± 0.43	**0.00003**	0.00 ± 0.02	0.17 ± 0.64	**0.0012**
CON10B(CI_Restless_T_score)	53.09 ± 11.07	53.47 ± 11.09	0.6499	51.96 ± 11.23	51.31 ± 9.44	0.6226
CON11B(CI_Emotional_T_score)	49.98 ± 11.30	48.55 ± 10.18	0.3897	48.58 ± 10.37	46.60 ± 7.53	0.1199
BRI13B(GEC_T_score)	50.11 ± 10.74	48.92 ± 10.30	0.4843	48.71 ± 11.84	47.74 ± 10.15	0.5018
The total score of the Pediatric Sleep Questionnaire	0.49 ± 0.18	0.51 ± 0.18	0.2845	0.29 ± 0.21	0.42 ± 0.22	**<0.00001**
Pediatric Quality of Life Inventory Parent Total Scale Score	77.99 ± 15.49	79.03 ± 15.91	0.7770	82.25 ± 14.64	81.00 ± 15.28	0.5490
Total score of the OSA-18	2.97 ± 1.00	3.11 ± 1.13	0.2915	2.05 ± 1.02	2.58 ± 1.15	**0.0002**
Differential Ability Scales II	94.93 ± 10.81	97.16 ± 10.61	0.1401	97.22 ± 10.66	97.83 ± 12.74	0.4877
TAA (N2)	2.91 ± 0.63	3.53 ± 0.63	**<0.00001**	2.74 ± 0.64	3.37 ± 0.70	**<0.00001**
TAA (N3)	2.88 ± 0.70	3.68 ± 0.70	**<0.00001**	2.73 ± 0.73	3.59 ± 0.79	**<0.00001**
TAA (REM)	3.48 ± 0.68	3.76 ± 0.57	**0.0014**	3.35 ± 0.63	3.47 ± 0.68	0.1468
HP (N2)	16.11 ± 5.89	23.50 ± 5.47	**<0.00001**	12.89 ± 5.08	20.03 ± 4.79	**<0.00001**
HP (N3)	14.10 ± 6.26	21.10 ± 6.19	**<0.00001**	10.96 ± 5.22	18.33 ± 5.40	**<0.00001**
HP (REM)	14.90 ± 4.47	19.03 ± 5.09	**<0.00001**	13.09 ± 3.92	17.10 ± 4.04	**<0.00001**

Data are presented as mean ±SD. All *p*-values have been obtained using one-way ANCOVA adjusted for likely confounding factors of age (5 to 10 years of age), race (black, white and other), BMI z-score and gender.

Table 5 Cross-tabulation of Cluster transitions from baseline to follow-up vs study arm.

Transition	Study arm		Total
	WW	eAT	
BA2FB	47	15	62
BB2FA	8	47	55
BA2FA	59	87	146
BB2FB	44	16	60
Total	158	165	323

Table 6 Comparison of interested physiology and neurophysiological measurements between all transition classes on baseline WW group

Measurements	A→B (N =37)	B→A (N =5)	A→A (N =45)	B→B (N =31)	p-value
OAHI3	3.67 ± 2.41	5.80 ± 2.04	3.51 ± 3.48	10.13 ± 6.81	**<0.00001**
CAI0P	0.96 ± 0.66	0.88 ± 0.64	0.70 ± 0.69	1.10 ± 0.84	0.1041
RPCTCO2G50	7.68 ± 14.67	14.56 ± 31.55	4.17 ± 14.68	12.26 ± 20.03	0.2171
PCTLT90	0.01 ± 0.02	0.00 ± 0.00	0.04 ± 0.25	0.16 ± 0.37	**0.0497**
CON10B(CI_Restless_T_score)	52.03 ± 10.08	67.00 ± 14.37	51.04 ± 9.10	52.10 ± 9.58	**0.0053**
CON11B(CI_Emotional_T_score)	46.81 ± 11.30	64.20 ± 14.74	46.98 ± 7.32	46.29 ± 7.02	**0.0007**
BRI13B(GEC_T_score)	48.32 ± 8.78	62.80 ± 13.37	48.07 ± 10.27	47.58 ± 9.76	**0.0128**
The total score of the Pediatric Sleep Questionnaire	0.50 ± 0.15	0.65 ± 0.19	0.47 ± 0.18	0.48 ± 0.19	0.1990
Pediatric Quality of Life Inventory Parent Total Scale Score	78.27 ± 13.87	70.88 ± 20.98	79.44 ± 14.81	80.48 ± 15.51	0.6703
Total score of the OSA-18	3.01 ± 0.98	3.61 ± 1.53	2.85 ± 1.01	3.10 ± 1.18	0.3815
The Differential Ability Scales II (DAS), a measure of generalized intellectual functioning	93.27 ± 9.60	89.60 ± 8.26	93.84 ± 10.58	97.55 ± 12.69	0.4692
TAA (N2)	3.02 ± 0.62	4.24 ± 0.77	2.86 ± 0.69	3.41 ± 0.59	**<0.00001**
TAA (N3)	2.97 ± 0.68	4.33 ± 0.81	2.85 ± 0.75	3.63 ± 0.66	**<0.00001**
TAA (REM)	3.51 ± 0.68	4.08 ± 0.52	3.45 ± 0.62	3.51 ± 0.64	0.2541
HP (N2)	18.20 ± 5.51	21.50 ± 5.31	15.16 ± 6.20	23.48 ± 4.53	**<0.00001**
HP (N3)	16.53 ± 5.65	18.46 ± 5.92	12.90 ± 6.30	21.23 ± 5.54	**<0.00001**
HP (REM)	16.22 ± 4.25	18.73 ± 6.23	13.91 ± 4.30	18.51 ± 5.02	**0.0003**

Data are presented as mean ±SD. All *p*-values have been obtained using one-way ANCOVA adjusted for likely confounding factors of age (5 to 10 years of age), race (black, white and other), BMI z-score and gender.

Table 7 Comparison of interested physiology and neurophysiological measurements between all transition classes on baseline eAT group

Measurements	A→B (N =10)	B→A (N =39)	A→A (N =77)	B→B (N =12)	p-value
OAHI3	4.17 ± 3.70	9.78 ± 7.23	3.24 ± 3.03	7.88 ± 3.39	**<0.00001**
CAI0P	0.66 ± 0.49	1.30 ± 2.58	1.05 ± 1.07	1.21 ± 0.91	0.7443
RPCTCO2G50	8.84 ± 18.45	14.15 ± 20.70	5.49 ± 14.46	34.80 ± 26.92	**0.00002**
PCTLT90	0.00 ± 0.00	0.30 ± 0.53	0.03 ± 0.22	0.06 ± 0.12	**0.0012**
CON10B(CI_Restless_T_score)	51.90 ± 11.33	53.51 ± 11.39	54.95 ± 12.37	51.25 ± 9.70	0.5702
CON11B(CI_Emotional_T_score)	51.80 ± 14.97	48.97 ± 11.03	53.01 ± 12.01	46.50 ± 6.72	0.1262
BRI13B(GEC_T_score)	49.70 ± 14.33	48.18 ± 9.81	52.22 ± 11.15	49.00 ± 8.79	0.1758
The total score of the Pediatric Sleep Questionnaire	0.44 ± 0.15	0.52 ± 0.18	0.51 ± 0.19	0.51 ± 0.13	0.4790
Pediatric Quality of Life Inventory Parent Total Scale Score	78.91 ± 19.82	78.96 ± 16.39	76.90 ± 16.22	78.92 ± 14.10	0.8869
Total score of the OSA-18	2.93 ± 1.13	3.07 ± 1.14	3.02 ± 1.01	3.08 ± 0.81	0.9724
Differential Ability Scales II	95.20 ± 14.98	97.95 ± 8.78	96.34 ± 10.92	96.75 ± 10.97	0.8161
TAA (N2)	2.99 ± 0.40	3.52 ± 0.57	2.88 ± 0.63	3.55 ± 0.71	**<0.00001**
TAA (N3)	2.79 ± 0.39	3.69 ± 0.68	2.87 ± 0.71	3.54 ± 0.72	**<0.00001**
TAA (REM)	3.43 ± 0.75	3.87 ± 0.49	3.48 ± 0.71	3.91 ± 0.48	**0.0040**
HP (N2)	19.09 ± 5.10	23.46 ± 6.00	15.27 ± 5.69	24.51 ± 6.36	**<0.00001**
HP (N3)	17.81 ± 5.80	21.22 ± 6.49	13.16 ± 6.17	21.51 ± 7.35	**<0.00001**
HP (REM)	15.81 ± 3.33	19.15 ± 4.53	14.72 ± 4.68	20.05 ± 6.85	**<0.00001**

Data are presented as mean ±SD. All *p*-values have been obtained using one-way ANCOVA adjusted for likely confounding factors of age (5 to 10 years of age), race (black, white and other), BMI z-score and gender.

