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Carbon Dioxide Waveform Features During Pre and Post Treatment Asthmatic Patient in Emergency Department

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Abstract: *Capnography, measured respired carbon dioxide in human respiration, is showing promising use in various areas of medicine, including monitoring of airway patency, quality of CPR efforts, and as indicators of abnormal gas exchange. The quantitative characterization of the carbon dioxide (CO_2) waveforms has potentially been shown to indicate changes in respiratory airflow, which may be clinical use in discriminating asthmatic severity. The potential clinical application must be evaluated by identifying CO_2 waveform indices which change significantly during an acute asthmatic attack. Hence, we aim to assess the CO_2 waveform indices (Area and Slope), extracted computationally from three different regions, upward expiratory (4-10 mmHg and 11-15 mmHg) and alveolar phase during pre- and post-treatment using newly developed human respiration, carbon dioxide (CO_2) measurement device. We recruited 23 asthmatic patients via convenience sampling method. A signal processing algorithm was applied for automatic segmentation and feature computations, and a paired sample t-test, and Box-whisker plot was performed to know the significant difference of features during the pre- and -post intervention. We found that both the parameters (Area and Slope) were most notable for lower part of expiratory phase (4-10 mmHg, $p<0.05$), followed by the alveolar period ($p<0.05$), while upper part of upward expiratory phase (11-15 mmHg) was insignificant for Area ($p > 0.05$) and significant for slope ($p < 0.05$). Thus, the inclusion of the features above into the lately developed device may have the potential for the assessment of respiratory distress conditions like asthma in and out of clinical settings as a patient-independent method.*

Keywords: *Carbon dioxide, waveform, treatment, asthmatic, emergency, department*

1. Introduction

Measurement of human respired carbon dioxide (CO_2) using capnography has demonstrated promises application in numerous areas of medicine, including monitoring of airway patency, quality of CPR efforts, and as indicators of abnormal gas exchange [1-5]. Due to the well-known difference observe with coaching and patient effort, a recommendation for the evaluation of the peak expiratory flow rate (PEFR) and forced expiratory volume in 1-second (FEV1) require consideration of the best of three efforts [6,7]. Besides, patients who cannot cooperate due to the diseases process or age are unable to perform these assessment methods. As a substitute, the assessment of features extracted from the morphology of the CO_2 waveform, measured by capnography, has been proposed as a pointer of bronchospasm in asthma [6-15].

The typical morphology of the CO_2 signal is the depiction of the altering partial pressures of CO_2 in the inhalation and exhalation gases throughout the respiratory cycle. The partition of the CO_2 waveform into four

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phases was introduced in [16]. The concentration of alveolar gas is reflected by a flattened plateau phase (BC). A healthy alveolar plateau phase, even though it looks like the flat, does consist of a somewhat positive slope, which represents the incessant gas exchange between the capillary blood vessels and alveoli [17]. At the end of the alveolar phase (angle '*a*'), inhalation starts, and the CO_2 concentration quickly drops. The CO_2 concentration was insignificant during inspiration as depicted in segment DE of the CO_2 waveform [18].

Further, the angle between the alveolar phase and upward expiratory phase becomes broadened, and the slope of the alveolar plateau phase increases in patients with obstructive airway disease as a result of asynchronous evacuating of the alveoli [7,8,12]. Normal low-resistance airways relatively hyperventilate alveoli provided with oxygen and have lesser CO_2 gases than the areas of the lung, which are poorly ventilated as an outcome of airway obstruction [19]. During exhalation, alveoli supplied by normal airways vacate especially ensuing in lower initial CO_2 gases followed by a delayed increase in CO_2 concentration as the gases mixed with the poorly ventilated alveoli and with the gases from the usual areas [20,21].

