

Assessment on Methods Used to Detect Asthmatic and Non-Asthmatic Conditions Using Capnogram Signal

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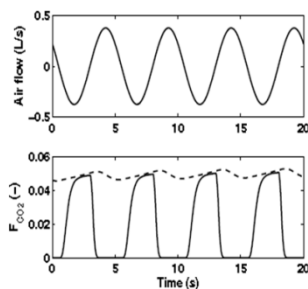
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Graphical abstract



Abstract

In this paper, a review on methods for detecting asthmatic conditions using capnogram is presented. This includes an investigation on capnography as a new approach for monitoring asthma and related researches. Manual analysis of capnogram is time-consuming and led to erroneous due to human factor such as tiredness and lack of expertise. Therefore, in this preliminary study, a new method based on signal processing approach is developed to automatically detect asthmatic patients. This developed algorithm is expected to cluster different states of asthmatic conditions by using the RBF (Radial Basis Function) network, instantaneously. In the future, this developed algorithm is expected to help health-care professional involved in respiratory care as it would be possible to monitor severity of asthma automatically and instantaneously.

Keywords: Monitoring; asthma; capnogram; capnography; signal processing

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1.0 INTRODUCTION

Asthma is a moderate to severe form of respiratory disorder that affects the lungs. It causes repeated episodes of wheezing, breathlessness, chest tightness, and night-time or early morning coughing. Tens of millions of people throughout the world suffer from asthma. Airways are the paths that carry air to the lungs. As the air moves through lungs, the airways become smaller, like branches of a tree. During an attack, the sides of the airways in the lungs become inflamed and swollen. Muscles around the airways tighten, and less air passes in and out of the lungs [1].

Although there are many signs of asthma, and the symptoms of an asthma attack, however, these symptoms generally do not occur between asthma attacks, and asthma sufferers can live a normal, physically fit life in between their attacks [2].

Traditionally, one of the asthmatic tests is to make a record on a spirometer of the forced expiratory vital capacity (FVC) [3]. It measures the amount of air that a person can breathe out, and involves a maximal inspiration followed by a rapid, forceful, and complete exhalation until there is absolutely no

more air to blow out. Furthermore, peak flow meter is another approach for asthmatic testing. It measures the rate at which air is forced out of the lungs. These results generally come with a graphic display which named the flow-volume curve. One of the information regarding the flow-volume curve is the point of maximal expiratory flow. It is the expiratory flow at the moment that it is the fastest during the entire exhalation [4].

Spirometry and peak flow meter are useful diagnostic tools, but there are some complications and contraindications. Also, the reliable results cannot be obtained as the instructions for the patients are complicated and chest pain is the result of the tests. Hence, both tracings are derived from the same single maneuver that is taking a full, deep breath in, and then blast it out as hard and fast as patients can until they can empty no more air from their lungs. In addition, children under the age of 6 years are generally not able to perform an adequate test. However, there are much more limitations in the spirometry method [5].

Clinical assessment is another approach to detect airway obstruction of patient with acute asthma. Normally, during assessment process, most medical practitioners rely on the presence of wheeze sounds, but some physicians may be lacking in their judgment of the asthmatic severity.

Nowadays, capnography is widely considered a new method to monitor the asthmatic condition [5]. It uses the technology of infrared to determine the concentration of carbon dioxide and capnogram is the graphical display of instantaneous CO_2 concentration (mmHg) versus time (second). It can show the different respiratory situation of patient, including asthma. Unlike peak flow meter or spirometer where the patient must follow a set of instructions; capnogram is taken while the patient is breathing as comfortably as able [6].

In this preliminary study, the research on capnograph and capnogram are put in two categories. The first are researches that consider the medical diagnosis using capnography and capnogram. This group makes the majority of researches [15-20, and 23-27]. The second groups are researches that investigate the mathematical characteristics of capnogram and capnography to enhance both the capability of capnogram and processing capnogram signals to detect asthmatic and non-asthmatic conditions.

