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Real-time human respiration carbon dioxide measurement device for cardiorespiratory assessment

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Keywords: infrared CO₂ sensor, Arduino Mega2560, TFT, cardiorespiratory, reliability, validation, evaluation

Supplementary material for this article is available [online](#)

Abstract

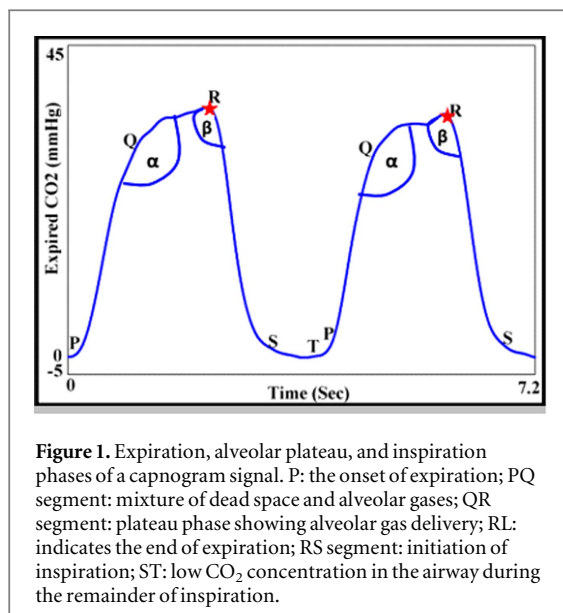
The development of a human respiration carbon dioxide (CO₂) measurement device to evaluate cardiorespiratory status inside and outside a hospital setting has proven to be a challenging area of research over the few last decades. Hence, we report a real-time, user operable CO₂ measurement device using an infrared CO₂ sensor (Arduino Mega2560) and a thin film transistor (TFT, 3.5"), incorporated with low pass (cut-off frequency, 10 Hz) and moving average (span, 8) filters. The proposed device measures features such as partial end-tidal carbon dioxide (EtCO₂), respiratory rate (RR), inspired carbon dioxide (ICO₂), and a newly proposed feature—Hjorth activity—that annotates data with the date and time from a real-time clock, and is stored onto a secure digital (SD) card. Further, it was tested on 22 healthy subjects and the performance (reliability, validity and relationship) of each feature was established using (1) an intraclass correlation coefficient (ICC), (2) standard error measurement (SEM), (3) smallest detectable difference (SDD), (4) Bland–Altman plot, and (5) Pearson's correlation (*r*). The SEM, SDD, and ICC values for inter- and intra-rater reliability were less than 5% and more than 0.8, respectively. Further, the Bland–Altman plot demonstrates that mean differences \pm standard deviations for a set limit were 0.30 ± 0.77 mmHg, -0.34 ± 1.41 mmHg and 0.21 ± 0.64 breath per minute (bpm) for CO₂, EtCO₂ and RR. The findings revealed that the developed device is highly reliable, providing valid measurements for CO₂, EtCO₂, ICO₂ and RR, and can be used in clinical settings for cardiorespiratory assessment. This research also demonstrates that EtCO₂ and RR (*r*, -0.696) are negatively correlated while EtCO₂ and activity (*r*, 0.846) are positively correlated. Thus, simultaneous measurement of these features may possibly assist physicians in understanding the subject's cardiopulmonary status. In future, the proposed device will be tested with asthmatic patients for use as an early screening tool outside a hospital setting.

1. Introduction

Human respiration carbon dioxide (CO₂) contains significant information that can assist physicians in identifying spot ventilation derangements, extubation outcomes, bronchospasm and the effectiveness of therapy in the operating room, neonate intensive care units, intensive care units (ICU), critical care units (CCU) and in the clinical environment [1–3]. Further, features extracted from CO₂ signals, such as EtCO₂, respiratory rate (RR), time spent at EtCO₂, exhalation duration, Hjorth parameters (activity, mobility and

complexity), $V_{CO_2} \times \text{slopeIII}/RR$, end-exhalation slope, the slope ratio (SR), and area ratio can be used to monitor and diagnose cardiopulmonary diseases, such as chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure (CHF), pulmonary embolism (PE), and pneumonia [4–12]. To date, to the best of our knowledge, the capnograph is the only device on the market that serves this purpose.