Appendix

Table S1 Cross-tabulation of classification result from LDA vs study time for all data

Cluster * Study Cross-tabulation

Count

		Study		
		Predicting/ Baseline	Training/ Followup	Total
Cluster	A	208	201	409
	B	115	122	237
Total		323	323	646

Table S2 Comparison of interested physiology and neurophysiological measurements between all transition classes on all baseline data

Measurements	**A→B (N =47)**	**B→A (N =44)**	**A→A (N =122)**	**B→B (N =43)**	p-value
OAHI3	3.78 ± 2.70	9.33 ± 6.95	3.34 ± 3.19	9.51 ± 6.10	**<0.00001**
RPCTCO2G50	7.93 ± 15.34	14.20 ± 21.71	5.01 ± 14.50	18.55 ± 24.10	**0.0003**
PCTLT90	0.00 ± 0.02	0.27 ± 0.51	0.03 ± 0.23	0.13 ± 0.32	**<0.00001**
CON10B(CI_Restless_T_score)	52.00 ± 10.23	55.05 ± 12.36	53.51 ± 11.39	51.86 ± 9.50	0.4061
CON11B(CI_Emotional_T_score)	47.87 ± 12.17	50.70 ± 12.31	50.79 ± 10.89	46.35 ± 6.86	0.0782
BRI13B(GEC_T_score)	48.62 ± 10.04	49.84 ± 11.12	50.69 ± 10.98	47.98 ± 9.42	0.4168
The total score of the Pediatric Sleep Questionnaire	0.49 ± 0.15	0.54 ± 0.19	0.49 ± 0.19	0.49 ± 0.17	0.4394
Pediatric Quality of Life Inventory Parent Total Scale Score	78.40 ± 15.08	78.04 ± 16.89	77.84 ± 15.70	80.04 ± 14.98	0.8873
Total score of the OSA-18	3.00 ± 1.00	3.13 ± 1.18	2.96 ± 1.01	3.09 ± 1.08	0.7656
Differential Ability Scales II	93.68 ± 10.80	97.00 ± 9.04	95.42 ± 10.82	97.33 ± 12.11	0.5030
TAA (N2)	3.02 ± 0.58	3.60 ± 0.63	2.87 ± 0.65	3.45 ± 0.62	**<0.00001**
TAA (N3)	2.93 ± 0.63	3.76 ± 0.72	2.86 ± 0.73	3.60 ± 0.67	**<0.00001**
TAA (REM)	3.49 ± 0.68	3.90 ± 0.49	3.47 ± 0.67	3.62 ± 0.62	**0.0025**
HP (N2)	18.39 ± 5.38	23.24 ± 5.90	15.23 ± 5.86	23.77 ± 5.04	**<0.00001**
HP (N3)	16.80 ± 5.64	20.91 ± 6.42	13.06 ± 6.20	21.31 ± 6.01	**<0.00001**
HP (REM)	16.13 ± 4.04	19.11 ± 4.66	14.42 ± 4.54	18.94 ± 5.54	**<0.00001**

Data are presented as mean ±SD. All *p*-values have been obtained using one-way ANCOVA adjusted for likely confounding factors of age (5 to 10 years of age), race (black, white and other), BMI z-score and gender.

Chapter 7 Conclusion

This chapter summarises the work conducted, and key findings of this thesis and suggests future research directions.

Decades of sleep research have revealed paediatric sleep disordered breathing to be a significant health problem. Current clinical scoring rules have been well defined for diagnosing the more severe end of the SDB spectrum in children, such as obstructive sleep apnea. However, the clinical marker is not effective at identifying mild SDB. Health consequences related to the mild end of SDB have been underestimated. Therefore, development and testing of more effective physiological markers are required to cover the full range of SDB. This thesis proposes and develops advanced signal processing and analysis techniques to create alternative physiological markers, and verifies them against large, well-described, clinical datasets. Furthermore, a machine learning approach has been applied to make alternative diagnosis suggestions by combining the information from AHI and the created alternative markers. This chapter summarises the main findings of the studies conducted for this thesis, and discusses potential future research directions for developing better diagnostic markers and criteria for childhood SDB.

7.1 Thesis Summary

Chapter 1 gives a brief introduction to sleep disordered breathing. A review of the literature on paediatric SDB research, and the related health consequences in children with SDB, identifies that more effective diagnostic makers are need to identify children with mild SDB.

The two main physiological systems affected SDB are the respiratory and autonomic nervous systems. The physiological variables that can be measured to reflect the changes in these systems are reviewed in Chapter 1. For the respiratory system, airflow and thoracoabdominal movement are the direct and indirect measurements of the system. Heart rate variability, pulse wave amplitude, and pulse transient time are the common indicators for autonomic activation. Based on these factors, research questions have been formulated with a focus on

investigating if the physiological variables TAA, HP, and PWA, are more sensitive identifiers for mild SDB in children than only using AHI. Chapter 2 presents the biomedical signal processing methods developed, and is applied to measure and analyse the proposed physiological variables. Furthermore, these methods are used in the clinical studies discussed in this thesis.

Chapter 2 describes the estimation of TAA using an analytic method called Hilbert Transform and establishes a framework for determining the validity of the estimated TAA. This method is used in the CHAT study presented in Chapter 3. Two methods were developed to measure PWA. A direct method calculates the amplitude difference of each pulse located between every two consecutive heartbeats, and is applied on the Adelaide Women's and Children's Hospital study dataset in Chapter 5. An alternate, simplified, PWA estimation was developed where a continuous PWA signal is calculated without knowing the locations of heartbeats, by simply calculating the difference of extracted upper and lower envelops of the photoplethysmography signal. Since actual PWA can only be calculated if a valid pulse can be detected between two consecutive heartbeats, this method avoids invalid pulses caused by filtering during PPG signal acquisition. In contrast, this method does not provide true PWA calculation, instead, giving an estimation of changes in the PWA trend. This new method has been tested with the same dataset from Adelaide Women's and Children's Hospital, presented in Appendix A.

As the autonomic system is a complex physiological system, symbolic dynamic analysis, as a nonlinear analysis method, is developed to understand the dynamic changes of the measured physiological variables, such as heart period. This analysis method is applied in the CHAT study in Chapter 4. Additionally, a joint symbolic dynamic method was developed to explore the joint dynamic of heart period and PWA to give a more reliable view of autonomic

activations, and is applied in the study presented in Chapter 5. The symbolic dynamic analysis, however, only reveals how frequently a general pattern change trend exists in the system, while the details of the signal dynamic changes cannot be captured. Therefore, an extensive dynamic analysis was proposed to obtain more information that includes the depths and durations of the changes occurring in the system. This analysis has been tested with the simplified PWA estimation method using the dataset from Adelaide Women's and Children's Hospital, and is presented in Appendix A.

Further investigation involved a data driven analysis, using unsupervised machine learning, and was applied to the CHAT study presented in Chapter 6. It combined the heart period and TAA data with AHI, exploring the nature of subjects by differentiating them into two groups, and the transition changes of subjects from one group to another, from the beginning and the end of the trial.

The findings from the studies conducted in this thesis provide answers to all the open questions listed in the introduction, for both the respiration and autonomic nervous systems. For respiration, in order to maintain respiratory flow during a partially blocked up-airway, a greater respiratory effort is required to overcome the resistance. As TAA is a non-invasive measure of inspiratory effort, the study in Chapter 3 shows TAA can be calculated from a non-invasive rib and abdominal signal, and is strongly affected by different sleep stages. In this study, evidence indicates adenotonsillectomy can not only help children with OSAS reduce their AHI, but also can reduce TAA during scored respiratory event free sleep, which indicates an overall reduction in inspiratory effort. However, this was not observed in children whose AHI normalised spontaneously. Additionally, in the AHI spontaneous normalised group, a negative health-related outcome, indicated by quality of life, is

associated with high TAA value. Thus, the finding from this study demonstrates that TAA can provide additional information for identifying mild SDB in children.

