Predicting Upper Airway Abnormalities by Detecting Inspiratory Flow Limitation with Temporal Features of Nasal Airflow

by

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A thesis submitted in conformity with the requirements for the degree of Master of Health Science in Clinical Biomedical Engineering

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Abstract

The purpose of this thesis is to explore the potential of the temporal features extracted from nasal airflow as the source for detecting inspiratory flow limitation non-invasively. This thesis focused on developing and validating algorithms capable of extracting physiologically meaningful features from nasal airflow recording, followed by classification of flow limited breaths, utilizing supervised and un-supervised learning. The feature values and the classification results were compared with the upper airway-anatomical measurements such as neck circumference, upper airway cross-sectional area, and neck fluid volume. Three features (deviation index, peak amplitude variability, and peak number) were found to be significantly correlated with the upper airway measurements. Un-supervised classification suggested that participants with more neck fluid volume before sleep are associated with more flow limited breaths. The findings corroborated our understanding that inspiratory flow limitation is associated with upper airway anatomical abnormalities.
Acknowledgments

I am deeply grateful for the guidance, help, and support from my supervisors, Dr. Milos R. Popovic and Dr. Azadeh Yadollahi, and other members of my committee: Dr. José Zariffa, Dr. Paul Yoo, and Dr. Kei Masani. I would also express my appreciation to Daniel Vena, Bojan Gavrilovic, Swati Bhatawadekar and the rest of the sleep science team of Toronto Rehab and REL for their generous support throughout my master’s study.

Additional thanks are extended to CIHR Operating Grant for funding the saline study from which the data of my thesis project were borrowed. Also thanks to CIHR Training Grant in Sleep and Biological Rhythms Toronto for funding my thesis project. Thanks to the University of Toronto and Toronto Rehab for their financial support.

Without the help and support of these individuals and organizations, this research would not have been possible.

Finally, I would like to thank my parents and my girlfriend Rachel Franz for their love which continues to be my source of strength and support in all my endeavours.
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List of Abbreviations

AHI: Apnea-hypopnea index

AUC: Area under curve

IFL: Inspiratory flow limitation

NC: Neck circumference

NFV: Neck fluid volume

OSA: Obstructive sleep apnea

REM: Rapid eye movement

SDB: Sleep-disordered breathing

UA: Upper airway

XSA: Cross-sectional area
... At first

Senseless as beasts I gave men sense,

possessed them from mind...

In the beginning, seeing, they saw amiss,

and hearing, heard not, but like phantoms huddled

In dreams, the perplexed story of their days

Confounded.

- Aeschylus, Prometheus Bound
1 Introduction

Sleep is an essential part of human life. However, it was estimated that 26% of the adults of age 30 to 70 years in the United States are affected by sleep-disordered breathing (SDB)\(^1\). SDB is a condition characterized by a spectrum of respiratory disorders that occur during sleep, ranging from mild snoring to severe obstructive sleep apnea (OSA). SDB causes immediate negative health consequences such as intermittent hypoxia, fragmented sleep, and pronounced fluctuation in heart rate, blood pressure and intrathoracic pressure. In the long run, SDB is associated with cognitive impairment, hypertension, cardiovascular morbidities, and poor quality of life\(^2\).

Figure 1. Sleep-disordered breathing is a continuum of breathing disorders during sleep.

According to the American Association of Sleep Medicine, the severity of SDB is quantified by apnea-hypopnea index (AHI), the average number of apneas and hypopneas during sleep. Apnea is defined as the complete collapse of the upper airway (UA) with more than 90% reduction of airflow. Hypopnea is defined as the partial collapse of the UA with more than 50% reduction of airflow, associated with a 3% reduction in the oxygen saturation level or arousal from sleep. Both apneas and hypopneas should last at least 10 seconds\(^3\).

A few issues arise when using AHI as the only diagnostic tool. First, AHI reports the number of consecutive apneic/hypopneic breathing only for a period over 10 seconds. Consequently, AHI does not reflect the degree of airflow reduction of each individual breath. Additionally, AHI is capable of accurately diagnosing severe SDB such as Obstructive Sleep Apnea, but not sensitive enough to capture mild UA collapses such as UA resistance syndrome. Furthermore, AHI is insufficient for the diagnosis of upper airway resistance syndrome, a mild form of SDB characterized by frequent electroencephalogram arousals occurring in the absence of apneas and
hypopneas\textsuperscript{4}. Though not detected by AHI criteria, upper airway resistance syndrome can be correlated with clinical sequelae such as excessive-daytime somnolence and long-term cardiovascular comorbidities\textsuperscript{4}. Lastly, pregnant women and children tend to have clinical complications of OSA with a much lower AHI than adult men. As a result, diagnosis based on AHI may not be sensitive enough to evaluate the pathophysiology of breathing disorders in these populations. For these reasons, a sensitive metric capable of assessing sleep disturbance on a breath-by-breath basis is highly desirable.

In fact, another phenomenon associated with narrowed UA - inspiratory flow limitation (IFL) - provides a different perspective for evaluating SDB. IFL is characterized by sustained inspiratory airflow with increased respiratory drive, which can be imagined as breathing through a straw - the airflow is limited no matter how forceful the breathing is. IFL can be observed as flattening of the flow tracing on polysomnography (a multi-parametric sleep test), different from the dramatic reduction of airflow essential to the diagnosis of apnea and hypopnea. While the diagnostic criteria for apnea and hypopnea require the 10 second cutoff, IFL can be detected on a breath-by-breath basis\textsuperscript{2}. Moreover, it has been shown that the presence of IFL is vital to the understanding of upper airway resistance syndrome and subsequently as a diagnostic tool for this population\textsuperscript{4}. In addition, IFL is associated with adverse health outcomes among pregnant women with pre-eclampsia (a syndrome potentially fatal for both fetus and mother) and chronic pediatric snorers who were otherwise not diagnosed with sleep apnea\textsuperscript{5}. Because of the extra sensitivity for detecting anomaly of UA, IFL can be an alternative or compliment to the existing clinical metrics for evaluating SDB\textsuperscript{4}. However, the significance of IFL has only recently been recognized and more relevant studies are yet to be performed\textsuperscript{4}. Nonetheless, challenges exist because some of the previous studies required invasive measures, and the detection of IFL was largely manual and laborious. In my thesis, I aim to investigate a novel method of detecting IFL automatically and non-invasively, with which I further examine the impact of UA narrowing on the prevalence of IFL for each participant during sleep. In the future, the proposed method could be used to investigate potential health consequences of milder degrees of UA narrowing in more susceptible populations, such as upper airway resistance syndrome patients, pregnant women and children.
2 Relevant Literature

In this section, we first discuss why IFL happens and the clinical significance of IFL. Then we discuss the measurement of airflow used to infer IFL, followed by the clinical protocol for manually scoring IFL. Expanding from there, we will introduce the past studies for automatic classification of IFL breaths. Lastly, we discuss rostral fluid shift - one of the physiological mechanisms that contribute to the UA narrowing during sleep, and whether IFL can be used to detect the effects of rostral fluid shift on UA narrowing.

2.1 Mechanism of IFL

UA narrowing contributes to IFL. At the inception of each inspiratory cycle, contraction of diaphragm and external intercostal muscles initiates breathing by expanding the rib cage, creating negative intrathoracic pressure that inflates the lungs. During that process, there are three scenarios that would happen: first, with little or no obstruction in the UA, flow increases in proportion to the pressure gradient between the upstream pressure at the naris and the downstream intraluminal pressure, resulting in a linear pressure-flow relationship\(^6\). The subsequent flow-time relationship resembles a bell-shaped curve as illustrated in the Figure 2-a\(^6\).

Secondly, in the case of a partially collapsed UA with high compliance (similar to a collapsible tube) as seen in the patients with IFL\(^6\), the linear pressure-flow relationship could be maintained only up to a certain point with increasing respiratory drive. Beyond that point the amount of airflow that passes through the UA could not be increased, despite greater respiratory effort\(^6\). Correspondingly, a plateau or flattened region of the inspiratory airflow appears (Figure 2-b)\(^6\).

Thirdly, if intraluminal pressure continues to become more negative, the Bernoulli Effect prevails. The airflow potential energy is converted to kinetic energy in high resistance region of the UA, where airflow velocity increases when UA narrows, leading to a drop in lateral wall pressure that further narrows the UA\(^7\). Under this situation, the flow decreases as the pressure increases, resulting in a scooped region in the flow-time contour (Figure 2-c). This is known as Negative Effort Dependence, and it can be interpreted as a severe case of IFL.
Figure 2 The top row describes the pressure-flow relationships of the 3 scenarios: normal, Inspiratory flow limitation (IFL) and Negative Effort Dependence. The bottom row shows the time-flow relationships correspondingly. The dashed curves indicate inspiratory phase and solid curves indicate expiratory phase.