Several studies, conducted in subjects with asthma [6-15, 22], have shown a significant association between the FEV1, PEFR, and indices of the CO_2 waveform. One of the first studies conducted by You et al. (1992) on adult asthmatic subjects, reported the excellent correlation between the capnographic index (end-tidal slope) and spirometric index (FEV1%). Subsequently, You et al. (1994) proposed multiple indexes to provide more representative of bronchial obstruction. They measured eight indices from the morphology of the CO_2 waveform and reported a strong correlation between measured CO_2 waveform indices and spirometer index (FEV1%). Later, Yaron et al. (1996) found that the derivative of the alveolar phase was significantly changed with and without asthma. Further, Howe et al. (2011) reported that the slope of the alveolar phase and angle "a" were significantly differencing during pre-and post-treatment. However, these methods were manual and applied time setting criteria to select the part of the breath cycle. Howe et al. [8] and Langhan et al. [14] divulged that time-based setting criteria seem to be tricky in implementing in the real-time environment. They also advocated that quantification and analysis of CO_2 waveform cannot be easily employed in the Emergency Department (ED).

Furthermore, the studies conducted by M.B. Malarvili et al. [12], Betancourt et al. [13], Kazemi et al. [15], and Malik et al. [23] disclosed the computer-based algorithm for the classification of asthma and non-asthma. They investigated time and frequency domain indices and proposed to incorporate into the CO_2 measurement device to differentiate asthma and non-asthma conditions. These studies are great of interest because capnography measurement is patient independent, and can be used with young children, elderly, injured or even wakefulness, and could, hence, be used for the monitoring airways obstruction in many clinical conditions comparing with standard pulmonary function test. However, the feasibility of these indices must be confirmed during pre- and post-medication before implementing into the real-time mode, to provide a better measure of changes in severity correlating to clinical improvement.

Therefore, the study aims to 1) Record and analyze the morphology of CO_2 waveform using newly develop respiratory CO_2 measurement device based on diverting method [19]; 2) Analyze the variation in the CO_2 waveform during pre-and post-treatment; 3) Assess the discrimination capabilities of CO_2 waveform's features before and after medication that might be incorporated into the developed device for the assessment of asthma as a patient independent way.

2. Experimental

The study was conducted as a prospective case series on patients with symptoms advocative of asthma presented to the ED for two months. The study was performed in the ED of a popular university hospital. The study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (Ref: (13) KKM/NIHSEC/P17-1027).

The CO_2 data were recorded using newly developed side stream based human respiration CO_2 measurement device, which can digitize 100 times per second the carbon dioxide signal with the 0.01-second interval [24]. The CO_2 waveform was recorded from each patient during pre- and post-treatment and processed for individuals.

Firstly, we decided to segment each four valid breath cycle into sub-cycles by employing simple threshold method, on the contrary to manual and visual inspection. Each breath cycle of four breath cycles of each patient was segmented into two regions 4 to 10 mmHg, and 11-15 mmHg, by creating threshold as presented in Figure 1. In addition, an alveolar phase was parted from each breath cycle for 0.75 sec by recording for 1 sec from End-tidal Point and subtracting 0.25 sec to ensure the constancy of points of measurement.