The study presented in Chapter 4, using the same dataset in the TAA analysis, shows that autonomic activation can be quantified by the dynamic of the heart period. Similar to the results found in the TAA study, the heart rate dynamic is also affected by sleep stages. Adenotonsillectomy is found to reduce the monotonic changes in heart rate patterns during respiratory event free sleep in children with OSAS, which is independent of AHI normalisation. Additionally, heart rate dynamics in children whose AHI normalised spontaneously was significantly lower at baseline, which was not identified previously. This is a significant finding which indicates that heart rate patterns can identify children with mild OSAS, who can avoid surgery.

As pulse wave amplitude and heart rate response differ under different physiological stress, PWA was found to be more beneficial at identifying hypoxic events related to autonomic activation compared to heart rate. Additionally, PWA is easier and cheaper to obtain, only using a PPG signal. In Chapter 5, PWA is combined with heart period information, studying the use of joint symbolic dynamic analysis on the Adelaide Women's and Children's Hospital Study dataset. Compared with healthy children, it was confirmed that upper airway obstruction elevates the frequency of autonomic activation in children with SDB during sleep and clinical scored respiratory-event-free sleep. This study confirmed the finding from Chapter 4, where adenotonsillectomy helped reduce autonomic activation in children with SDB. While heart rate dynamics showed a greater ability to identify children with SDB in NREM sleep compare to PWA, the evidence of joint results can distinguish them from healthy subjects, even in REM sleep. This suggests the joint PWA-HP dynamic can provide additional information on paediatric SDB assessment.

Instead of following the current diagnosing criteria for children with SDB, the data-driven analysis methods are used for separating the children into groups based on physiological and neurophysiological symptoms measured from TAA, HP and AHI. The study, therefore, presented in Chapter 6, investigated the possibility of using machine learning to predict children with SDB who can benefit from adenotonsillectomy, by adding the respiratory effort, and autonomic activation information, with the current clinic marker AHI. The results indicated that children with mild physiological and neurophysiological symptoms could avoid adenotonsillectomy, and children who have UAO symptoms post-surgery may have sleep-related hypoventilation disease, which requires further treatment. These findings have indicated possible alternative diagnostic criteria that may assist surgeons predict which child requires adenotonsillectomy with greater accuracy.

7.2 Future Research Directions

In this section, future research directions are discussed that extend the work done in this thesis.

7.2.1 Simplified PWA estimation and extensive dynamic analysis on children with sleep disordered breathing

The study in Chapter 5 showed the advantage of including PWA to help identifying children with SDB, rather than the use of heart rate alone. However, for PWA estimation, the conventional method of estimating PWA requires the extraction of heartbeat R peak positions from ECG signals in advance. As heartbeat R peak positions are crucial for PWA estimation, as shown in Chapter 2 section 2.2.1, the simplified PWA estimation developed is presented in Appendix A. For the signal dynamic analysis presented in both Chapters 4, and 5, the symbolic analysis only provides information for the most effective length of three heartbeats.

However, the continuous changes for more than three heartbeats, and the continuous change in signal amplitude, cannot be captured. The proposed extensive dynamic analysis in Appendix A can compensate for this limitation. It would be interesting if the improved methods on a larger clinic dataset to investigate autonomic nervous system dynamics in children with SDB can further verify the efficacy of including PWA as an alternative marker.

7.2.2 The effect of change in inspiration effort on autonomic activation in children with sleep disordered breathing

The study presented in Chapter 3 showed the elevated inspiration effort for children with OSA during respiratory event free period. Additionally, studies presented in Chapters 4, and 5, demonstrated the altered autonomic activation in children with SDB. These further proved that mild upper airway obstruction may still exist without AHI being detected, and it may be associated with some important physiological changes in children with SDB. It would be interesting to investigate if autonomic activation extracted by HP, or PWA, is affected by inspiration effort measured by TAA, and how autonomic activation changes with the change in inspiration effort.

7.2.3 Predicting surgical treatment candidates for childhood upper airway obstruction using machine learning

The study in Chapter 6 showed the benefit of using the physiological and neurophysiological symptoms measured from TAA, HP, and AHI, to identify the children with SDB who can benefit from surgery. Due to the subjects in this study only having mild and moderate OSAS conditions, the separation of the group from the cluster analysis was not very clear. The same study conducted on a large clinical trial, that includes more severe cases of OSAS, may help distinguish the groups better. Additionally, as previously discussed, PWA provides extra information for identifying children with SDB, and it can be included as a reference

physiological and neurophysiological symptom into a similar study. Further studies could also investigate if this method can identify children with SDB from healthy controls since this dataset does not contain healthy subjects.

7.3 Closing statement

Open questions from Chapter 1 have been addressed through the studies conducted in this thesis. Physiological variables TAA, HP, and PWA, can provide additional information on children with mild SDB, and they are potentially becoming the alternative markers for this disease. All work presented in this thesis is unique and original, laying the groundwork for future clinical sleep research on creating a better diagnosis of paediatric sleep disorder breathing.

Appendix A

A Method for Estimating Pulse Wave Amplitude Variability in children with Sleep Disordered Breathing

LIU, X., PAMULA, Y., KOHLER, M. & BAUMERT, M. 2019, July. A Method for Estimating Pulse Wave Amplitude Variability in children with Sleep Disordered Breathing, In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE. (In press)

Statement of Authorship

itle of Paper	A Method for Estimating Pulse Wave Amplitude Variability in children with Sleep Disordered Breathing
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	**LIU, X.**, PAMULA, Y., KOHLER, M. & BAUMERT, M. 2019, July. A Method for Estimating Pulse Wave Amplitude Variability in children with Sleep Disordered Breathing, In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE.

Principal Author

Name of Principal Author (Candidate)	Xiao LIU		
Contribution to the Paper	Conception, design and developed the engineering methods in the manuscript. Performed analysis on all samples, interpreted data, wrote manuscript and acted as corresponding author.		
Overall percentage (%)	90%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	31/05/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Yvonne Pamula		
Contribution to the Paper	Critical revision of the manuscript.		
Signature		Date	8/08/2019

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Contribution to the Paper	Data collection, revision of the manuscript.		
Signature		Date	6/6/19

Name of Co-Author	Mathias Baumert		
Contribution to the Paper	Conception, interpretation, critical revision of the manuscript.		
Signature		Date	3/15/13

A Method for Estimating Pulse Wave Amplitude Variability in children with Sleep Disordered Breathing

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***Abstract*—Sleep disordered breathing (SDB) is a common pediatric disorder, which results in increasing respiratory workload during sleep, restless night time sleep and excessive daytime sleepiness. It has significant negative effects on children with SDB on their physical growth and cognitive related developments. Chronic autonomic activation was suggested to be one of the possible key drivers causing cardiovascular structural changes in SDB children and increasing the risk of developing cardiovascular disease in their future. The aim of this study was to investigate the effect of SDB on autonomic activation changes in children, by analyzing the pulse wave amplitude (PWA) dynamics using a simple envelope estimation method extracting PWA from PPG signal.**

Children with SDB (n = 40) showed a significantly wider dynamic distribution in PWA compare to matched controls (n = 40), which suggests a higher and stronger level of autonomic response in SDB children.

In conclusion, the PWA dynamic is altered in children with SDB during sleep and indicate changes in autonomic activation.

I. Introduction

Sleep disordered breathing (SDB) is relatively common in children. It is mostly caused by an obstructed upper airway due to enlarged tonsils and adenoids. Children with SDB commonly have impaired cognitive and behavioral functions. Studies have shown that SDB may also be a key driver for cardiovascular structural changes, and it may increase the risk of developing cardiovascular disease later on [1, 2].

While the apnoea-hypopnoea index (AHI) is efficient for diagnosing severe forms of upper airway obstruction, the mild forms of SDB that are related to increased inspiratory load but do not classify as hypopnea are not captured by the AHI. Studies have shown that cardiovascular and cognitive changes may develop even in children at the milder end of the SDB spectrum, and increasing concerns about the effectiveness of the AHI for diagnosing children with SDB have been expressed [3-5].