2.2 Clinical Significance of IFL

IFL usually precedes snoring and apnea, and it is considered the earliest sign of impending UA collapse. Recurrent IFL is associated with excessive daytime sleepiness, changes in blood oxygen saturation and end-tidal CO$_2$, which are clinical and physiological responses that have also been noted with apneas and hypopneas. Furthermore, Both IFL and obstructive hypopnea result from UA narrowing and partial collapse. Although obstructive hypopnea is accompanied by IFL or asynchronous movements of chest and abdomen, IFL may appear outside of hypopnea. Further evidences also corroborated the hypothesis that IFL may be a more sensitive indicator of UA anatomic abnormalities than hypopnea. For instance, one study showed that OSA patients with prolonged IFL are associated with more nasal and palatal anatomical abnormalities than the patients with the same OSA severity but no IFL. Another study compared different continuous positive airway pressure (the standard treatment of sleep apnea using positive pressure ventilation) titration levels targeted to eliminate IFL or OSA. The results suggested that treating IFL instead of simply treating OSA led to better clinical outcomes.
2.3 IFL Detection

The gold standard method for detecting IFL entails the monitoring of both the respiratory airflow and the driving pressure. The driving pressure is obtained from esophageal manometry, which is an invasive process and may alter sleep structure. Alternatively, the airflow tracing on polysomnography alone can be used to detect IFL, as discussed in section 2.1. It has been shown that IFL detection with airflow tracing yields similar results compared to esophageal manometry. Compared to esophageal manometry, airflow monitoring is convenient and non-invasive. Hence, detection of IFL using airflow shape analysis is highly desired.

Conventionally, respiratory airflow was recorded non-invasively with a tight-fitting facemask connected to a pneumotach, a device that transduces airflow rate to proportional pressure drop. The pressure drop can then be picked up by a pressure transducer that outputs analog signal proportional to flow rate. However, the use of facemask and the connected pneumotach alters the UA anatomy by retro-positioning the mandible, thus affecting the normal breathing patterns. An alternative for measuring airflow is the nasal cannula/pressure transducer system. The nasal cannula is placed at the nares and is attached to a pressure transducer therefore the system does not affect the UA anatomy. The nasal cannula is also inexpensive and convenient to set up. A comparison of the measurements from both facemask and the nasal cannula revealed that the signal obtained from nasal cannula was nearly linearly correlated with that from facemask in the range of normal breathing, with up to only 6% of error. At very high breathing level (hyperventilation following a period of hypoventilation) and low breathing level (apnea) the relationship was non-linear. In the context of this study, those two levels are excluded from analysis because they are irrelevant to IFL. Therefore, the nasal cannula/pressure transducer system is capable of accurately approximating respiratory airflow for IFL detection compared to the full facemask connected to a pneumotach.

2.3.1 Manual Non-Invasive Detection of IFL

Akin to most of the sleep research, the common practice of IFL identification is done manually due to the varying nature of the physiologic signal under analysis. Therefore, disagreement occurs even between veteran annotators. To overcome this limitation, in 2015, an ad hoc committee consisting of clinicians and researchers collectively formulated a flow chart (see Appendix A) that helps guide the clinical scoring of IFL. The flow chart incorporated decision
stumps based on the temporal features of the inspiratory contour, including the degree of scooping and flattening, prolonged inspiratory duty cycle, snoring, and adjacent breath types.

Even with standard scoring criteria, the airflow shape analysis is still a subjective process. Consequently, several limitations are inevitable. For example, breath-by-breath annotation is a laborious and time-consuming process, which makes it impossible to analyze large datasets. In addition, human errors and perceptual disagreement are common. For instance, one study showed that inter-rater agreement varied from 69% to 98%.

**2.3.2 Automatic Detection of IFL**

To overcome the limitations of manual annotation, various approaches in the past were devised to automatically detect IFL with respiratory flow tracing. As the gold standard method requires both the flow and pressure measurements, several studies first generated templates for normal and IFL flow contour from the flow and pressure measurements using invasive measures. They then classified each individual breath by comparing the deviation of the recorded inspiratory contour from the template, which indicates the severity of IFL. Although excellent classification accuracies were observed, these studies are not ideal because they still required invasive measurement of pressure to formulate templates.

To detect IFL non-invasively, automatic algorithms based on airflow shape have been developed for commercial products treating sleep apnea. However, these algorithms are proprietary and not available to public. Also, very little validation has been documented. In another study, supervised machine learning using artificial neural network was designed to automatically classify each inspiratory contour, with training data collected from human annotation. Good agreement with manual classification was reported. However, the input data were extrapolated from the flow contour directly. The neural network was treated as a black box without referencing to the temporal features of the contour, which makes it difficult to fine-tune the classifier once it is constructed.

Another study took a different approach by investigating the relationship between anatomic abnormalities and the inspiratory flow shape patterns in patients with compromised UA anatomy. With unsupervised learning, recorded breaths were clustered into 7 classes of representative shapes with their relationship to anatomic flow abnormalities.
Figure 3 The distribution of flow shape classes in patients with potential inspiratory flow limitation and control subjects. 9 healthy young men were referred to as control group; 10 postmenopausal women with OSA were referred to as female patients; 19 men with OSA were referred to as male patients. The 7 classes of inspiratory flow shapes are explained in Table 1.

Table 1 Classes of inspiratory flow shapes

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Interpretation</th>
<th>IFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rounded bell curve</td>
<td>Normal inspiration</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Two peaks during inspiration</td>
<td>Upper airway reopening after initial</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Clinical Findings</td>
<td>Associated Findings</td>
<td>Result</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>3</td>
<td>Three or more peaks</td>
<td>Soft-tissue vibration during inspiration</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Peak during the initial phase followed by a plateau</td>
<td>Initial opening indicates effective phasic upper airway dilation</td>
<td>Yes/No</td>
</tr>
<tr>
<td>5</td>
<td>Peak at mid inspiration with plateau on both sides</td>
<td>Significance uncertain; intensive phasic muscle activity at mid inspiration</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Peak during late phase preceded by a plateau</td>
<td>Marked tracheal traction support during lung inflation</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Plateau throughout inspiration</td>
<td>Collapse of noncompliant upper airway</td>
<td>Yes</td>
</tr>
</tbody>
</table>

That study sought to identify clinical subtypes by analyzing flow patterns. It can be seen that there are significant differences in the control and the male and female patient groups, and also between men and women. Therefore, it is reasonable to deduce that, by extracting the temporal patterns of the inspiratory contour, we could differentiate normal population and populations that are more susceptible to SDB\(^{19}\). The author speculated that with increasing knowledge of the physiologic correlates of the various flow shapes, the inspiratory shape recognizer can be sensitive enough to detect risk behaviour of the UA.

### 2.4 UA Narrowing due to Rostral Fluid Shift

IFL arises from the narrowing of UA. There are many factors that contribute to UA narrowing, among which UA soft tissue (soft palate, tongue, tonsil, lateral pharyngeal wall) enlargement is a
major player. Excessive tissue mass compresses the UA, increasing the pharyngeal intramural pressure and leading to UA narrowing. UA soft tissue enlargement may arise from factors including gender, genetics, obesity, and edema. The edema accumulation in UA has been shown to be related to rostral fluid shift. The transition of fluid between capillaries and interstitial space is controlled by hydrostatic and colloid osmotic forces, as suggested by Starling forces. During the day, gravity and sedentary lifestyle leads to fluid accumulation in the interstitial space of legs. At night, when lying down to sleep, gravitational effect diminishes. As a result, part of the fluid which is accumulated in the legs is absorbed in the capillaries and redistributes to the UA soft tissue through the vascular bed. Moreover, rostral fluid shift also increases internal jugular vein volume due to increased venous return. The enlarged internal jugular vein also compresses the UA and causes it to narrow. Lastly, the pharyngeal mucosal space consists of the mucosa and structures of the nasopharynx, the oropharynx, and the laryngopharynx. Transudation of fluid into this space also results in the narrowing of UA.