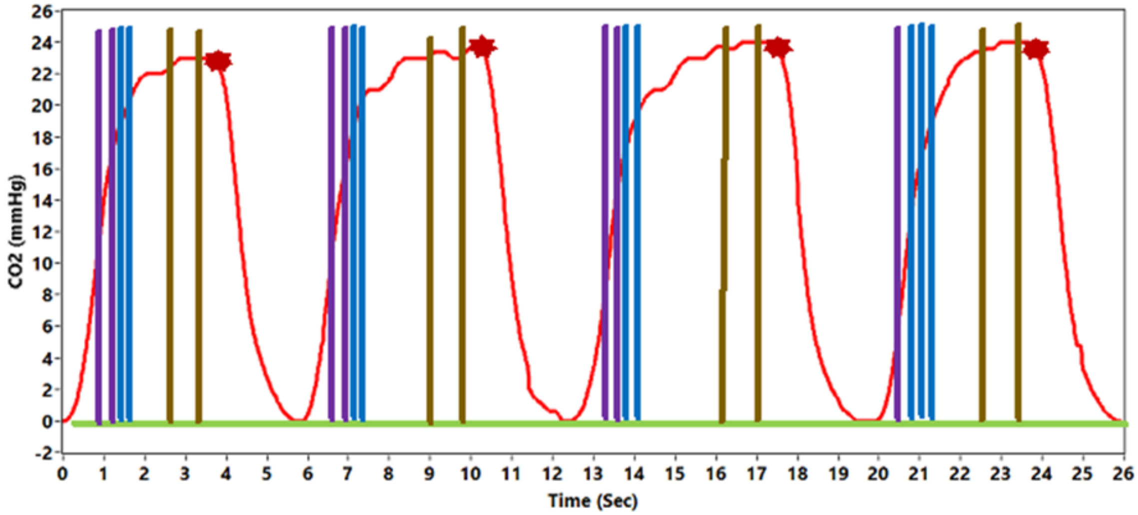

Fig. 1. Illustration of segmented part of each breath cycle from four breath cycle.

Further, two features, *area* (AR_i) and *slope*, were computed from the segmented part of each breath cycle using Equation (1) and (2). The slope of the upward expiratory phase (i.e., 4 to 10mmHg, 11-15mmHg) and alveolar phase was estimated using the general least squares linear fitting method. It computes the intercept and slope of the CO_2 waveform by lessening the residue according to the (2), which possibly permit the inclusion of all-out CO_2 signal.

$$AR_i = \frac{dt}{6}\sum_{j=0}^{i}\left(R_{j-1}(t) + 4R_j(t) + R_{j+1}(t)\right) \tag{1}$$

Where, *dt* and *R(t)* signify the sampling interval and CO_2 signal, respectively.

$$\textbf{Slope (S)} = \frac{1}{C}\sum_{j=0}^{C-1} b_j \left(M_j - S_j\right)^2 \tag{2}$$

where C is the length of slope (S), which reflects the CO_2 signal, b_j, and M_j are the jth element of Weight and best linear fit, respectively and Sj is the jth element of S.

The scientific software (Labview, version 2017) was employed for the automated segmentation, and feature extraction from CO_2 waveform morphology and the analysis were performed in a Laptop Intel (R) Core (TM) i3 CPU, 2 GHz, and OS Windows 10 (64 bit) environment. Further, the features capability assessment during pre- and post-treatment were performed in SPSS (Version 24.0; SPSS Inc., Chicago, IL). Paired sample t-test was performed to verify the significance of features based on the p-value and $p < .05$ was presumed statistically significant

3. Result and Discussion

The measured mean and SD PEFR of the asthmatic subjects before medication was 188.39± 79.22 L/min, compared with 271.07± 107.47 L/min after the treatment. Table 1. depicts the mean AR_i and *Slope* for the pre- and post-treatment for both upper and lower part of upward expiratory and alveolar phase.

TABLE I: Illustration of a mean of CO_2 signal's features during pre- and post-medication

Segmented Part	Features	Pre-medication	Post-medication
		Mean ± SD	**Mean ± SD**
4-10 mmHg	AR_i	1.68 ± 0.37	1.38 ± 0.47
	Slope	0.25 ± 0.06	0.33 ± 0.12
11-15 mmHg	AR_i	1.79 ± 0.77	2.13 ± 0.80
	Slope	0.39 ± 0.16	0.32 ± 0.10
Alveolar Phase	AR_i	21.66 ± 6.48	25.82 ± 6.76
	Slope	0.12 ± 0.09	0.05 ± 0.03