The autonomic system regulates body functions under physiological stress. When the body is under stress, it changes the cardiac output and vascular stiffness, which results in a changing heart rate and blood pressure. Further, it leads to changes in peripheral vascular resistance and stroke volume. The aforementioned processes are observable in changes of the pulse transit time and pulse wave amplitude. Frequently increasing inspiratory load would cause chronic autonomic nervous system activation and is a key reason for changes in cardiovascular structure and function in children with SDB [6-10]. Commonly, autonomic activation information can be extracted from cardiac and pulse signals, by measuring heart rate variability [11], pulse transit time (PTT) [12] or pulse wave amplitude (PWA) [2, 13-17]. These measures can respond in a similar or different pattern to autonomic activation under different stressors [15].

The aim of this study is to develop a simple technique to measure PWA continuously, to probe the level of autonomic activation in children with SDB by measurement the depth and duration of the autonomic changing trends. Furthermore, we assessed the difference in autonomic activation between children with SDB and a group of normal children. We hypothesized that children with SDB would have comparably more frequented and stronger autonomic activations during sleep.

II. Methods

A. Patients

This study was approved by the Women's and Children's Health Network Human Research Ethics Committee, South Australia, with parental consent and child assent obtained from all participants. Participants were 40 children aged 3.25-12.9 years, with a history of frequent snoring, awaiting Adenotonsillectomy for suspected UAO and a matched group of 40 non-snoring healthy controls. More details of the study protocol are published elsewhere [18-22]. Both groups underwent overnight PSG to evaluate sleep and breathing parameters. Participants were screened to ensure they had not undergone previous ear, nose, throat or craniofacial surgery, or had a medical condition (other than UAO) associated with hypoxia or sleep fragmentation or were taking medication known to affect sleep or cardiorespiratory physiology.

B. Overnight polysomnography

Overnight PSG was conducted without sedation or sleep deprivation and began close to each child's usual bedtime with a parent present throughout the procedure. The S-Series Sleepwatch® System (Compumedics®, Australia) was used to continuously record: EEG (250 Hz; C3-A2 and C4-A1), left and right EOG, ECG (modified lead II, 500 Hz), sub-mental and diaphragmatic EMG with skin surface electrodes, leg movements assessed by piezoelectric motion detection, oronasal airflow by thermistor, respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography (RIP),

This research was supported by the Australian Research Council (DP0663345).

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SpO2 by pulse oximetry (Nellcor N-595; 500 Hz) and transcutaneous CO2 (TcCO2) using a heated (41°C) transcutaneous electrode (TINA, Radiometer Pacific). Each child was monitored continuously overnight via infrared camera by a pediatric sleep technician, who also documented observations of sleep behaviour including the presence or absence of snoring.

C. Data analysis

1) Pulse Wave Amplitude measurement

The finger PPG signal was extracted from PSG and analyzed in this study. The PPG signal was filtered with a 500th order bandpass FIR filter with cutoff from 1 to 10 Hz. To reduce the computational time the PPG signal was downsampled to 100 Hz from originally 500 Hz.

PWA was defined as the pulse amplitude difference between a systolic peak to its following diastolic valley in each cardiac cycle. Since the PWA is a discrete measurement with one value per heartbeat, continues PWA measurement can be obtained by applying interpolation. A simple method to estimate continues PWA involves estimating the difference between the upper and lower peak envelops of the pulse signal. The envelope function of Matlab® 2018b is used for this estimation. The envelope is determined using spline, interpolation over local peaks separated by at least 50 samples which are half of signal sampling rate. The estimated PWA signal is filtered with a 0.1 Hz (about 6 breath/min) low pass FIR filter, in order to remove the respiratory modulation. All results are normalized by removing the mean and then divided by its standard deviation.

2) PWA trend estimation

Trends continuously dropping or rising PWA was detected based on slopes between every two samples. Continuous series of non-positive slopes were considered as a dropping trend, vice versa, continuous series of non-negative slops were considered as a rising trend. For every detected trend, the depth and duration of the trend were recorded. Dropping and rising trends have a negative and positive depths in the normalized unit respectively. The duration of each trend was recorded in seconds.

3) Analysis of PWA dynamics

PWA dynamics were assessed by capturing the depth and duration of each drop and rise in this measurement. A PWA histogram matrix of dropping and rising trends was created for this analysis. The matrix was 121 in depths by 201 in durations and created for visualizing the distribution of depths and durations of the trends. The bin width of the depths was set as 0.05 in normalized amplitude from range -3 to 3, and the bin width of the durations were set to be 0.1 seconds from 0 to 20 seconds.

4) Threshold test for PWA dynamics

The threshold is defined for one particular depth and duration combination out of all detected trends in percentage. There are 30 logarithmically spaced threshold points from 10^{-2} to $10^{-1.5}$ used in this test. As a result, the percentage of the number of bins equal or above the defined threshold out of the overall number of bins in the depth and duration histogram matrix is returned. That was used as an indicator to distinguish the difference between control children and children with SDB.

D. Statistical analysis

The Kruskal-Wallis test was used to analysis the PWA data difference between baseline SDB and control children. Matlab® 2018b was used for this statistic analysis. Subject demographics were analyzed using one-way ANOVA between SDB and control groups in IBM SPSS Statistics 25. Subject demographic and PWA measurements are presented as mean ± SD unless stated otherwise and $p < 0.05$ was considered statistically significant.

III. Results

A. Study Participants

A total of 78 children were included in the analysis in this study, 39 children in each control and SDB groups at baseline study. Two children of out all 80 participants were excluded due to missing of the PPG recording, one from each group. Group demographic profiles were comparably similar in term of age and BMI z-score (Table 1) with no significant difference were found between control and SDB groups. The

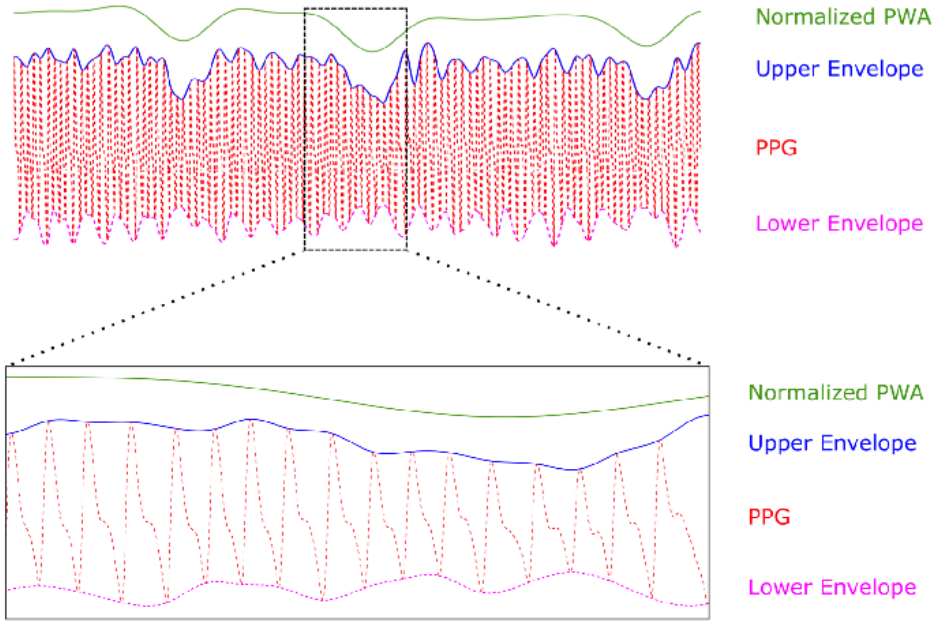

Figure 1. Illustration of PWA estimation and a zoomed in section. Measurement color repersentation: Green – estimated normalized PWA; Blue – upper envelope of PPG; red – PPG; and magenta – lower envelope of PPG

mean age of the participants is 7.56 years, and 57.7 % were male. SDB group demonstrated with a significant higher OAHI with a p-value of 0.0015 than controls as expected.