Previous studies from the sleep laboratory of the Toronto Rehabilitation Institute demonstrated that when lying down to sleep at night, leg fluid volume decreases and thoracic and neck fluid volumes increase. Fluid accumulation in the neck increases neck circumference, narrows the UA, increases UA collapsibility, and exacerbates sleep apnea. This is especially prominent among patients in edematous states such as heart failure and renal failure. However, those studies were only able to capture the changes of UA anatomy before and after sleep due to the limitation of the measurements. Automatic and continuous assessment of IFL could be a sensitive tool for investigating the effect of fluid shift on SDB pathophysiology.
3 Objectives

The first objective of my thesis project is to develop an automatic algorithm capable of detecting IFL from the nasal airflow alone. The algorithm should accurately classify each breath based on the patterns of the time-flow profile in the inspiratory phase. The classifier will be trained, validated and tested on the data annotated manually.

The second objective is to investigate the relationship between IFL prevalence and the anatomical changes in the UA induced by fluid shift during sleep. I hypothesize that an increase in neck circumference, a decrease in UA cross-sectional area and an increase in neck fluid volume after sleep while lying supine are correlated with higher prevalence of IFL.

4 Methodology

4.1 Instrumentation

4.1.1 Polysomnography and Software

A polysomnography is a sleep study conducted in a sleep laboratory, which is considered the gold standard for assessing SDB. A polysomnograph contains about 20 physiological signals such as nasal airflow, electroencephalograph, electrocardiogram, electrooculography, and respiratory inductance plethysmograph. Sleep technologists visually examine those signals and determine sleep structure and efficiency. Sandman® Elite™ is the diagnostic software currently deployed in the sleep laboratory of Toronto Rehabilitation Institute. For each participant who finished a sleep study, the software displays the recorded signals concurrently, and generates and exports data files in various formats including European Data Format (the standard format for storing polysomnography data) and text format for compatibility and easy parsing with other software applications. An event file is also generated, matching the sleep stages, and apneic and hypopneic periods to the data file. These two files were extensively analyzed by the algorithms developed in this thesis project for signal processing purposes.
4.1.2 Nasal Cannula/Pressure Transducer

A nasal cannula connected to a pressure transducer (BiNAPS®, Salter Labs®, USA) was used to record nasal airflow as part of the polysomnography routine. The nasal cannula, when attached to the nostril, transduces airflow speed to pressure. The analog pressure signal was then digitalized and amplified by built-in electronics. On-device filtering was performed, generating two signals – airflow ([0.05, 5] Hz) and snoring ([10, 70] Hz). Both signals were transmitted to the PC and displayed in the Sandman® Elite™ polysomnography software suite for analysis. Compared to the other similar commercial products (such as Validyne, USA or Protech PTAF2, USA\textsuperscript{28}) the BiNAPS transducer cannot be calibrated against a standard reference instrument such as a Rouse manometer. As such, the airflow signal amplitude shows relative variations in the airflow and not quantitative changes in airflow. Also, the signal baseline could sporadically drift from zero-intensity line. Furthermore, according to Nyquist-Shannon sampling theorem, the device sampling frequency should be higher than twice that of the highest signal frequency to ensure successful sampling. However, airflow with snoring may contain frequency components as high as 70Hz, greater than half of the system sampling frequency (85.33Hz). Although the airflow contour may very well maintain intact after sampling, the snoring information could not be adequately captured. Therefore the snoring signal was not used in this thesis project.
4.1.3 UA Anatomical Measurements

In my thesis, the following 3 UA anatomic properties were analyzed:

- Neck circumference (NC)
- UA cross-sectional area (UA-XSA)
- Neck fluid volume (NFV)
4.1.3.1 Measurement Techniques

A measuring tape was used to evaluate NC just above the cricothyroid cartilage. A line was drawn at the same level to ensure the consistency from repeated measurements$^{28}$. The average UA-XSA from velum to glottis was measured by acoustic pharyngometry, utilizing the physical principles of acoustic reflection$^{29}$. Bioelectrical impedance was used to measure the NFV. It is a non-invasive technique for estimating fluid volume of tissues. Based on Ohm’s law, the impedance of a tissue to electric current is inversely related to its fluid content and directly related to its length:

$$R = \frac{\rho L^2}{V}$$  \hspace{1cm} (1)$$

where $\rho$ is the resistivity of fluid, $L$ is the segment’s length, and $V$ is the fluid volume. Therefore, the tissue fluid volume can be approximated by measuring the impedance of the tissue segment, knowing the resistivity and length of the segment.
Equation 1 is based on the assumption that length of the segment is much larger than its circumference, which is not valid for the neck. To estimate the NFV in the neck, a more sophisticated equation was applied, taking into account both neck length and its circumference\textsuperscript{30}.

\begin{equation}
V = \left(\frac{\rho^2 L^5 C^2}{4\pi R^2}\right)^{1/3}
\end{equation}

where \(C\) is the neck circumference, and \(\rho\) is blood resistivity. Different factors such as age, sex, and hematocrit level could affect resistivity, \(\rho\)\textsuperscript{31}. In our study, we adopted \(\rho = 47\Omega\text{cm}\), which was estimated in a study of 73 healthy subjects\textsuperscript{32}. The neck impedance was measured with the instrument module (Biopac Systems, EBI100C). Two electrodes injected high frequency (50 kHz), low amplitude (400 \(\mu\text{A}\)) current to the neck, while two sensing electrodes simultaneously measured voltage across the neck to estimate bioelectrical impedance. The sensing electrodes were placed on the right side of the neck below the right ear and at the base of the neck. The injecting electrodes were placed 2.5cm away from the sensing electrodes. The electrodes were secured to the skin with adhesive tape. At the beginning of the study, neck length (\(L\) in Equation 2) was recorded with a measuring tape. To estimate NFV before and after sleep, the measurement of NC before and after sleep while supine was used as \(C\) in Equation 2.

4.1.4 Software for Data Analysis

Matlab\textsuperscript{®} R2014a from MathWorks was used for algorithm development and data analysis throughout this thesis project.

4.2 Participants

The data of my thesis project was borrowed from a previous study completed by Dr. Yadollahi et al. at Toronto Rehabilitation Institute\textsuperscript{33}. The objective of that study was to investigate the effects of fluid overloading on sleep apnea severity. But in this thesis project, only data from the control group was utilized where body fluid displacement was purely due to posture change.
Subjects were recruited by advertisement. The inclusion criteria were non-obese men, with a body mass index < 30 kg/m$^2$, and blood pressure ≤ 140/90 mm Hg. The previous studies have suggested that men are more susceptible to UA collapse in response to overnight rostral fluid shift than women$^{34,35}$. Therefore, only men were included in this study.

The exclusion criteria were a history of cardiovascular, renal, neurological, or respiratory diseases; taking any prescribed medication for these disorders; taking any over-the-counter medication that might influence fluid retention; or a previous diagnosis of OSA.

The demographic information of recruited participants is attached in the Appendix B.

### 4.3 Experimental Procedure and Data Acquisition

The study took place at the sleep laboratory of the Toronto Rehabilitation Institute. Participants arrived in the sleep laboratory at noon following a night of sleep deprivation of less than 4 hours to facilitate the induction of drowsiness, and were instrumented for sleep studies. At the inception of the study, baseline UA anatomical properties (NC, UA-XSA and NFV) were measured while participants were lying on supine position. Immediately following the baseline measurements, the participants underwent a full daytime polysomnography in which nasal airflow was captured by the BiNAPS® nasal airflow/pressure transducer system. Daytime sleep was adopted instead of a full-night study because of its convenience. After the completion of the polysomnography, the same UA measurements were repeated to compare the changes in the UA anatomy.

### 4.4 Signal Processing Roadmap

After acquiring the data from the previous study, I first developed algorithms to preprocess the raw nasal airflow signal. I then manually classified IFL and normal breaths from a subset of data, utilized to represent the full dataset. On the annotated dataset, I developed the code to extract and validate the temporal features of the nasal airflow contour. I constructed and validated the feature-based binary classifiers for automatic detection of IFL, trained and validated with the manual classification results. I then evaluated the statistical relationship of the IFL% and UA measurements, as well as the relationship of feature values and UA measurements. Lastly, I used
unsupervised classification to find relationship between the feature clusters and UA measurements. The flow chart of project progression is shown in Figure 6.