In this paper, at section 2 capnography as a new approach for detection asthmatic conditions is discussed. In addition, a literature review on researches and their limitations about capnography and capnogram is presented. It contains, the research that investigated methods to enhance the capability of capnogram and capnograph, and in continue the significant research that have been done to diagnosis bronchospasm and asthma by using capnogram signals. Furthermore, in section 3 a new method based on digital signal processing techniques, and artificial neural networks is proposed to cluster different states of asthmatic conditions. Also, section 4 contains a discussion of proposed method limitations followed by section 5 in which a conclusion is made.

2.0 AN OVERVIEW OF THE CAPNOGRAPHY AND CAPNOGRAM

Capnography is a new method used to monitor asthmatic conditions. It shows changes in respiration of patients. It is taken while the patient is breathing as comfortable as possible without requiring any instructions. As shown in Figure 1, a normal capnogram has four phases and an end-tidal point [7]. Each phase reflects the usual process of CO_2 elimination.

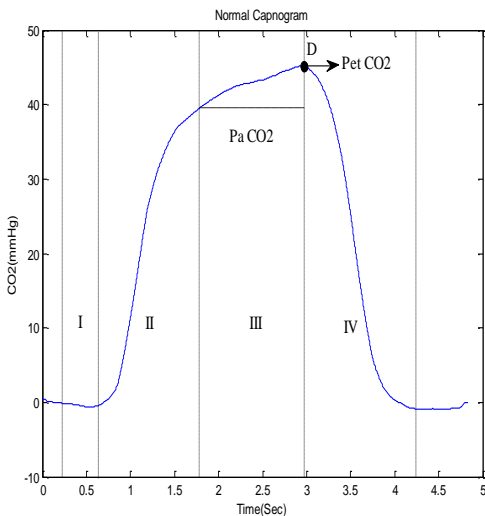


Figure 1 A normal capnogram

The flat phase I represents early exhalation that is relatively CO_2 -free. As exhalation continues, alveoli containing CO_2 are increasingly recruited and exhaled with non- CO_2 -containing gases. This creates a near-vertical rising phase II. Near the termination of normal exhalation is a plateau phase III. At the end of the plateau phase is *D*, the point that the measured alveolar CO_2 levels best approximate PaCO_2 . This sampled CO_2 level is known as PetCO_2 . As inspiration occurs, a near vertical rapidly falling phase IV is observed.

When ventilation and perfusion function normally, PetCO_2 should read 2-5 mmHg higher than the PaCO_2 [8]. A variety of clinical causes can lead to incomplete alveolar emptying [9]. Therefore, the true end tidal point was never reached. Figure 2 shows a normal capnogram, and an asthmatic patient one with an obstruction in tubing and other parts of the breathing circuit. It should be noticed that the ascending limb of the asthmatic capnogram is prolonged and is not flat, as it should be normally. These changes give rise to the so called "shark's fin" morphology capnogram in patients with airway obstruction. However, there is more shape of abnormal capnogram that could be found depending on the patient's condition in [10].

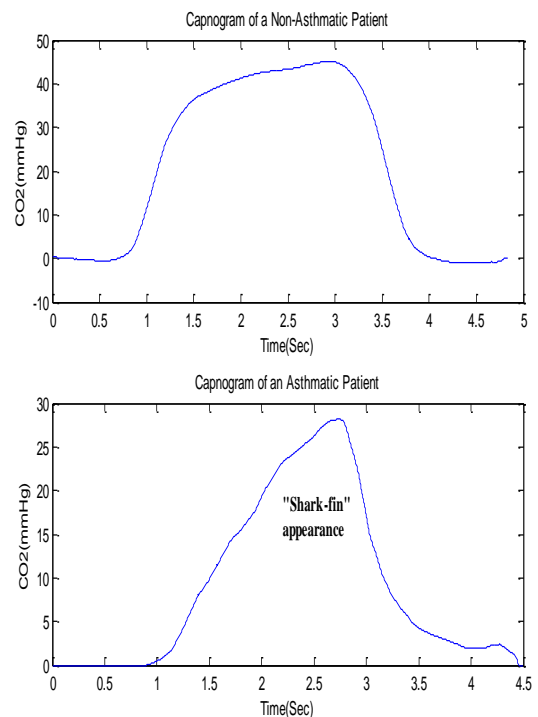


Figure 2 Comparing normal and bronchospastic capnograms

2.1 Researches on Both Diagnosis of Asthma Using Capnogram Signal and Enhancement the Capability of Capnograph and Capnogram

This section is presented a review on studies have been conducted to analyze capnograph and capnogram. Some of these researches discussed methods to present capnogram in a way that is more useful, and the others, presented approaches to diagnose asthma based on signal processing techniques of capnogram.