TABLE I. SUBJECT DEMOGRAPHICS AT THE BASELINE STUDY

	Control (n = 39)	**SDB** (n = 39)
Age (years)	7.67 ± 2.69	7.45 ± 2.78
# males	19	26
BMI z-score	0.29 ± 0.89	0.61 ± 1.35
OAHI	0.31 ± 1.13	5.24 ± 9.16 **

Data are presented as mean ± SD. **: p < 0.01;

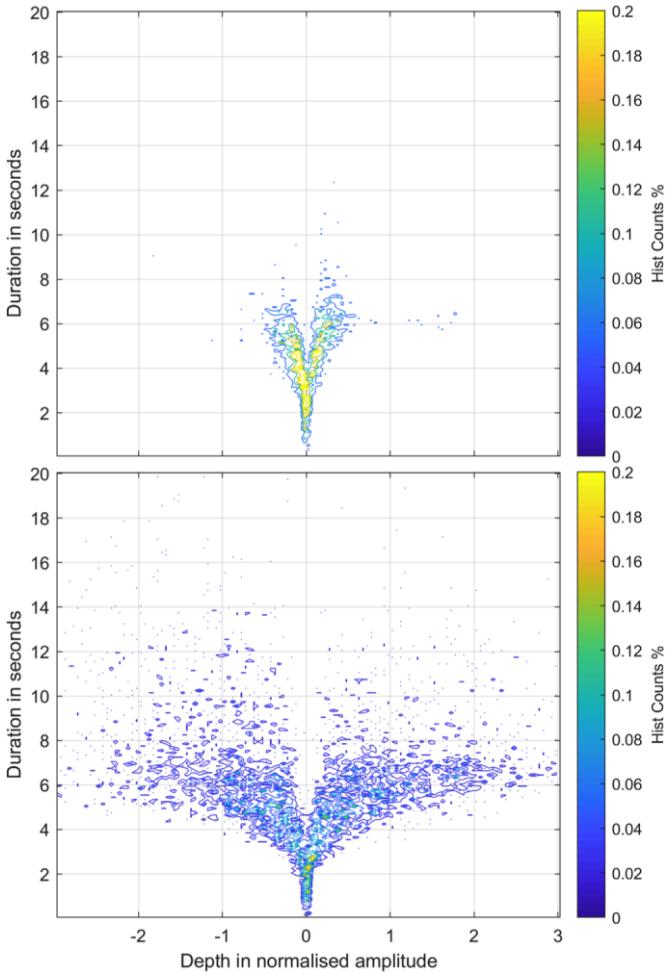

Figure 2. PWA dynamics – Examples of dropping and rising trends distribution in contour plots of one normal child (Top) and one child with SDB (Bottom). Positive depth refers to rising trends, vice verse, negtive refers to dropping trends. The color bar indicates the percetage of the counts out of all trends in a paticular range of depth and duration combination

B. Pulse Wave Amplitude measurement

An example of PWA calculated from PPG signal was shown in Figure 1, where the PWA signal is in cyan, PPG signal is in red; upper and lower envelops of the PPG signal is in blue and magenta.

C. PWA dynamics analysis

A sprout looking distribution was found for the trends. Examples are shown in contour plots in Figure 2. The one on the top is from a normal child with OAHI of 0. The one on the bottom is from a child with SDB with OAHI of 11.92. The trend distributions in these two plots appear quite different. In the normal child, the trends distribution is concentrated with a higher percentage of trends were distributed around the center of the plot with the depth of the trends close to zero duration between 2 to 6 seconds. In contrast, the trends distribution is much more spread out in the child with SDB.

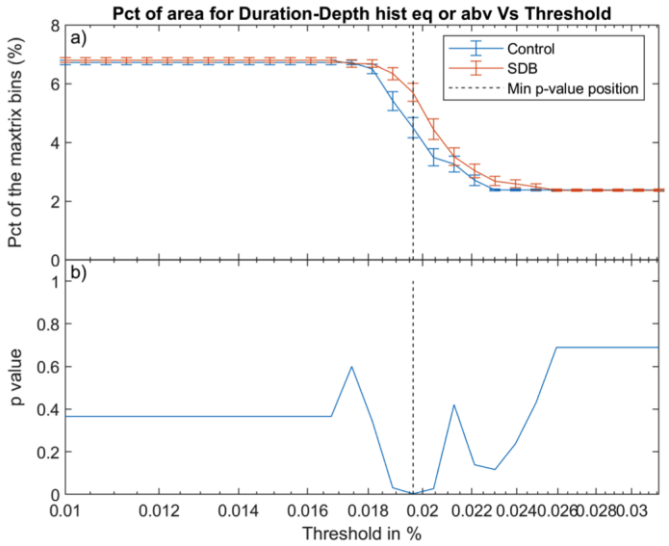

Figure 3. Percetage of the area for duration-depth trends histogram equal or above chosen threshold

D. Threshold test on PWA dynamic

From the threshold test, a range of thresholds was shown to effectively distinguish the control group from SDB group, where 0.0196 % is the best threshold that can separate controls with SDB group with a p-value of 0.003 (Figure 3). SDB children showed a significantly higher PWA dynamic than controls. The mean and standard error of each of the control and SDB groups at this threshold is 4.496 ± 0.342 and 5.699 ± 0.3063.

IV. DISCUSSION

In this study, we investigated autonomic activation through PPG by assessing PWA dynamics during sleep in children with SDB and healthy children. The main finding is a wider distribution of PWA dynamics in children with SDB than in controls. Children who experience SDB are likely to have an increased number of longer and larger trends in PWA. This may indicate children with SDB experience longer and stronger autonomic activations that are more frequently compared to healthy controls. A threshold of the percentage

of a particular trend exists that allowed us separating children with SDB from normal children.

By applying a simple envelope-based method on PPG, PWA can be easily estimated. Our method does not require R-peaks detection from the ECG signal to locate corresponding pulse waves from the same cardiac cycle, which reduces the processing complexity.

Additionally, since the PWA can be extracted continuously, the calculation provides a chance to capture all the possible changing trends different in durations and amplitudes, instead of the more general trend change in every three heartbeats that analyzed in our previous study [17]. A significant group difference was found in PWA between controls and SDB at baseline, even though it was not found in the previous study [17], which once more shown the altered autonomic response in children with SDB. Further studies could be conducted to analyze the adenotonsillectomy effect on PWA dynamics in SDB children during sleep and the respiratory event free sleep. While our previous study showed increased respiratory load measured in thoraco-abdominal asynchrony in children with SDB [23], it could be a direct trigger of causing autonomic response, and it would be interested to investigate the effect of respiratory load change on PWA.

V. Conclusion

Pulse wave amplitude measurement may be helpful to quantify changes in autonomic activation in children with sleep disordered breathing. The envelope method may provide an easier and more accurate estimation of PWA and a better reflection of autonomic activation in children with SDB.