**Figure 6 Roadmap for project progression.**

### 4.5 Signal Preprocessing

There are a few issues related to the nasal airflow signal. First of all, breathing disorders depend on the stage of sleep - the UA collapsibility is different across various sleep stages. For instance, it has long been observed that OSA worsens during rapid eye moment (REM) sleep. Thus the airflow contour could differ significantly from stage to stage. Furthermore, the raw nasal airflow, although filtered by the built-in hardware of the pressure transducer, contained intrinsic noise and motion artefacts due to body movement or displacement of the cannula. Additionally, because of the lack of calibration, the signal baseline occasionally drifted off from the zero intensity line. Consequently the onset of inspiration and expiration could not be easily identified by the zero-crossings of the airflow. From section 4.5.1 to section 4.5.3, I elaborate more on the preprocessing algorithms designed to address those issues.
4.5.1 Stage-Dependent Signal Segmentation

To avoid the bias to the airflow contour due to stage dependence, only the nasal airflow data from non-REM sleep stage 2 were extracted because most of the sleep time is spent on non-REM sleep stage 2 and because respiration is relatively stable during that sleep stage.

For each participant, the start and end time instances of each segment of non-REM sleep stage 2 were identified from the event file generated from Sandman Elite™. An algorithm was developed to extract all the non-REM sleep stage 2 segments from the entire recording. Meanwhile, the algorithm also identified the zero-crossings of the airflow tracing and the zero-intensity line (presumed to be the signal baseline). The zero-crossings were assigned as preliminary onsets for individual inspiratory and expiratory periods. The preliminary onsets were later refined by the onset detection algorithm.

4.5.2 De-Noising

4.5.2.1 Determining Gaussian Window Size

As previously discussed, the normal flow contour resembles a sinusoidal or bell shape. We also know that the convolution product of two Gaussian functions remains a Gaussian function. As a result, a smoothing filter based on a Gaussian kernel will be able to maintain the bell shape of normal nasal airflow signal, while reducing the high frequency noises. An experiment was set up to find the most optimum window size for the Gaussian filter. A series of inspiratory airflow during wakefulness was selected and averaged to formulate the template contour. The resulting waveform was considered the representative airflow contour with no IFL. The waveform was then convolved with Gaussian functions of different window sizes. Two criteria were evaluated:

- The Euclidean difference between filtered and ideal Gaussian signals, which describes the similarity between the filtered normal inspiratory airflow and an ideal Gaussian function.
- Histogram difference between filtered and original signals, which describes the similarity between the filtered inspiratory airflow and the original signal.
Ideally, both criteria should be minimized. However, these criteria depend on the window size of the Gaussian Kernel. Thus by sweeping through different window sizes, the optimal value that minimizes both criteria will be obtained.

4.5.2.2 Comparing 3 Filters for De-nosing

The Gaussian filter was successfully designed which yielded satisfactory de-noising effects. On the other hand, low-pass filters and wavelet filters were commonly utilized in the previous relevant studies\(^7,16-18,36\). Therefore, an experiment was designed to compare the de-noising performances of low-pass filter, Gaussian filter, and a wavelet filter.

In order to mimic the real-world situation where the signal is contaminated by noise, I added white Gaussian noise of signal-to-noise ratios of 18dB. Based on previous observation of the raw airflow, I determined that the composite signal is similar enough to the raw signal. Three filters were constructed to process the noisy signal. A low pass filter was constructed using Butterworth filter with passband frequency of 5Hz and an order of 10. The 5Hz cutoff frequency was selected because previous literature indicates that 5Hz is effective in retaining the respiratory airflow while removing noise\(^16\). A Gaussian filter was created with a window size of 0.4s, with step of 0.05s. Wavelet thresholding has been proven to be one of the most successful de-noising methods and has rendered many successful applications in the area of biomedical signal processing\(^37\). A mother wavelet of symlet4 was chosen. Other settings include: Universal thresholding, scales = 3, and soft thresholding. The composite signal was then processed by those filters to find the filtered signal.

I proposed three criteria to evaluate how powerful the filters are in restoring the noisy signal to the original signal: (1) normalized mean-squared error (NMSE), (2) maximum cross-correlation, and (3) roughness.

MSE is the standard measure of the difference between the original and the estimated signal, in this case, the filtered signal and the original signal. We used normalized MSE, which is calculated by normalizing the squared difference of the processed signal with the original signal by the signal squared sum. It can be obtained using the following expression:
where \( n \) denotes the length of the signal, \( s \) represents the original signal and \( s_c \) is the estimated signal after de-noising. Intuitively, a small NMSE is associated with good filtering effect that restores the noisy signal to be close to the original signal, indicating good performance.

Cross-correlation is a standard method of estimating the degree to which two series are correlated. The maximum of the cross-correlation function indicates the point in time where the signals are best aligned. It describes the highest proximity of two signals. With this metric, we can determine which filtered signal is most close to the original signal. This metric is defined in the following form:

\[
X_{CORR_{MAX}} = \frac{\text{MAX}\{xcorr(X,Y)\}}{\text{MAX}\{\text{autocorr}(X)\}} \times 100\% \tag{4}
\]

where \( X \) is the template and \( Y \) is the filtered signal. A large max cross-correlation value is associated with close resemblance of the original signal and the filtered signal, indicating good performance.

Roughness of the resulting signals is calculated with the following equation (also used in the Hodrick-Prescott filter):

\[
\text{Roughness} = \frac{\sum_{t=3}^{n}(Y_t-2Y_{t-1}+Y_{t-2})^2}{\sum_{t=3}^{n}(X_t-2X_{t-1}+X_{t-2})^2} \times 100\% \tag{5}
\]

where \( X \) is the template and \( Y \) is the filtered signal. A small roughness value is preferable for visual classicization as well as for onset detection.

The de-nosing performance of filters was compared and presented in Results.
4.5.3 Onset Detection

Onset detection is crucial for identification of the inspiratory and expiratory phases, which largely affects the accuracy of feature extraction, as failure to do so could lead to erroneous expression of features extracted from each inspiratory contour. In previous studies, the onsets were extracted by locating the intersections of the signal and the pre-specified constant baseline\(^\text{19}\) (method 1). However, in reality, the onset levels deviate from the static baseline intermittently, as discussed in section 4.1.2 and illustrated in Figure 7. Another study estimated the baseline by calculating the median level of the signal within a window of fixed size\(^\text{36}\) (method 2). Yet there is one major drawback of this method. A unique pattern is commonly present in the data of several participants, where the inspiratory onsets are preceded by a period of silent pause at the end of expiration. It is, therefore, difficult to locate the exact onset of inspiration by identifying the intersecting point of the airflow signal and the estimated baseline. Another study located the onsets to the point of maximum rate of change, within the threshold range for zero flow\(^\text{17}\) (method 3). Nonetheless, this method may fail to capture the beginning of the inspiratory phase in which the airflow slope is less than the maximum slope.
To overcome these problems, an algorithm was designed to find the inspiratory onsets based on slope analysis. At the end of expiration (which is equivalent to the onset of inspiration), lung volume stays relatively unchanged. This is reflected by a flat slope of the airflow. During inspiration the diaphragmic muscle is activated, creating negative pressure in the lung and forcing air to flow to the lung. This corresponds to a sharp rise of signal intensity. Therefore, for each inspiratory contour, the algorithm starts from the preliminary onsets obtained from the zero crossings, and transverses forward and backwards to search for the steadiest slope and the steepest slope. The inspiratory onset was determined as the point with the steadiest slope preceding the point with the steepest slope, as demonstrated in Figure 8.

**Figure 7** Filtered airflow of a series of breaths, with onsets denoted and inspiratory phases highlighted. Note that the baseline shifts within a certain range away from the zero-intensity line (marked with solid line).
Once the onset point of inspiration is identified, the end point of inspiration is matched at the same level of airflow on the falling part of the inspiration. After the identification of each onset point, additional error-checking was performed. The algorithm accounted for other potential outliers during segmentation of inspirations. For instance, breaths with very low volume such as the ones corresponding to apnea were eliminated because they do not contain much information for classification but random fluctuation and noise; onsets that are too close to each other (<0.5 seconds) are removed because in general one cycle of breathing lasts at least 3 seconds.

An experiment was set up to compare our onset detection algorithm with the ones implemented by other researchers. A segment of nasal airflow signal of 500 seconds was randomly selected. The inspiratory and expiratory onsets were manually scored as the gold standard. Because filters and onset detection algorithms influence onset detection together, the raw signal was first processed with the three filters discussed before. Following that, methods 1-3 and our proposed method were performed\textsuperscript{19,36,17}. The results were compared to the manual detection. For each criterion, the mean and standard deviation were calculated. The most optimum combination of filter and onset detection should produce the least discrepancy from the manual annotation.
4.6 Manual Scoring of IFL events

A subset of the entire inspiratory airflow data recording was chosen from all participants, which contains signals with reasonably low noise and clear contour. Each inspiratory contour was manually labelled by an experienced rater to be either normal or IFL.