2.1.1 Designing a Capnogram Analyzer Expert System

One of the oldest researches on this issue is designing an expert capnogram analysis. Bao *et al.* in their research have designed a real-time expert system for measuring CO₂ concentrations expands an anesthesiologist's repertoire [11]. Their capnogram analyzer expert system (CAES) was customized using both traditional pattern-recognition methods and artificial intelligence (AI) approach for narrating and classifying the signals. The pattern-recognition technique was applied to extract features from the digitized CO₂ waveforms, and the AI approach was involved abstracting CO₂ waveforms from numeric representation to higher-level symbolic representation.

The CAES consists of three essential components: segmentation, single breath cycle identification, and waveform classification. The primary criterion for identifying a complete breath cycle is that the difference in the CO₂ concentration at the two points anchoring the cycle should be within a threshold. It is defined as the pre-specified percentage of the maximum amplitude of the CO₂ waveform in the data packet. The significant limitation of this study is that, there are approximately 6,000 capnograms, which documented numerous shape variations [10], and making rule to define them is practically impossible.

2.1.2 Evaluation of Slopes by Neural Network

Rayburn *et al.* have presented a neural network evaluation of slopes from sequential volume segments of the expiratory carbon dioxide curve [12]. According to their method, single breath tested for CO₂ curves from a number of 7 tidal breathing patients were collected using standard pulmonary spirometric methodology. The expiratory CO₂ signal was digitized at 100 Hz. The CO₂ value for each 1 mL change in expiratory volume was computed by linear interpolation. Volume based CO₂ signals were divided into 10 equal segments, each accounting for 10% of the total expiratory volume. A slope was computed for each segment. The 10 segment slopes were used as inputs for two fully connected back propagation neural network that was used to compute FEV₁/FVC or the % predicted FEV₁.

Although, this study has supported recent research that advocates capnography as a non-invasive monitoring system and further has demonstrated a role for neural network as an investigative tool in basic research and development. However, using just 7 samples for training the back propagation neural network (BPNN) is one of the limitations of this research. Furthermore, according to their results, they were unable to effectively compute equivalent spirometric data within acceptable clinical tolerance. This may be attributed to the nature of the respiratory maneuver under the two systems. It means that, spirometry requires patient compliance and maximal respiratory maneuvers whereas capnography is conducted under normal conditions.

2.1.3 Bayesian Method for Breath-by-Breath Identification

In 2006, Buijs *et al.* introduced a Bayesian method for breath-by-breath identification of the volumetric capnogram [13]. The method integrates a model of CO₂ exchange in the lungs, which is nonlinear due to the nature of human tidal breathing. It contains a particle filtering algorithm for estimating the model parameters and changes therein. This model accounted for tidal-breathing and incorporated a rebreath compartment, an airway dead space compartment, and a compartment representing the alveoli. By using this model a prediction for the unmeasured alveolar CO₂ tension could be made. Based on the model

simulations, it is shown that the adaptive algorithm is capable of rapidly tracking fluctuations in the parameters. The model structure presented in their research is based on physiological knowledge, where the model parameters have clear physical meanings. This has the advantage that the model can be used to aid in the interpretation of the capnogram. However, if the current method wants to aid the clinician in the interpretation of capnographic data, it should be provided an online determination of physiologically relevant parameters. Figure 3. shows the simulation of a capnogram, using default model parameters.