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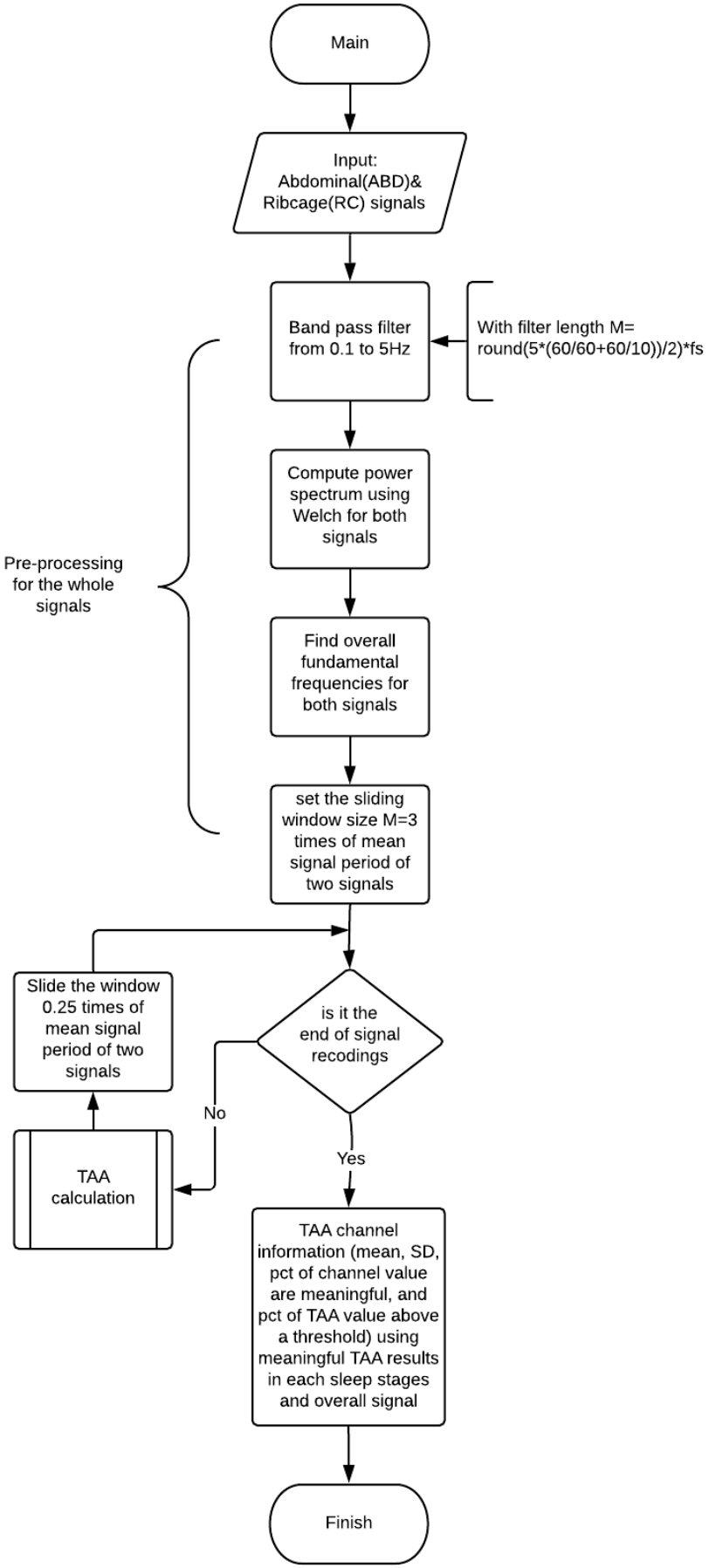
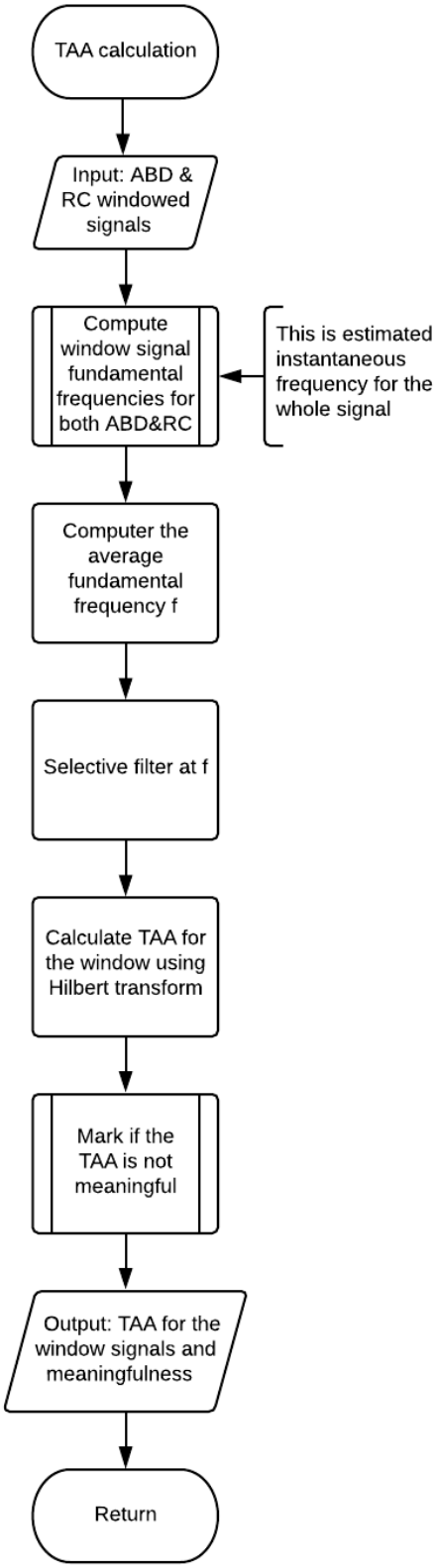
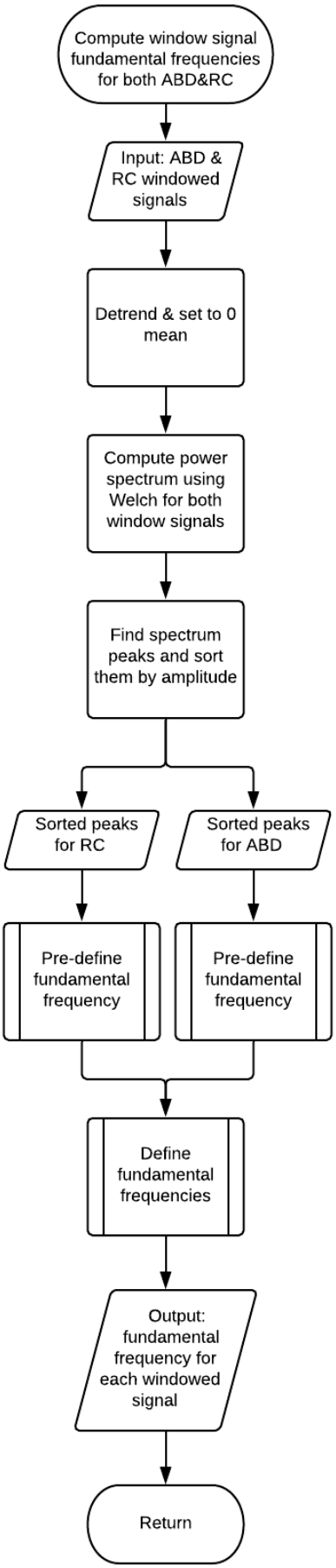
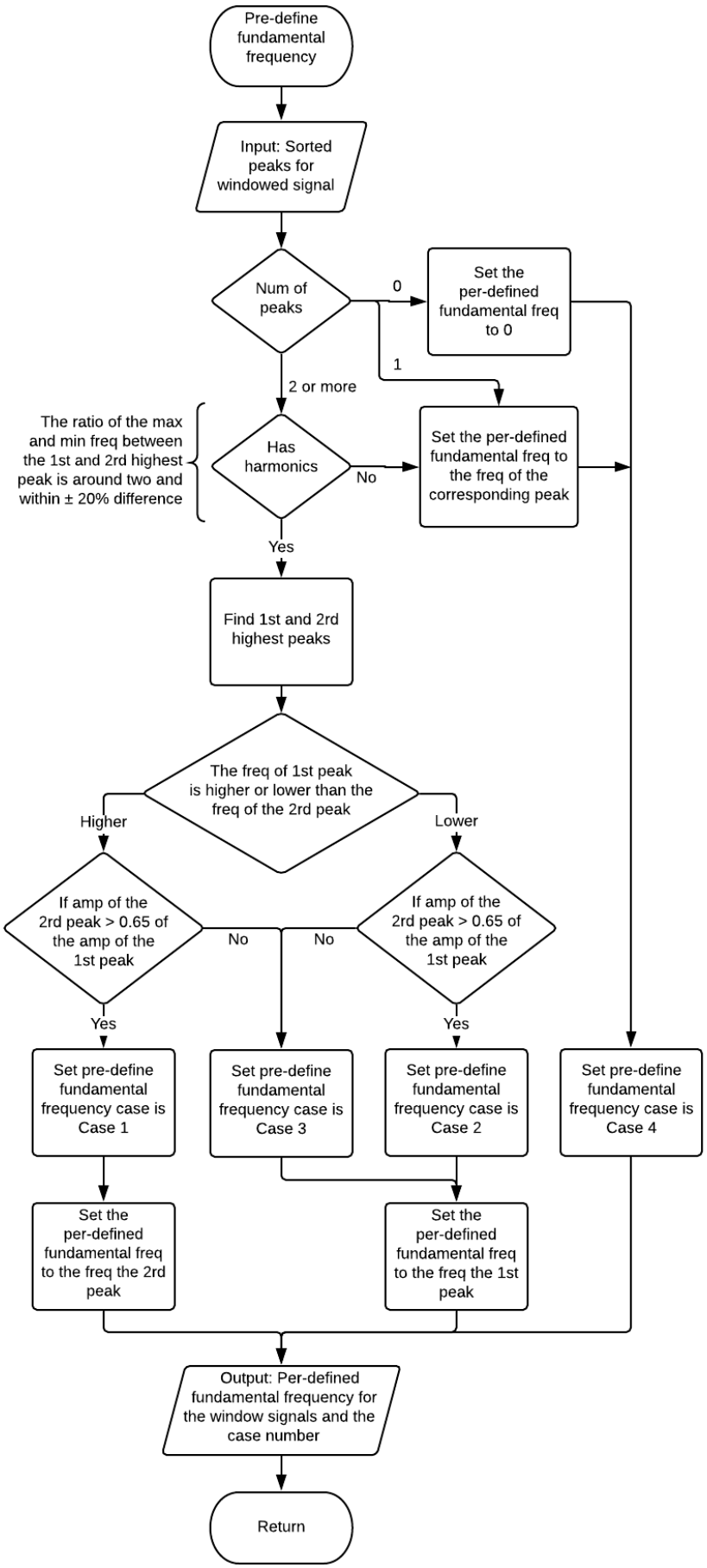
Appendix B