A custom graphical user interface (Figure 9) was designed in Matlab® R2014a to facilitate the manual annotation. Each segment of nasal airflow in non-REM sleep stage 2 was loaded into the graphical user interface and displayed. A user could browse through the breaths and select the type of the breath under analysis, indicated by a red vertical bar. The analysed breath number and total breath number were displayed. A flag variable was appended to the data file to designate the type of each breath according to the manual annotation. The manual labelling results were used to develop and validate the temporal features as well as the classifiers.
Figure 9 A user-friendly graphical user interface used to label the type of breath as normal or inspiratory flow limited (IFL).

4.7 Feature Extraction

8 features were estimated to explore the temporal patterns of the inspiratory contour, and to construct the classifier for IFL detection. The selection of these features was inspired by the past relevant literature as well as visual observation. They are listed as the following:

- Number of Peaks
- Scooping index
- Kurtosis
- Peak amplitude variability
- Deviation Index
- Ti/Ttot
- Flattening index
- Skewness
4.7.1 Number of Peaks

This feature simply captures the number of peaks present in the inspiratory contour. A breath with multiple ripples is associated with snoring and transient change of UA resistance – an indication of respiratory disturbance. As a result, higher number of inspiratory flow peaks is linked with higher propensity of IFL. The number of peaks was calculated as the number of local maxima using the “findpeaks” function in Matlab®.

![An inspiratory contour with two peaks highlighted in red.](image)

Figure 10 An inspiratory contour with two peaks highlighted in red.

4.7.2 Scooping Index

The scooping of the airflow contour is related to negative effort dependence, a variation of IFL discussed in section 2.1. The figure and equation for the calculation of scooping index are shown as the following.
4.7.3 Kurtosis

Kurtosis is commonly used in probability theory and statistics to measure the "peakedness" of the probability distributions. The kurtosis of an ideal normal airflow with Gaussian distribution is 3. A “flat-topped” waveform will have a kurtosis of less than 3, and a “high-peaked” waveform will have a kurtosis greater than 3. Kurtosis was calculated with the “kurtosis” function in Matlab®.
4.7.4 Peak Amplitude Variability

Peak amplitude variability is defined as the deviation of peak amplitude of individual inspiratory contour relative to the mean peak amplitude of the nasal airflow from the entire segment. This metric is similar to the coefficient of variation, which measures the dispersion of probability distribution. The greater the peak amplitude variability, the more deviated the contour is from the average. This feature was formulated based on the observation that the intermittent occurrence of apnea and hypopnea result in alternation between hyperventilation and hypoventilation, whose peak airflow amplitude vary dramatically.

This feature is calculated by dividing the peak amplitude of individual inspiratory contour by the mean peak amplitude of the entire nasal airflow segment, as shown in the following.
4.7.5 Deviation Index

The deviation index portraits the degree of deviation of the inspiratory contour from an ideal breath, resembling a bell shaped curve\textsuperscript{17}.

To calculate the deviation index, we compared the airflow signal with an artificial sinusoid of the same peak amplitude and duration, but adjusted in time scale so that the peak time instances are aligned. The deviation index is calculated by dividing the difference by the total area of the airflow signal in the middle 50% of the period (Figure 14). As the breath deviates further from the template with increasing levels of flow limitation, the deviation index becomes larger.

\[ \text{Peak Amplitude Variability} = \frac{F_{\text{peak}}}{F_{\text{peak}}} \]

Figure 13 An inspiratory contour example illustrating the calculation of peak amplitude variability. Red solid line indicates mean peak amplitude from the entire segment.
4.7.6 Inspiratory Duty Cycle (Ti/Ttot)

The Ti/Ttot, also known as inspiratory duty cycle, is defined as the period of time spent on inspiration (Ti) over the entire duration of respiratory cycle (Ttot), including inspiration and expiration. Previous studies have shown that under mild to moderate flow limitation, inspiratory duty cycle increases to compensate for the hypoxemia\(^3\).
4.7.7 Flattening Index

The major distinctive pattern of IFL is the flattening of the contour. The flattening index was a metric created to determine the degree of flattening. Although similar algorithms have been used in commercial products such as Continuous Positive Airway Pressure to evaluate IFL, they are not made available to public and they are subject to patent protection. As such, I developed an algorithm to estimate flattening index based on detecting slope of the airflow signal.

The slope was calculated as the difference between adjacent data points. A slope threshold was formulated by multiplying a constant with the median peak amplitude over 5 minutes. The median peak amplitude was used to account for the variation in average signal strength due to inconsistency of measurements such as mouth breathing or displacement of nasal cannula. The longest flattened region is found where all the slope values are within the slope threshold. The flattening index was calculated by dividing the longest flattened timespan by the total inspiratory timespan shown in Figure 16.

$$ Flattening \ Index = \frac{Flattened \ Sample \ Length}{Inspiratory \ Sample \ Length} $$

**Figure 16** An inspiratory contour illustrating the calculation of flattening index.
4.7.8 Skewness

In probability theory and statistics, skewness is a measure of asymmetry of the probability distribution. To generalize, a left skewed curve gives rise to a positive skewness value and vice versa. When there is flow limitation, the nasal airflow is left or right skewed (Figure 3, Class 4 and Class 6 flow shapes, respectively). Therefore, the skewness as a feature could be used to separate the representative asymmetric flow shapes.

![Image of airflow contour showing left skewed and right skewed flow shapes]

*Figure 17 An inspiratory contour illustrating a left skewed flow shape and a right skewed flow shape from the actual nasal airflow signal.*

4.8 Feature Validation

After the feature extraction, I investigated whether those features are capable of independently differentiating the two classes of normal and IFL breaths. If individual features could successfully differentiate the two classes, then a classifier based on feature extraction outputs could also be used to classify IFL.

To validate the features, for each participant, I first grouped the breaths to 2 classes (normal and IFL) based on manual annotation. Within each class, I then calculated the feature values. The feature values were averaged for each participant. Student’s t-test or rank-sum test was conducted for normally and non-normally distributed features. Normality of data was determined by Anderson-Darling test. P<0.05 is associated with significant inter-class difference. This
procedure is delineated in Figure 18. Out of the proposed features, the ones that separated two classes with statistical significance were selected for further signal processing.

Moreover, for each class, the feature values of all subjects were calculated to generate the Receiver Operating Characteristic. I compared a varying threshold with the feature values to classify each inspiratory contour. With varying threshold, the specificity and sensitivity of classification changed to generate the receiver operating curve and calculate its area under the curve.

4.9 Classification

After the features were extracted and validated, I developed two algorithms to classify IFL and normal breaths utilizing supervised learning and un-supervised learning. In the case of supervised learning, the classifier model was trained with the feature outputs and validated with the manual labeling of the class. On the other hand, un-supervised learning was also deployed because instead of using a small subset of manually annotated data, we could train and test the classifier with the whole data without the inference of human errors.
4.9.1 Supervised Classification

Figure 19 delineates the steps for construction and validation of the supervised classifier. Cross validation was performed to split the manual annotation data into training and validation data. The classification performances of the four classifiers were compared and the most optimum classifier was chosen to classify the full dataset.

![Schematic diagram](image)

Figure 19 The schematic for the construction and validation of the feature-based classifier using supervised learning.

Four classifier models were selected in this study: logistic regression, support vector machine, neural network and Adaboost ensemble model. The configurations of the classifiers are shown in Table 2. In addition, we compared them with a similar classification method reported by Norman et al.\textsuperscript{16}. Instead of features, that study utilized discretized airflow contour as inputs to the classifier.

**Table 2 Classifiers and Configurations**

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Logistic Regression Model</th>
<th>Support Vector Machine</th>
<th>Neural Network</th>
<th>Adaboost</th>
<th>Norman et al.\textsuperscript{16}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Configuration</strong></td>
<td>Link function: logistic function</td>
<td>Kernel: radial basis function</td>
<td>3 layers, with (N+1,4,1) neurons in each layer, where (N = #) of selected features</td>
<td>Number of learning cycles: 100; Learner model: decision stumps</td>
<td>3 layers, with 25, 20 and 5 neurons in each layer</td>
</tr>
</tbody>
</table>
K-fold (K=5) cross validation was utilized to divide data into 80% for training and 20% for testing. Inter-classifier results were compared in the Results section. The classifier with highest specificity and sensitivity was selected to be the most suitable classifier for classification based on the small dataset (manual annotation). This classifier was used to classify the whole dataset of the 16 subjects into normal and IFL. These results were used to validate the second objective which is to investigate the impact of fluid accumulation in the neck on the prevalence of IFL.