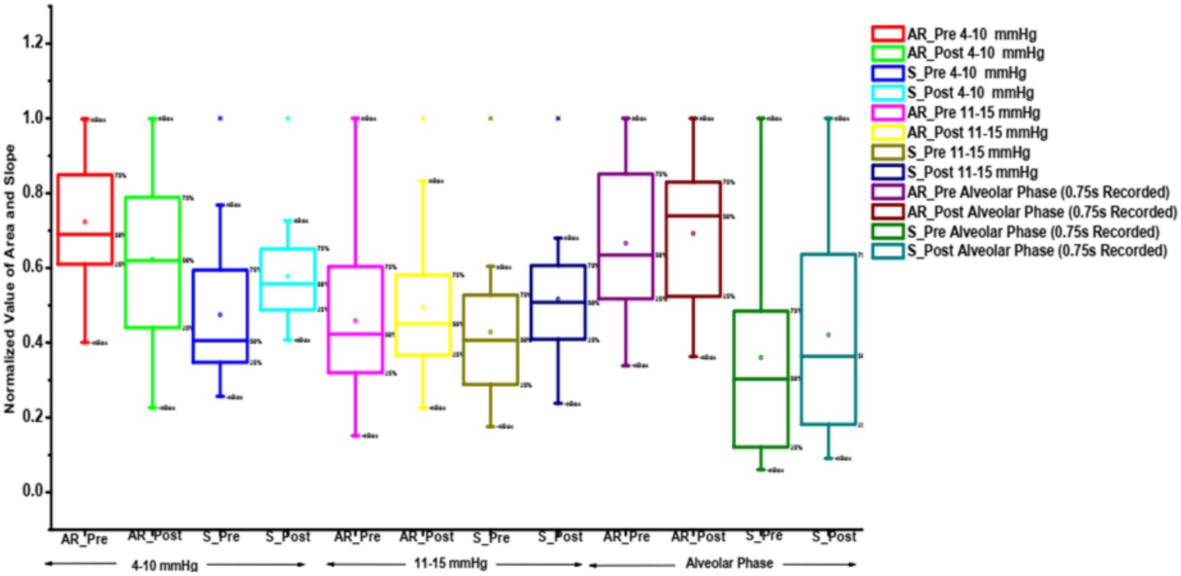

Fig. 2. Illustration of CO_2 signal's features (area and slope) during pre- and post-medication using Box-and-whisker plot.

Figure 2 reflects the box and whisker plots for the CO_2 signal's features (AR_i and *Slope*) for the segmented part (upward expiratory and alveolar) of each breath cycle during pre and post-medication. A box plot reveals more information such as minimum, lower quartile, mean, median, upper quartile, and maximum than a bar graph compared with the bar graph. Besides, the significance of each feature during pre- and post-treatment for the segmented regions were identified using a paired t-test. Finding suggests that the *area* and *slope* for the lower part of the upward expiratory phase was slightly higher significant ($p<0.05$) in contrast to the alveolar and upper part of the upward expiratory phase. We also noticed that the *area* for the upper region of upward expiratory phase was insignificant ($p=0.056$), while slope was significant ($p=0.017$).

Many previous studies have been performed in a controlled situation for the assessment of CO_2 waveform features with asthmatic patients, either asthmatic condition has been steady for some hours, or in histamine challenge test [2-4,23,25]. In contrast, this study was performed with the acute attack asthmatic patients presenting to the emergency department (ED). Besides, the advantage of this study is that the ED physicians treated all the asthmatic patients as per the department protocol without any interference from the researcher. All patients involved reported with an acute attack of asthma in the study were provided medical care for it and were considered fit for release.

Most patients are not able to perform more objective tests like the PEFR during acute attacks, thereby making these tests less useful in critical circumstances. This has apparent weaknesses as we know some patients find difficulty in assessing their symptoms [25] and physician judgments are also sometimes less reliable in identifying the degree of airway obstruction [26]. A further area of concern is that oxygen itself may provide symptomatic improvement, and the tachycardia induced by beta-agonists may falsely hinder assessment of severity.