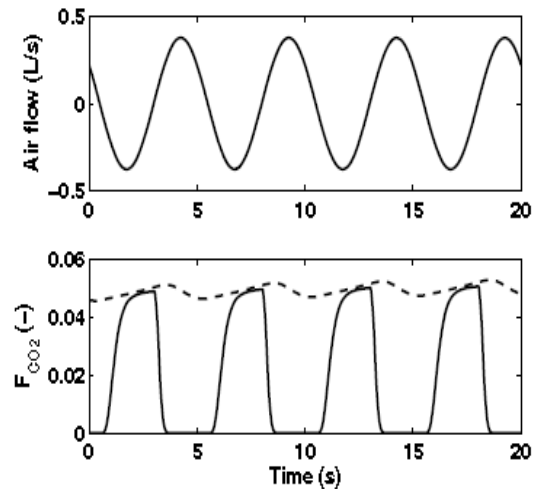


Figure 3 Simulation of a capnogram, using default model parameters; Top panel: Airflow signal, Lower panel: Fractional CO₂ concentrations in the rebreath volume (solid line) and alveoli (dashed line)

However, accurate physical models often contain nonlinearities, such as the time-variant airflow and alveolar volume, as well as the alternation between inspiration and expiration in the tidal-breathing model. Because of these nonlinearities, identification of the model parameters requires some type of optimization algorithm [21]. These algorithms are often offline and require the assumption that the model parameters are constant over the analyzed period. In addition, division into single compartments for airway dead space and alveolar volume seem to be quite crude, as the human airways consist of numerous bronchi and millions of alveoli, which all may have different properties in terms of gas exchange.

Furthermore, the metabolic rate is a lumped parameter, which reflects changes in e.g. pulmonary blood flow, CO₂ production in the tissues and possible mismatches between ventilation and blood perfusion in the alveoli.

Hence, the model cannot distinguish between these events. So, in order to warrant the future use in a clinical setting, extensive testing on both simulated and experimental data is required to further characterize the limitations of the method.

2.1.4 New Capnograph Based on Electro Acoustic Sensor

Another research in this area belongs to Folke and Hok in which a new capnograph utilizing an electro acoustical sensor was presented [14]. In fact, they verify the possibility of performing an adequate capnogram using the electro acoustical sensor, as shown in Figure 4. The main point in their investigation was the influence of ambient temperature and relative humidity variations. Of course, the issue of inter-individual behavior in

various applicatory settings is left behind as a topic for future investigations, and it is not a complete research.

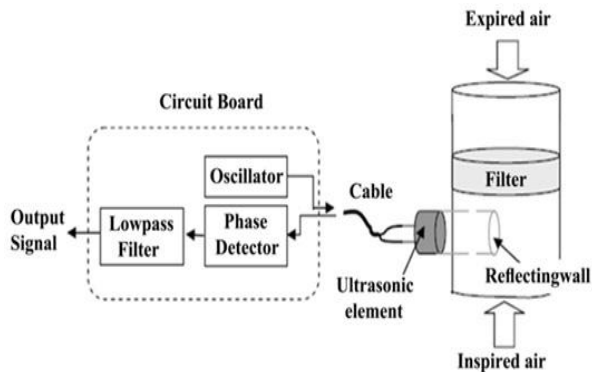


Figure 4 A schematic of the new capnograph prototype

2.1.5 Measuring 'S' Parameters

One of the first and fundamental studies in analyzing capnogram has been conducted by You *et al.* and the correlations between capnographic and spirometric indices were measured in 10 healthy subjects and 30 asthmatic patients [22]. The usefulness of eight descriptive indices was assessed by measuring their reproducibility and their sensitivity to airway obstruction. Three indices measured the slope of the capnogram during the various phases of expiration (S1, S2 and S3). Next index was the slope ratio (SR) between the intermediate, and the initial slopes was $(S2/S1)*100$. The area ratio (AR: $(A1/A2)*100$) that the A1 and A2 were calculated above a threshold of 2.5% of CO₂ between 0.2 and 1 second and three indices were used as the second derivative of the capnographic curve (SD1, SD2, and SD3). Their results showed that there exist large differences among the indices. According to their research, a high sensitivity to airway obstruction was seen for intermediate and terminal slopes (S2, S3, SR), followed by SD1, SD2, SD3 and the lowest ranges were seen with S1 and AR. This research introduced some basic and useful parameters, but it was in time domain and had a manual analysis of capnogram that lead to many irreversible mistakes due to human factors and lack of expertise. Furthermore, the thresholds to calculate the slopes and the area ratio are not accurate and are just a suggestion. In addition, measuring these indices manually comes with lots of errors. Figure 5 shows the eight shape indices tested.