### 4.9.2 Un-supervised Classification

Automatic clustering of the features using kmeans algorithm was performed. Data standardization is essential in avoiding the magnitude bias during clustering. Therefore, after feature extraction, the features values were first standardized by subtracting the mean and dividing by the standard deviation to ensure standard normal distribution.

The standardized feature values were then processed by the kmeans function of Matlab®, which partitions the feature vectors of the inspiratory shapes into two clusters: the normal and the IFL clusters. The clustering process was repeated 100 iterations to remove the bias from the random initialization, to avoid the bias from sensitivity to local minima. The clusters of each feature were represented by the most frequently appearing cluster centroids. All selected features were used for kmeans clustering. To verify that the derived clusters were physiological meaningful, I plotted the average contour were derived from all the breaths of each participant.

Classification is achieved by comparing the Euclidean distance of the feature vector. After classification, I validated the features using the same method as shown in section 4.8. Boxplots were generated for the two classes with results of t-test or rank-sum test for normally and non-normally distributed features, respectively. Normality of data was determined by Anderson-Darling test. P<0.05 is associated with significant inter-class difference.

### 4.10 Statistical Analyses

The classification results from both algorithms were utilized to investigate the relationship between IFL breath and the UA anatomy. In addition, the average feature values were utilized to investigate the relationship between features and the UA anatomy. The normality of the data was
tested with the Anderson–Darling test. Pearson correlations were applied on normally distributed data and Spearman’s rank correlations were applied on non-normally distributed data. A correlation is considered significant with a two-tailed p-value < 0.05.

Independent variables:

- Baseline NC, NFV, UA-XSA before sleep
- ΔNC, ΔNFV, ΔUA-XSA after sleep

Dependent variables:

- Average feature values from nasal airflow
- IFL (%) from both supervised and unsupervised classifications

The relationship between each individual features and IFL was also investigated with correlation analysis. The average feature values were independent variables and IFL (%) was the dependent variable.

5 Results

5.1 Data

16 non-obese men, age 39.9±14 years and AHI of 21.7±25.2 completed the protocol with total sleep time of 136±50 minutes. Participant demographics are shown in Appendix B. Although this was a daytime study, 13 participants had a full sleep cycle including both REM and non-REM sleep. 1080±448 inspiratory periods from every participant in non-REM stage 2 of sleep were investigated.

For the purpose of manual annotation, a subset of nasal airflow (2447 breaths) was chosen from the entire inspiratory airflow data to train the classifiers. To make sure the training data covers a variety of OSA severity, 832 breaths were drawn from 4 normal (AHI<5) subjects, 1370 breaths were drawn from 9 subjects with mild (5<AHI<30) OSA, 245 breaths were drawn from 3 subjects with severe (AHI>30) OSA.
5.2 Filter

Figure 20 shows the Euclidean difference between filtered and ideal Gaussian signals and the histogram difference between filtered and original signals for various window sizes. The most optimum window size ranges between 0.4 to 0.5 seconds where the two trends intersect. A window size of 0.4 seconds was chosen to perform de-noising while sufficiently maintaining the contour of the original signal.

Figure 20 Given normal inspiratory curve as the template, the optimal Gaussian window size was found by locating the intersecting point of Euclidean distance and histogram difference.

Results comparing three different filters show that the low-pass filter and wavelet filters achieved similar and slightly better de-noising performance (lower normalized mean square error and higher maximum cross-correlation) compared to the Gaussian filter. However, the signal processed by the Gaussian filter was much smoother, as seen in Figure 21 and Table 3.
Figure 21 An inspiratory contour template with plateau pattern, along with the contours resulting from de-nosing with the low-pass, wavelet and Gaussian filters.

Table 3 Evaluation of de-nosing effects of three filters

<table>
<thead>
<tr>
<th>Filter</th>
<th>NMSE,%</th>
<th>XCORR$_{\text{MAX}}$, %</th>
<th>Roughness, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-pass</td>
<td>0.27±0.06</td>
<td>99.7±0.09</td>
<td>8.3±40</td>
</tr>
<tr>
<td>Gaussian</td>
<td>0.85±0.27</td>
<td>97.1±0.40</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Wavelet</td>
<td>0.27±0.05</td>
<td>99.7±0.05</td>
<td>62.5±44</td>
</tr>
</tbody>
</table>
5.3 Onset detection

For a segment of 500-second nasal airflow recording, the onsets were detected using different methods. With various de-nosing methods, the differences between the manually determined onsets and the automatically determined onsets are shown in Table 4.

Table 4 Comparison of automatic onset detection methods with various filters. Method 1 was derived from constant baseline\textsuperscript{19}; method 2 was derived from median intensity of sliding window\textsuperscript{36}; method 3 was found by locating the points of maximum rate of change\textsuperscript{17}

<table>
<thead>
<tr>
<th></th>
<th>Method 1</th>
<th>Method 2</th>
<th>Method 3</th>
<th>Slope analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-pass</td>
<td>29±35</td>
<td>27±35</td>
<td>29±23</td>
<td>31±30</td>
</tr>
<tr>
<td>Gaussian</td>
<td>33±35</td>
<td>29±34</td>
<td>24±22</td>
<td>20±11</td>
</tr>
<tr>
<td>Wavelet</td>
<td>25±34</td>
<td>24±34</td>
<td>28±31</td>
<td>42±35</td>
</tr>
</tbody>
</table>

Overall, among all the combinations, my proposed method based on slope analysis combined with Gaussian filter achieved the smallest errors from to the manually determined onsets. Hence, this combination was recommended for preprocessing.

5.4 Feature Validation

Illustrated in Figures 22-24, three features (Peak#, scooping index, and kurtosis) achieved significant difference separating the IFL from normal breaths in the manually annotated data. Among these 3 features, the peak# and scooping index were strong features with large area-under-curve (AUC).

Illustrated in Figure 25-26, two features (peak amplitude variability and deviation index) achieved borderline significance in separating the IFL from normal breaths in the manual annotation.

Illustrated in Figure 27-29, there were no significant difference in the mean feature values of Ti/Ttot, flattening index and skewness in separating the two classes. This perhaps was due to the
inaccuracy of onset detection. Compared to the other features, Ti/Ttot and flattening index are more sensitive to the onset detection results.

Figure 22 The boxplot and Receiver Operating Characteristics plots for the peak#.
Figure 23 The boxplot and Receiver Operating Characteristics plots for the scooping index.

Figure 24 The boxplot and Receiver Operating Characteristics plots for the kurtosis.
Figure 25 The boxplot and Receiver Operating Characteristics plots for the peak amplitude variability.

Figure 26 The boxplot and Receiver Operating Characteristics plots for the deviation index.
Figure 27 The boxplot and Receiver Operating Characteristics plots for the Ti/Ttot.
Figure 28 The boxplot and Receiver Operating Characteristics plots for the flattening index.

Figure 29: the boxplot and Receiver Operating Characteristics plots for the skewness.
5.5 Supervised Classification

From the results of Section 5.4, the features that were capable of separating the two classes were peak#, scooping index, kurtosis, peak amplitude variability, and deviation index. Their values formed the inputs for the classifiers. Using the manual scoring as the gold standard, the classification results with the four classifiers are summarized to Table 5. The classification results were compared with the another similar study conducted by Normal et al.\textsuperscript{16}.