The CO_2 waveform, measured via a capnographic, indicates variations in bronchospasm that reflect the heterogeneity of the exhaled air. A decrease and increases in *area* and *slope,* respectively, for the lower part of the expiratory (4-10 mmHg) and alveolar phase were observed. Where the change in the morphology of CO_2 waveform can be seen from the naked eye, for example, “shark fin” look, more subtle variations require computation of other features. As this is a new concept, most of the studies to date, this has been performed manually [6-8,9,12,13]. This study presents a slightly different method. Keeping in mind that this concept may be possibly implemented a lately developing human respiration CO_2 measurement device [25], we employed a simple threshold method for the segmentation of complete breath cycle into sub-cycle. For the *slope* and *area,* the first part was restricted between 4 and 10 mmHg because it is believed that CO_2 has to come from lungs to reach to 4 mmHg, second part was limited between 11-15 mmHg, whereas third region, part of alveolar phase was confined for 0.75s as recorded for 1s from end-tidal point and subtracted for 0.25s. These indices (AR_i and *slope*) were extracted using Simpson’s rule and general least-squares linear fitting method.

The mean AR_i and Slope for the pre-treatment were significantly higher and steeper, respectively than the post-treatment for both upward expiratory and alveolar phase, as illustrated in Table 1. Table 1 shows that the mean value of AR_i of the asthmatic patient for the lower part (4-10 mmHg) of the upward expiratory phase was higher than the medicated patients, and the slope was steeper with the medicated patient. Besides, AR_i for the upper part (11-15 mmHg) of the expiratory phase was more moderate before the medication compared with a medicated patient, whereas slope was minimum with asthmatic before vaccination compared to medication. Besides, AR_i of alveolar phase was lower before treatment than that of the after-treatment, with minimum deviation from its mean. However, the difference of mean and SD was significantly higher (mean, 4.16) and lower (SD,0.28) respectively, for the alveolar phase compared with upward expiratory phases during pre- and post-treatment. Besides, the pre-treatment mean slope values were markedly steeper compared with post-treatment. Moreover, the mean and SD differences were 0.08 and 0.06 for the upward expiratory phase (4-10 mmHg) than that of the other parts.

On the other hand, it can be noticed (Refer Figure 2) that both sets of features have few outliers during pre- and post-treatment; however, most of the data were within the range. It should be noticed that both the mean and median of *Area* are higher for the lower region of upward expiratory phase before treatment while lower for the upper part of the upward expiratory and alveolar phase. Also, after medication, the mean and median of the *Area* were closed to the lower quartile of the pre-treatment for the segmented region (4-10 mmHg), while higher than the lower quartile after treatment for the upper part of upward expiratory phase (11-15 mmHg). In addition, the lower quartile of the *Area* was approximately equal for the alveolar period during pre- and post-treatment. Besides, the upper quartile of *Area* was higher after treatment for the ranges (4-10 mmHg), while lower for the field (11-15 mmHg) and alveolar phase. Also, it should be noticed from Figure 2 that both the mean and median of *the slope* was higher after-treatment for the upward expiratory and alveolar period. Besides, the lower quartile of the *slope* was more top after the treatment for both phases. Wherein, the upper quartile of the *slope* was higher for the upward expiratory and alveolar period during post-treatment.

4. Conclusion

This study explores the features (*Area* and *Slope*) of carbon dioxide (CO_2) waveform indices for various parts of each breath cycle. In short, the research shows some preliminary results in actual clinical circumstances that indicate that incorporation of CO_2 waveform indices into a lately developed device by our group which has the potential to be used as an indicator for severity and response in the continuous monitoring of asthmatic patients during an acute attack. Furthermore, the added advantages of this mechanism are that the monitoring device does not interfere with the ease of initiating therapy nor require active patient efforts. Further, the work now lies in recognition of proper waveform, implementation of the proposed indices into the real-time CO_2 measurement device, and the reporting of such indices in reproducible and an easily understood form that would significantly enhance the field of asthma monitoring. It is believed that this will assist a better sympathetic of asthma, improved management, and eventually a decrease in morbidity and mortality.

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