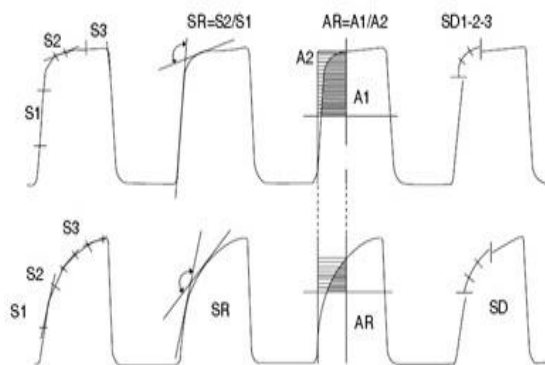


Figure 5 Schematic description of the capnographic indices measured on a normal (upper) and on an asthmatic (lower) capnogram

2.1.6 Calculating the dCO_2/dt of the Plateau Phase

In 1996, Yaron *et al.* conducted a research on utilizing the expiratory capnogram in the assessment of bronchospasm [28]. They calculated dCO_2/dt of the plateau phase for five consecutive regular expirations, and a mean calculated for each patient. They concluded that this parameter is an effort-independent, rapid, non-invasive measured that indicates significant bronchospasm in adult patients with asthma. Their results for post-treatment show significant changes in percent predicted PEFR and dCO_2/dt . The pre-treatment and post-treatment percent predicted PEFR values were 58% and 74%, respectively ($P<0.001$). Also, dCO_2/dt values were 0.27% and 0.19%, respectively ($P<0.005$). However, their study was on just 20 adults with acute asthma and 28 normal adult. Like previous study, this research defines a new parameter to analyze the capnogram for asthmatic patients. However, it is manual and difficult to calculate by a medical practitioner and physician to monitor the severity of asthma during monitoring the patients.

2.1.7 Measuring the $ETCO_2$ to Detect Asthmatic Conditions

In 2007, Melissa *et al.* carried out a research to find the relation between $ETCO_2$ and asthmatic patients [29]. In their study, data from 174 patients (86 with acute asthma and 88 healthy subjects) were taken by using a duo-port oral nasal cannula. Also, their vital signs and $ETCO_2$ level were measured on arrival and after bronchodilator treatment (for asthmatic patient).

Their findings showed that the $ETCO_2$ measurement was significantly lower in acute asthmatic patient compared to healthy patient ($p<0.001$). Moreover, the $ETCO_2$ measured after first and final bronchodilator treatment were significantly associated with number of treatment receives and hospital admission ($p<0.002$). But, younger patients are not able to tolerate the nasal cannula and this is a limitation for this method.

2.1.8 Evaluating the Slope of Phase III from the Volumetric Capnogram

Another research by Druck *et al.* demonstrated that the slope of phase III from the volumetric capnogram as a non-effort dependent surrogate for changes in peak expiratory flow rate [30]. The patients breathed quietly for at least one minute through a combined CO₂/flow sensor, and the best of three peaks expiratory flow rate measurements were then recorded. After that average values of the slope of phase III were computed over a 10-breath interval. Then percentage changes in slope measurements from the volumetric capnogram were compared to percentage changes in peak expiratory flow rates. The patient's correlation coefficient was calculated. The mean pre- and post-treatment peak expiratory flow measurements were 252-99 and 310-107 l/min. Percent changes in the phase III slopes were found to be correlated with the percent changes PEFR ($P<0.2$). This study has just suggested that changes in the volumetric capnogram slope of phase III may be useful as a non-effort dependent surrogate of peak expiratory flow rate and a measure of bronchospasm. In addition, the patient needs to follow special instruction and breathes quickly for one minute. Definitely, it could be difficult for an asthmatic patient, especially for the patient with chest pain. This process, nevertheless, needs lots of manual computing.