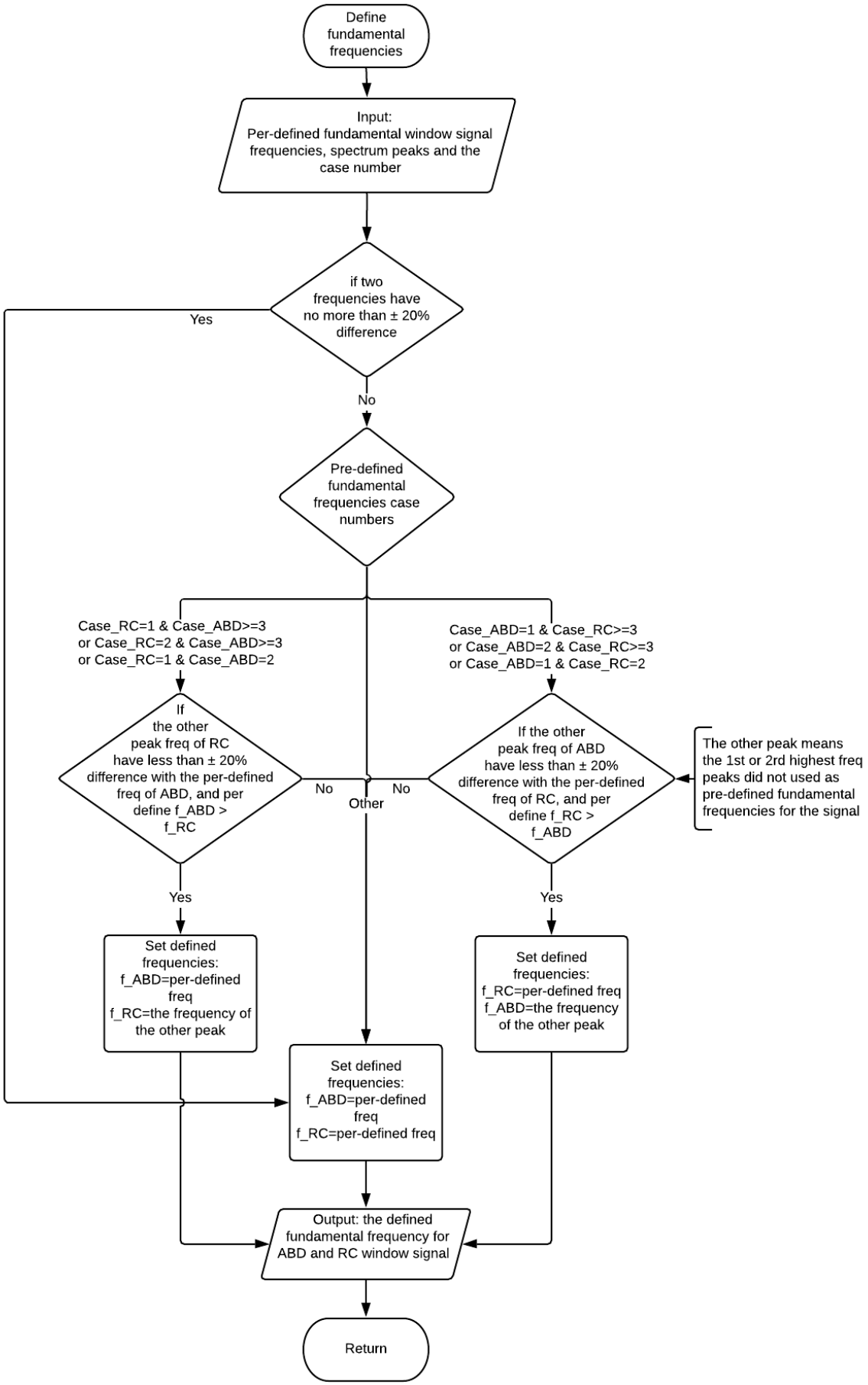
Framework flow chart for TAA estimation

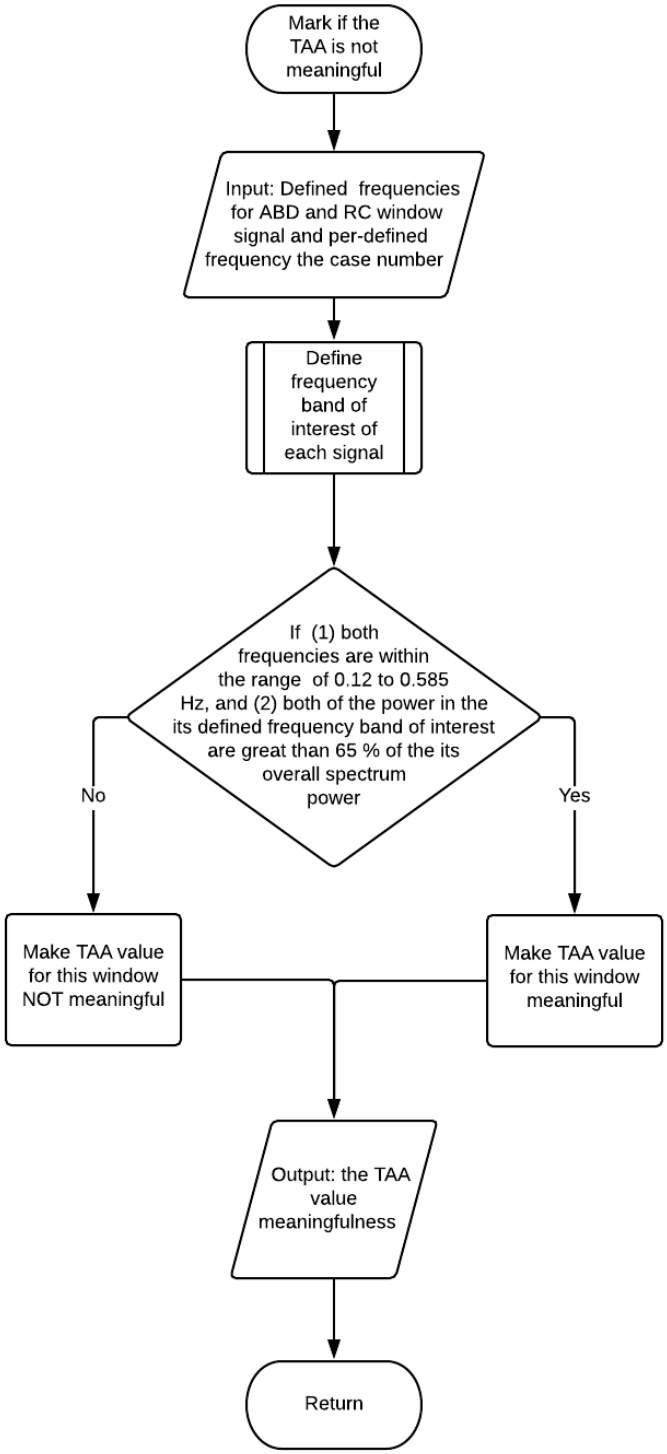

Main
Input: Abdominal(ABD)& Ribcage(RC) signals
Band pass filter from 0.1 to 5Hz
With filter length M= round(5*(60/60+60/10))/2)*fs
Compute power spectrum using Welch for both signals
Pre-processing for the whole signals
Find overall fundamental frequencies for both signals
set the sliding window size M=3 times of mean signal period of two signals
Slide the window 0.25 times of mean signal period of two signals
is it the end of signal recodings
No
Yes
TAA calculation
TAA channel information (mean, SD, pct of channel value are meaningful, and pct of TAA value above a threshold) using meaningful TAA results in each sleep stages and overall signal
Finish