Table 5 Supervised Classification Performances

<table>
<thead>
<tr>
<th></th>
<th>Neural Network</th>
<th>Logistic Regression</th>
<th>Support Vector Machine</th>
<th>Adaboost</th>
<th>Norman et al.\textsuperscript{16}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91±0.4%</td>
<td>91±0.4%</td>
<td>92±3.3%</td>
<td>91±0.6%</td>
<td>83.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>79±0.6%</td>
<td>78±0.7%</td>
<td>67±27%</td>
<td>79±0.9%</td>
<td>96.2%</td>
</tr>
<tr>
<td>Agreement</td>
<td>86±0.4%</td>
<td>86±0.4%</td>
<td>82±9%</td>
<td>86±0.4%</td>
<td>93%</td>
</tr>
<tr>
<td>Testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91±1.6%</td>
<td>91±1.7%</td>
<td>92±3.6%</td>
<td>90±1.8%</td>
<td>78.5%</td>
</tr>
<tr>
<td>Specificity</td>
<td>80±2.4%</td>
<td>78±2.7%</td>
<td>67±27%</td>
<td>78±0.3%</td>
<td>93.6%</td>
</tr>
<tr>
<td>Agreement</td>
<td>87±1.4%</td>
<td>86±1.6%</td>
<td>81±8.9%</td>
<td>86±1.6%</td>
<td>89.4%</td>
</tr>
</tbody>
</table>

It can be seen that neural network, logistic regression and adaboost achieved similar classification performances in the training and testing trials. Although the sensitivity of support vector machine was slightly better than the other classifiers, the specificity and agreement were much lower.
Among the four classifiers, the logistic regression model was selected to be the most optimum classifier, because of the good classification performance as well the simplicity of the design that requires less computational power.

Compared to the previous study performed by Norman et al., the feature based classification achieved higher sensitivity but lower specificity and lower agreement in the training phase. Nevertheless the classification agreement was very similar in the testing phase. Therefore it is concluded that the logistic regression model is a good classifier for detecting IFL breaths.

5.6 Unsupervised Classification

With kmeans algorithm, the cluster centroids were computed as follows:

IFL class: [Deviation Index, Peak Amplitude Variability, Peak #, Scooping Index, Kurtosis] = [0.617, -0.188, 1.07, 0.9, 0.962].

Normal class: [Deviation Index, Peak Amplitude Variability, Peak #, Scooping Index, Kurtosis, Skewness] = [-0.219, 0.0688, -0.384, -0.33, -0.346].

To validate the features for un-supervised learning, the inter-class feature differences were compared and plotted in Figure 30. Based on un-supervised clustering, all five features resulted in significant differences between the IFL class and the normal class, as shown in Figure 30.
Figure 30 Boxplots comparing the selected features for the IFL and normal classes. All selected features could significantly separate the two classes.

The averaged contour plots for the IFL and normal classes extracted from one of the participants are shown in Figure 31. Similar plots for the rest of the participants are shown in Appendix C. The solid curves indicate the average contour and the dashed curves indicate mean ±STD curves. It can be seen that most of the IFL flow shapes contain obvious flattening region and the normal flow shapes contain rounded bell shape.
Figure 31 The averaged inspiratory contour for IFL and normal classes for participant 1.

5.7 Correlation Analyses

Among the 16 participants, 15, 14, and 11 of them had measurements of NC, UA-XSA, and NFV, respectively. The correlations of the independent and dependent variables are tabulated as follows.

Table 6 Correlation Results. Red highlighted entries indicate significant correlations

<table>
<thead>
<tr>
<th></th>
<th>Deviation Index</th>
<th>Peak Amplitude Variability</th>
<th>Peak Number</th>
<th>Scooping Index</th>
<th>Kurtosis</th>
<th>IFL (%) Supervised</th>
<th>IFL (%) Unsupervised</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>0.06(0.84)</td>
<td>0.17(0.57)</td>
<td>-0.1(0.72)</td>
<td>-0.07(0.81)</td>
<td>0.11(0.69)</td>
<td>0.06(0.83)</td>
<td>-0.27(0.32)</td>
</tr>
<tr>
<td>∆NC</td>
<td>0.37(0.17)</td>
<td>0.74(&lt;0.01)</td>
<td>0.06(0.83)</td>
<td>-0.52(0.57)</td>
<td>-0.11(0.67)</td>
<td>-0.07(0.79)</td>
<td>-0.11(0.68)</td>
</tr>
<tr>
<td>UA-XSA</td>
<td>-0.67(0.01)</td>
<td>-0.69(&lt;0.01)</td>
<td>-0.54(0.04)</td>
<td>0.42(0.13)</td>
<td>-0.18(0.55)</td>
<td>-0.11(0.71)</td>
<td>0.31(0.28)</td>
</tr>
<tr>
<td>∆UA-XSA</td>
<td>0.22(0.45)</td>
<td>0.08(0.78)</td>
<td>0.37(0.27)</td>
<td>0.23(0.44)</td>
<td>0.17(0.56)</td>
<td>0.18(0.54)</td>
<td>0.01(0.97)</td>
</tr>
<tr>
<td>NFV</td>
<td>0.13(0.71)</td>
<td>-0.35(0.3)</td>
<td>0.50(0.12)</td>
<td>0.46(0.15)</td>
<td>0.1(0.78)</td>
<td>0.35(0.29)</td>
<td>0.5(0.12)</td>
</tr>
<tr>
<td>∆NFV</td>
<td>-0.39(0.24)</td>
<td>-0.35(0.29)</td>
<td>-0.28(0.40)</td>
<td>0.08(0.82)</td>
<td>0.16(0.63)</td>
<td>0.20(0.55)</td>
<td>0.27(0.418)</td>
</tr>
</tbody>
</table>

Three features were found to be significantly correlated with the UA measurements. The deviation index was strongly and negatively correlated with baseline UA-XSA. The peak amplitude variability was strongly and positively correlated with ∆NC; it’s also strongly and negatively correlated with baseline UA-XSA. There is one participant whose peak amplitude
variability was close to 2 - much higher than average feature value. That participant was shown to have an apnea index of 34 and that perhaps contributes to the high feature value. The peak was significantly and negatively correlated with the baseline UA-XSA. No significant correlations were observed between the other UA measurements and features.

![Figure 32](image)

Figure 32 Participants with smaller UA cross-section area (UA-XSA) are associated with more distorted airflow contours from a normal bell shape, and more variable peak airflow and; bigger increases in neck circumference is associated with more variability in peak airflow; narrowed UA before sleep is associated with more peaks in the airflow contours.

There were no significant correlations between the UA measurements and IFL% computed from the supervised learning model. This happens presumably because of the small sample size (n = 2447) and errors in the manual annotation. Initially, the IFL% derived from the unsupervised learning had no correlation with UA measurements. After further investigation into
the data, it was found that the onset detection algorithm could not confidently identify the majority of the onsets from one participant due to the unique breathing pattern exhibited in Figure 33. Currently the onset detection algorithm considers point B to be the inspiratory onset; however, due to the lack of physiological validation for the onset detection, the flattened period between point A and point B could either be attributed to the end of expiratory pause or UA obstruction. This ambiguity might lead to under-estimation of IFL (%). After removal of that participant’s data, a significant correlation was found between baseline NFV and IFL (%) as shown in Figure 34.

**Figure 33 Special breathing pattern with ambiguous onsets of either point A or point B.**
Participants with more fluid accumulation in the neck before sleep are associated with more flow limited breaths. Lastly, for the supervised classification, there was a significant correlation between the kurtosis and IFL(%). On the other hand, there was no significant correlation between the average feature values and IFL(%) from un-supervised classification, indicating that no feature can independently represent the k-means classification. The results are shown in Appendix D.

6 Discussion

This study evaluated the temporal features of the nasal airflow recording, based on which supervised and un-supervised classification methods were developed. The outcomes from the feature extraction and classification were validated with the UA anatomical measurements. The most significant discovery of this study is that the temporal features of the nasal airflow are strongly correlated with the UA anatomical measurements. Furthermore, un-supervised
classification utilizing those features demonstrated that the percentage of the breaths that were classified as flow limited is strongly correlated with UA anatomical compromises (such as increased NFV) that make it more susceptible to collapse. Moreover, the feature-based supervised classification methods could detect IFL as accurately as previously reported supervised learning based on discretized contour\textsuperscript{16}.

UA narrowing results in IFL, manifested by inspiratory flow shapes deviated from normal rounded contour. Although IFL has been reported to be associated with various clinical symptoms\textsuperscript{40-42}, we only recently gained limited understanding of the link between IFL and UA pathophysiology\textsuperscript{11,19}. Inspiratory airflow distortions such as flattening/scooping have been commonly utilized as a visual cue for manual detection of IFL. However, the previously reported classification methods only discretized the flow contour indiscriminately in order to generate inputs for classifiers\textsuperscript{16,19}. This largely ignores the variations that exist in the airflow shapes. Yet it is reasonable to deduce that the characteristics of the inspiratory flow could be analysed to study UA pathophysiology. Past attempts have been made to interpret the association between different flow shapes and UA behaviours leading to partial collapse, but they were speculative and had not been validated physiologically because it is difficult to directly assess the UA dynamical behaviours\textsuperscript{19,36}. To overcome those barriers, our proposed features quantitatively describe the temporal characteristics of the airflow. The physiological validity has been underpinned by the strong correlations between UA anatomical measurements and three proposed features (Deviation Index, Peak Amplitude Variability, and number of Peaks). Therefore, the features extracted from inspiratory flow shape can be a powerful analytical metric to investigate UA pathophysiology.