2.1.9 Comparing the Peak Flow Meter and Capnography Results for Patients with Acute Asthma

Nik Hishamuddin *et al.* conducted a study in 2009 to compare the results of peak flow meter and capnography for patients with acute asthma [31]. In their research, 128 patients with acute asthma were monitored with peak flow measurements and then had a nasal cannula attached for micro-stream sampling. The capnographic waveform was recorded for indices analysis. In addition, when the patients were adjudged well for discharge, a second set of results were obtained using the same technique. Then, the pre-treatment and post-treatment results were compared.

According to their results, peak flow measurement showed significant improvement post treatment ($p < 0.001$), and on the capnographic waveform, there was significant different in slope of phase 3 and alpha angle ($p < 0.001$) but not in the slope of phase II ($p < 0.35$). They concluded that peak flow measurements and capnographic indices can indicate improvement, however, capnographic waveform analysis present several advantages which is effort independent and provide continuous monitoring. But in this study, the database was small and no distribution regarding to age and sex were noted, and the waveform selected for analysis was a selection bias.

2.1.10 Hjorth Parameters

One of the recent studies on capnogram to detect asthma was conducted by Kean *et al.* [32]. This study extracted the Hjorth parameters from the capnogram signal. Hjorth parameters use information from the curves and slopes of capnogram to produce 3 different parameters which are activity, mobility, and complexity [35]. The Hjorth parameters were extracted from the capnogram for two conditions. Firstly, it was extracted from the whole cycle of capnogram, named as HP1. Secondly, the Hjorth parameters were extracted from capnogram cycle ranging from beginning of phase II to time at the end tidal peak, named as HP2. The authors also have extracted features proposed by You *et al.* [22] to compare their performance against Hjorth parameters in differentiating asthma and non-asthma capnogram. In their study, a total of 13 features have been extracted from capnogram and according to their results, the slope ratio (SR) of the capnogram is the best among the parameters investigated to differentiate the asthmatic and non-asthmatic conditions. Furthermore, the Hjorth parameters have shown good performance through the HP2-Mobility for monitoring asthmatic patients using capnography. This research presented a computerized method to detect the different parts of capnogram signals besides introducing Hjorth parameters as the new features to detect the severity of asthma. However, it is again a time domain analysis with the idea that the capnogram is a stationary signal. Moreover, the authors just used 34 samples that it could not be enough for confirming the reliability of the procedure.

2.1.11 Comparing the Capnogram Indices and Peak Flow Meter Readings in Asthmatic Patients

The latest research in this issue has been done by Teo *et al.* in 2011 [36]. In this study, 30 patients with acute asthma were monitored with clinical severity scoring and peak flow measurements and had a nasal cannula attached for sidestream sampling of expired carbon dioxide. Furthermore, after treatment, when they had improved enough for discharge, a second set of results were obtained for capnographic waveform

recording. The pre-treatment and post-treatment results were then compared with t-samples t-test analysis.

According to the reported findings, on the capnogram of the pre-treatment and the post-treatment, there was a significance difference in the slope of phase III ($p < 0.001$) and alpha angle ($p < 0.001$) but not in phase II slope ($p < 0.35$). Also, there was significance change in peak flow meter reading but it was poorly correlated with the capnogram indices. In addition, the capnogram indices can indicate improvement in the airway diameter in acute asthmatics in end tidal point.

The bottom line is that, this research study was conducted in slightly less controlled condition, and the study population was small. Moreover, the waveforms used for analysis was a selection bias, i.e. the data is selected as the morphology looked similar to the researcher and were not deformed by artifacts.

3.0 PROPOSED METHOD

All researches mentioned above show significant correlation between the capnogram and asthmatic patient. However, most of them are just manual studies conducted through the conventional time domain method. In addition, they are based on assumption that the capnogram is a stationary signal, while most physiological signals are non-stationary. Therefore, the analysis based on assumption that capnogram is stationary has limitations and requires further analysis based on concrete facts. As such, it is proposed here to develop a computerized system to detect the severity of asthma by processing the capnogram signal using digital signal processing techniques. Figure 6 shows the overall algorithm of the proposed technique in tracking asthmatic patients utilizing the capnography technique.