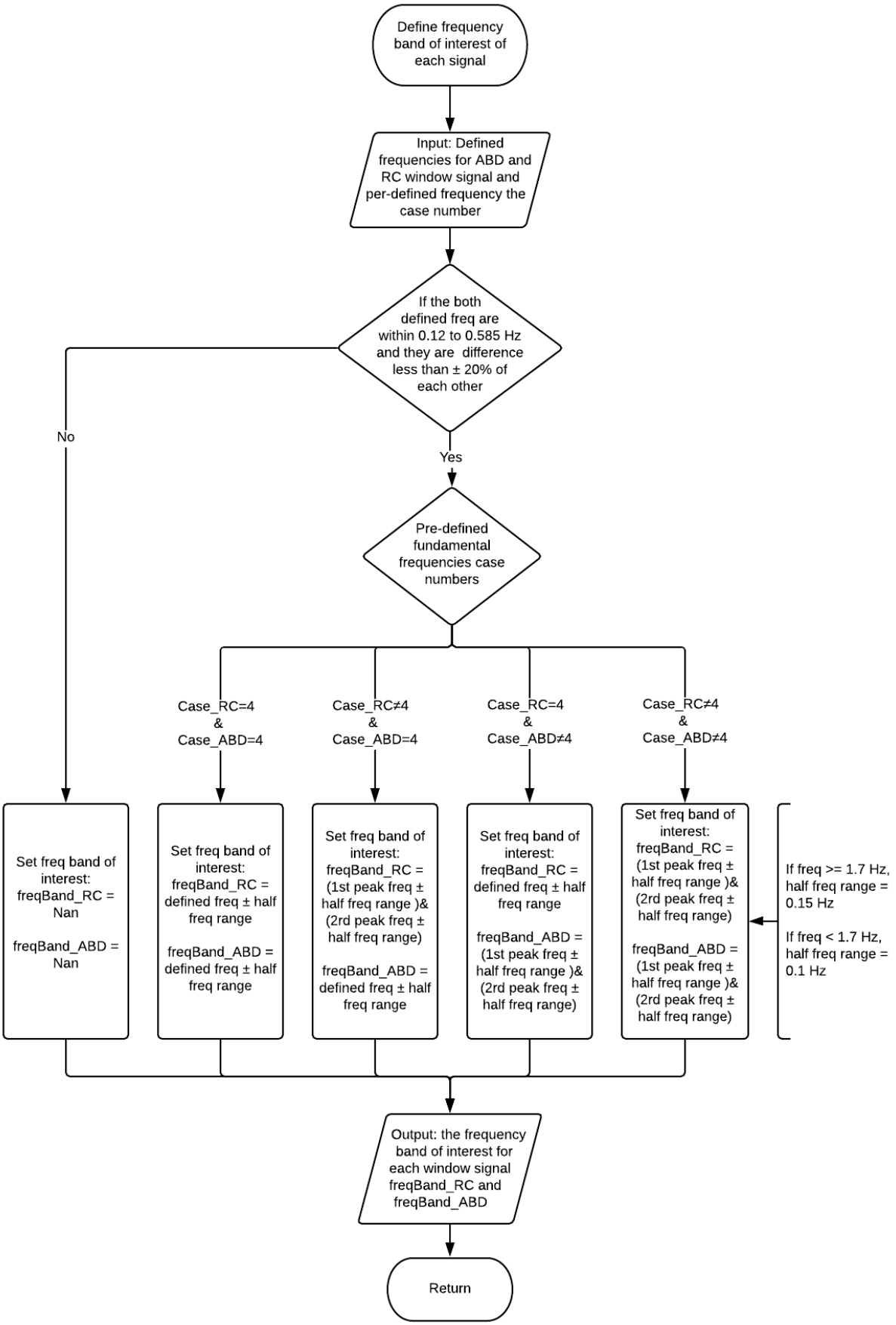

TAA calculation
Input: ABD & RC windowed signals
Compute window signal fundamental frequencies for both ABD&RC
This is estimated instantaneous frequency for the whole signal
Computer the average fundamental frequency f
Selective filter at f
Calculate TAA for the window using Hilbert transform
Mark if the TAA is not meaningful
Output: TAA for the window signals and meaningfulness
Return


Compute window signal fundamental frequencies for both ABD&RC
Input: ABD & RC windowed signals
Detrend & set to 0 mean
Compute power spectrum using Welch for both window signals
Find spectrum peaks and sort them by amplitude
Sorted peaks for RC
Sorted peaks for ABD
Pre-define fundamental frequency
Pre-define fundamental frequency
Define fundamental frequencies
Output: fundamental frequency for each windowed signal
Return


Pre-define fundamental frequency
Input: Sorted peaks for windowed signal
Num of peaks
0
Set the per-defined fundamental freq to 0
1
2 or more
The ratio of the max and min freq between the 1st and 2rd highest peak is around two and within ± 20% difference
Has harmonics
No
Set the per-defined fundamental freq to the freq of the corresponding peak
Yes
Find 1st and 2rd highest peaks
The freq of 1st peak is higher or lower than the freq of the 2rd peak
Higher
Lower
If amp of the 2rd peak > 0.65 of the amp of the 1st peak
No
No
If amp of the 2rd peak > 0.65 of the amp of the 1st peak
Yes
Yes
Set pre-define fundamental frequency case is Case 1
Set pre-define fundamental frequency case is Case 3
Set pre-define fundamental frequency case is Case 2
Set pre-define fundamental frequency case is Case 4
Set the per-defined fundamental freq to the freq the 2rd peak
Set the per-defined fundamental freq to the freq the 1st peak
Output: Per-defined fundamental frequency for the window signals and the case number
Return


Define fundamental frequencies
Input: Per-defined fundamental window signal frequencies, spectrum peaks and the case number
if two frequencies have no more than ± 20% difference
Yes
No
Pre-defined fundamental frequencies case numbers
Case_RC=1 & Case_ABD>=3 or Case_RC=2 & Case_ABD>=3 or Case_RC=1 & Case_ABD=2
Case_ABD=1 & Case_RC>=3 or Case_ABD=2 & Case_RC>=3 or Case_ABD=1 & Case_RC=2
If the other peak freq of RC have less than ± 20% difference with the per-defined freq of ABD, and per define f_ABD > f_RC
If the other peak freq of ABD have less than ± 20% difference with the per-defined freq of RC, and per define f_RC > f_ABD
The other peak means the 1st or 2rd highest freq peaks did not used as pre-defined fundamental frequencies for the signal
No
No
Other
Yes
Yes
Set defined frequencies: f_ABD=per-defined freq f_RC=the frequency of the other peak
Set defined frequencies: f_RC=per-defined freq f_ABD=the frequency of the other peak
Set defined frequencies: f_ABD=per-defined freq f_RC=per-defined freq
Output: the defined fundamental frequency for ABD and RC window signal
Return


Mark if the TAA is not meaningful
Input: Defined frequencies for ABD and RC window signal and per-defined frequency the case number
Define frequency band of interest of each signal
If (1) both frequencies are within the range of 0.12 to 0.585 Hz, and (2) both of the power in the its defined frequency band of interest are great than 65 % of the its overall spectrum power
No
Yes
Make TAA value for this window NOT meaningful
Make TAA value for this window meaningful
Output: the TAA value meaningfulness
Return


Define frequency band of interest of each signal
Input: Defined frequencies for ABD and RC window signal and per-defined frequency the case number
If the both defined freq are within 0.12 to 0.585 Hz and they are difference less than ± 20% of each other
No
Yes
Pre-defined fundamental frequencies case numbers
Case_RC=4 & Case_ABD=4
Case_RC≠4 & Case_ABD=4
Case_RC=4 & Case_ABD≠4
Case_RC≠4 & Case_ABD≠4
Set freq band of interest: freqBand_RC = Nan
freqBand_ABD = Nan
Set freq band of interest: freqBand_RC = defined freq ± half freq range
freqBand_ABD = defined freq ± half freq range
Set freq band of interest: freqBand_RC = (1st peak freq ± half freq range)& (2rd peak freq ± half freq range)
freqBand_ABD = defined freq ± half freq range
Set freq band of interest: freqBand_RC = defined freq ± half freq range
freqBand_ABD = (1st peak freq ± half freq range)& (2rd peak freq ± half freq range)
Set freq band of interest: freqBand_RC = (1st peak freq ± half freq range)& (2rd peak freq ± half freq range)
freqBand_ABD = (1st peak freq ± half freq range)& (2rd peak freq ± half freq range)
If freq >= 1.7 Hz, half freq range = 0.15 Hz
If freq < 1.7 Hz, half freq range = 0.1 Hz
Output: the frequency band of interest for each window signal freqBand_RC and freqBand_ABD
Return

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