We further demonstrated that our proposed un-supervised IFL classification is capable of predicting UA compromises such as increased NFV, which is a risk factor that contributes to the collapse of the UA\textsuperscript{25,27,33}. This is consistent with the previous findings which showed that increased prevalence of IFL is associated with anatomical abnormalities in the UA\textsuperscript{11}. The potential clinical application is significant. As we know, the existing diagnostic criteria utilize AHI to indicate severity of sleep-disordered breathing. AHI may not be sensitive enough to evaluate the pathophysiology of sleep disordered breathing in special populations such as pregnant women, children, and those with upper airway resistance syndrome whose UA collapse is not as pronounced as patients with OSA. However, the consequences of those mild UA
collapses in these populations are significant and could result in serious health outcomes. Those outcomes include poor birth outcomes related to pre-eclampsia in pregnant women\textsuperscript{5,43}, as well as increased prevalence in mild ADHD-like behaviours in children\textsuperscript{44}. Therefore, indiscriminately applying the existing diagnostic criteria to patients in those special populations will result in suboptimal clinical outcomes. By leveraging the non-invasive nasal airflow recording and automated classification program, we can rapidly and conveniently evaluate milder, but usually prolonged, degrees of inspiratory flow limitation in these susceptible populations. Since unsupervised learning does not necessitate human input, which can be subjective and time-consuming, the algorithms can be applied to large clinical datasets conveniently and robustly. This will ultimately complement the existing diagnostic criteria and help develop more appropriate and personalized treatment to patients in those populations.

This study was subject to some limitations. (1) The average signal amplitude varies significantly among different subjects or at different time of sleep for the same subject. This might be attributed to the inconsistent amplifier gain due to the lack of calibration of the flow/pressure transducer, which in the future, could be replaced by one that can be calibrated. (2) The variation of average signal amplitude should theoretically not be problematic because only the features associated with the shape were considered. That is to say, during feature extraction, the features were calculated with normalization by the peak flow. Yet, the problems occur at low signal level, where the impact of noise is ineligible and contour distortion is more pronounced, which compromises the accuracy of feature extraction. Furthermore, the respiratory onsets become more ambiguous at very low signal intensity, which worsens the accuracy of onset detection and feature extraction as a whole. Admittedly, the extreme low signal level may be attributed to apnea, for which the proposed method would lose its analytical power. Thus, the proposed method is advised to be prudently used for populations with mild to moderate AHI. I attempted to introduce the absolute peak flow as a feature but it was later discovered that absolute peak flow can be substituted by peak amplitude variability and it was not used later on. Another factor contributing to low signal amplitude is mouth opening, where less air would go through the nasal cannula, resulting in low signal amplitude. In this case, a second sensor such as the respiratory inductance plethysmography can be used to measure variations in respiratory drive. Respiratory inductance plethysmography consists of two elastic bands measuring volumetric changes of chest and abdomen. If the respiratory drive measured by respiratory inductance plethysmography
does not change but the airflow amplitude reduces dramatically, we can deduce that there is potential mouth breathing, or misplacement of the nasal cannula. (3) Currently the onset detection was validated against manual detection, which can still be subjective and erroneous. This effect is most prominent on the participant who was excluded from correlational analysis whose inspiratory onsets could not be properly determined. A possible solution is to validate the onset detection with other more heavily studied approaches for onset detection utilizing other physiological signals such as lung sounds⁴⁵. (4) Another major challenge of my study is the lack of pressure measurement which determines the respiratory effort. As a result, the source of change of airflow amplitude cannot be accurately discerned – a reduction of airflow could either be due to obstruction in the UA or due to loss of respiratory drive (central sleep apnea). In my study the participants with mainly central sleep apnea were excluded. In the future, the respiratory inductance plethysmography could be incorporated to infer the respiratory drive: asynchronous movement of chest and abdomen indicates obstructive events and synchronous movement corresponds to central events.

In conclusion, we established an innovative method to non-invasively detect IFL with nasal airflow, which could be used to predict UA abnormalities. Notably, this is the first study that unveiled the underlying relationship between inspiratory airflow shapes and UA anatomical abnormalities. We showed that the temporal features of the inspiratory airflow were correlated with baseline neck circumference, neck fluid volume, and UA cross-sectional area. IFL classification based on un-supervised learning was shown to reflect the severity of UA compromises such as increased neck circumference and fluid volume. These results have clinical implication in special populations such as pregnant women, children, and patients with upper airway resistance syndrome.

7 Future work

From this study, we demonstrated that the temporal features extracted from the nasal airflow contour could reflect predisposing factors for UA narrowing such as increased NC and NFV. The expansion of this study will likely focus on two parts: improving the accuracy of onset detection and assessing susceptible populations.
To improve the accuracy of onset detection, we would like to compare the onsets detected from nasal airflow to other more established methods such as onset detection from movement of the chest or trachea during breathing, or based on tracheal sounds. From there we want to validate and improve our algorithm especially for breath types which we are currently incapable of analyzing.

With robust onset detection, the features will be re-evaluated. We will incorporate more physiologically meaningful features such as flattening of the curve and increased inspiratory duty cycle. The next step is to investigate the clinical implications of IFL on susceptible groups. For example, we would like to study the linkage between IFL and quality of life in pregnant women, children, and patients with upper airway resistance syndrome.
Figure 35 The flow chart delineating the process of manual scoring of IFL breaths. The temporal features of the nasal airflow are used to construct decision stumps to classify IFL and normal breaths.
## Appendix B

### Table 7. Participant demographics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td>16</td>
</tr>
<tr>
<td>Age, years</td>
<td>40±14</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175±6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83±10</td>
</tr>
<tr>
<td>Body Mass Index, kg/m</td>
<td>27±3</td>
</tr>
<tr>
<td>Neck Circumference, cm</td>
<td>43±3</td>
</tr>
<tr>
<td>UA Cross-Sectional Area, cm$^2$</td>
<td>2.6±0.6</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>113±9</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>77±9</td>
</tr>
<tr>
<td>Mean Arterial Pressure, mmHg</td>
<td>89±9</td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>70±9</td>
</tr>
<tr>
<td>Apnear Hypopnea Index, hour$^{-1}$ sleep</td>
<td>22±25</td>
</tr>
</tbody>
</table>
Appendix C

The average contour plots for participants 2-16. The solid curves indicate the average contour and the dashed curves indicate mean ±STD curves. It can be seen that most of the IFL flow shapes contain obvious flattening and most normal flow shapes contain rounded bell shape, with the exception of participant 10 whose IFL contour contains rounded bell shape with only slight steady slope.

![Participant 2](Image)

AHI = 13

![Participant 3](Image)

AHI = 2

![Participant 4](Image)

AHI = 3
Participant 9
AHI = 26

Participant 10
AHI = 8

Participant 11
AHI = 14

Participant 12
AHI = 19
Participant 13

AHI = 10

Participant 14

AHI = 2.8

Participant 15

AHI = 3

Participant 16

AHI = 61
### Appendix D

Table 8 Correlation results from supervised and un-supervised learning

<table>
<thead>
<tr>
<th></th>
<th>IFL (%) Supervised</th>
<th>IFL (%) Un-supervised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deviation Index</td>
<td>-0.19(0.5)</td>
<td>-0.23(0.41)</td>
</tr>
<tr>
<td>Peak Amplitude Variability</td>
<td>-0.12(0.68)</td>
<td>-0.09(0.74)</td>
</tr>
<tr>
<td>Peak Number</td>
<td>0.46(0.08)</td>
<td>0.37(0.18)</td>
</tr>
<tr>
<td>Kurtosis</td>
<td><strong>0.56(0.03)</strong></td>
<td>0.42(0.12)</td>
</tr>
<tr>
<td>Scooping Index</td>
<td>0.41(0.13)</td>
<td>0.38(0.16)</td>
</tr>
</tbody>
</table>
References


40 Tantrakul, V., Park, C.-S. & Guilleminault, C. Sleep-disordered breathing in premenopausal women: Differences between younger (less than 30 years old) and older women. *Sleep medicine* **13**, 656-662 (2012).