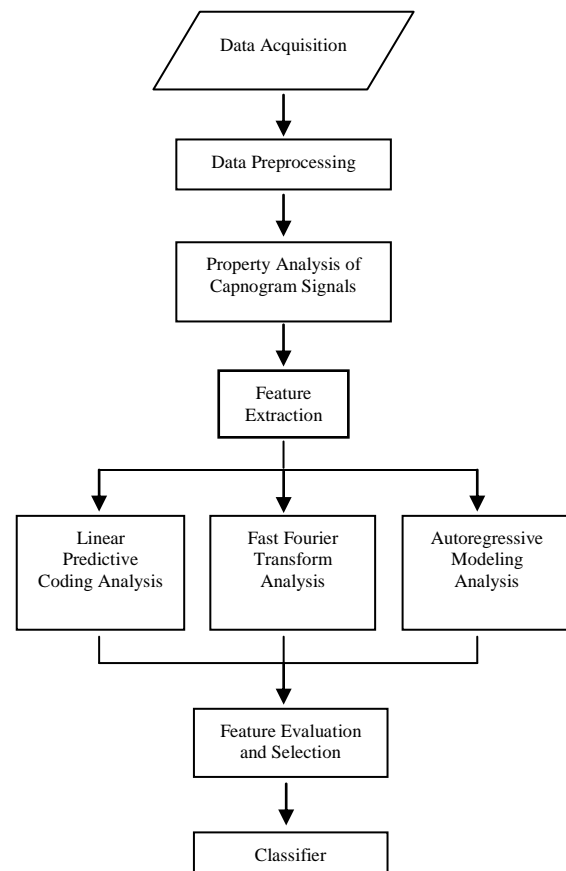


Figure 6 The overall algorithm of the proposed method

3.1 Data Collection

For this purpose, the capnogram data were collected from patients who visit Penang Hospital Emergency Department for complaint of asthma and breathing difficulties. With sensors attached to the patient's nose or mouth, the continuous capnogram was recorded using capnography patient monitor, Capnostream™20 Model CS08798. The capnogram data then extracted to the personal computer for analysis. Throughout the study, a total of 23 non-asthmatic capnogram, and 73 asthmatic capnogram were successfully collected at a sampling frequency of 200 Hz.

3.2 Preprocessing

Preprocessing was carried out to eliminate unnecessary noise in the recorded capnogram signals. In this research, the moving average filtering method was used to smooth the curve due to its simplicity and efficiency, especially for eliminating the high frequency noises within the capnogram signals [37]. This method smoothes data by replacing each data point with the average of neighbouring data points defined within a specific span.

Then, the properties of capnogram signals should be investigated. It means that as the most of the previous studies were based on the assumption that the capnogram is a stationary signal, further analysis is needed to proof the properties of capnogram including the non-stationary signals. In this study, there are two approaches to identify the capnogram in either stationary or non-stationary signals. These two methods are non-parametric method and parametric method. In non-parametric method, the mean of a segment of capnogram should be calculated at all times while in parametric method, the autocorrelation function or joint moment between the values of capnogram at two different times must be investigated.

3.3 Feature Extraction

Features of capnogram were extracted to characterize the airway obstruction severity conditions. The linear predictive coding (LPC) coefficients are proposed to use because these parameters are suitable for capnogram which has slope changes for a lot of airway abnormalities [9, 10].

In frequency domain, the power spectral density (PSD) of the capnogram signals is estimated by using the Fast Fourier Transform (FFT) as a classic method and the Autoregressive (AR) modeling as a non-stationary approach. This then has led to differentiation in frequency content of capnogram signal in asthmatic and non-asthmatic conditions. It is important to note that, till today, no study has been performed to analysis capnogram in frequency domain. Therefore, it was proposed to use FFT and AR modelling to investigate the spectral components of capnogram signals.

3.4 Feature Evaluation

The effectiveness of extracted features is assessed by Receiver Operating Characteristic (ROC) curve analysis. ROC curves can be used to compare the diagnostic performance of two or diagnostic tests [33]. It considers the results of a particular test in two categories; in our case the asthmatic and non-asthmatic conditions.

When the variable under study cannot distinguish between the two groups, i.e. where there is no difference between the two distributions, the area under the ROC curve will be equal to 0.5, so the ROC curve will coincide with the diagonal. When there is

a perfect separation of the values of the two groups, i.e. there is no overlapping of the distributions, the area under the ROC curve equals 1, so the ROC curve will reach the upper left corner of the plot. Furthermore, the P-value is the probability that the sample area under the ROC curve is found when the true population area under the ROC curve is 0.5 (null hypothesis: Area = 0.5). If P is low ($P < 0.05$), then it can be concluded that the area under the ROC curve is significantly different from 0.5; therefore, there is evidence that the capnogram test does have an ability to distinguish between the two groups [34].

3.5 Designing Artificial Neural Network

In near future the features will be selected to design a radial basis function (RBF) neural network to automatic clustering and classifying the patients with different asthmatic severity. Among all existing forecasting methods, RBF networks have been widely used, because they are capable of deducing hidden input–output relationships in data [35]. For Gaussian RBF (GRBF) networks, the above capability is inherited from the property that GRBF networks decompose a function into localized Gaussian functions through which local data features are represented. Such a local approximation approach has an advantage over the global approximation approach of multilayer perceptron (MLP) networks in terms of preventing local data features from fading away [38]. Figure 7. shows the architecture of a standard GRBF network.

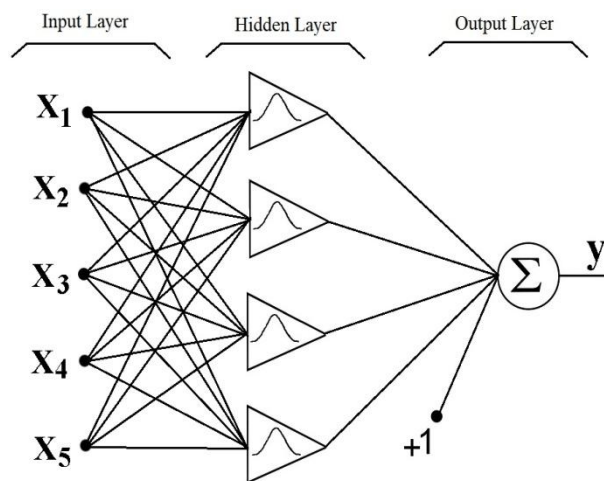


Figure 7 Architecture of a standard GRBF network

Artificial neural networks have been successfully applied to hosts of pattern recognition and classification tasks, time series prediction, data mining, function approximation, data clustering and filtering, and data compression. It can be used to solve a wide variety of problems while being robust to error in training data. So, the developed RBF network will help the medical practitioners and physicians to monitor severity of asthmatic patients.

4.0 DISCUSSION

Since, manual analysis of capnogram is time-consuming and lead to be erroneous due to the human errors such as tiredness and many other related faults, it is proposed that a computerized system should be developed to detect the severity of asthma by processing the capnogram signal using digital signal processing

techniques. The proposed method is an innovative idea that is useful for healthcare professionals involved in respiratory care as it would be possible to automatically monitor severity of airway obstruction and asthma.

It should be noted that, this method may have some limitations. It means that the proposed approach is not real time while the peak flow meter and spirometer are real-time techniques, however, they have their own mentioned limitations.

Furthermore, the total collected data were 96 while for training a neural network the more data give the better results. So, this limitation can be solved by using network with online learning capability.

Finally, existing methods used capnogram consider the end tidal point to assess the asthmatic and non-asthmatic conditions, so, it does not need any computation. For our proposed method, although it is a computerized approach, however, need some calculation specially to select a part of data without any artefact for extracting features.

5.0 CONCLUSION

Monitoring asthma and airway obstruction by using capnography is a new approach in medical technology. This preliminary study developed an algorithm based on digital processing of capnogram signals for monitoring and detecting asthmatic conditions to overcome the limitation of current methods. In the near future, this developed algorithm is expected to help healthcare professional involved in respiratory care as it would be possible to monitor severity of asthma automatically and instantaneously. Also, it is possible to implement this new index in capnographs to detect the severity of asthma in patients.

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