A capnograph is a non-invasive device that uses infrared technology and measures human respiration CO₂ from expired gases and an incessant plot of exhaled CO₂ over time, known as a capnogram. A



capnogram signal looks like a square wave; a complete two-breath cycle from a 2 min recording of a capnogram signal is displayed in figure 1. Each breath cycle has four phases and two angles (see figure 1). 'PQ', 'QR', 'RS', and 'ST' indicate the expiration, alveolar, the beginning of inspiration, and latency phase, respectively, whereas both angles (α and β) represent transitions between PQ, QR, and RS. Further, 'R' signifies the utmost value of CO₂ at the end of the breath that is designated as EtCO₂ [13–15].

However, these features have not been incorporated into capnography in a clinical setting as the findings are performed in an offline mode. Besides, capnography is bulky and expensive, and provides a poor estimation of the ventilation and perfusion (V/Q) status of the lung [16]. Therefore, there is an urgent need for a lightweight, inexpensive, precise, and quantitative CO₂ measurement device. Hence, in this paper, we propose a real-time human respiration CO₂ measurement device that can be used for cardiorespiratory assessment in a user friendly environment. In order to develop the proposed device, there are some important points to consider: namely, CO₂ features, existing technology, and a proper CO₂ sensor. These points are discussed in detail in the subsequent sections.

1.1. Significance of CO₂ features

Over the past few decades, many studies have been conducted on the extraction of capnogram features in association with heart–lung diseases [7–12, 17–26]. Of these, the study documented by Yaron *et al* [17] in 1996 investigated a parameter (alveolar slope) and measured the slope ($d\text{CO}_2/dt$) for five consecutive expired breaths among 18 asthmatic subjects. They concluded that the slope of the plateau of the capnogram varies from 0.27 ± 0.05 – 0.19 ± 0.07 for asthmatic patients during pre- and post medication. Since then, it has become increasingly apparent that the capnogram provides a new way to monitor the

inflammatory status in cardiorespiratory disorders. Later, Guthrie *et al* [18] employed a microcap plus device (Oridion Capnograph, Israel) for the measurement of EtCO₂ on 16 asthmatic patients, and suggested that non-invasive bedside measurement of EtCO₂ is feasible among children suffering from acute asthma. Further, Nagurka *et al* [19] studied the changes in extreme (both low and high) EtCO₂ on 299 asthmatic patients and recommended that initial EtCO₂ measurements may be a biomarker for asthmatic conditions outside a hospital setting. Further, Kesten *et al* [9] examined the RR correlation between 47 acutely ill asthmatic patients and 42 non-asthmatic patients. They concluded that RR increases during an asthma attack, which coincides with the findings of Kassabian *et al* [20] and Azab *et al* [21]. However, further studies are required to determine the feasibility of EtCO₂ and RR for the early detection of asthma episodes beyond a clinical assessment.

In addition, Howe *et al* [22] investigated four features (the α -angle and slope of three different phases of a capnogram) in connection with asthma using Novamatrix® capnometry among 30 asthmatic patients. The findings revealed that the slope of the phase III and α -angle can be used as indices to monitor asthmatic conditions. To support these finding, Kean *et al* [11] and Hisamuddin *et al* [23] both advocated considering the slope of the phase III and α -angle as indices for the diagnosis of asthma. In addition, Kean *et al* [11] also introduced new indices (Hjorth parameters, SR, area ratio) to identify asthmatic conditions. They concluded that the SR and the newly introduced Hjorth parameters (HP2—mobility) were the best parameters to discriminate between asthma and non-asthma. Further, Mieloszyk *et al* [10] explored four physiological parameters (exhalation duration, maximum CO₂, time spent at maximum CO₂, and end-exhalation slope) from 30 healthy, 56 COPD, and 53 CHF subjects using a capnogram signal, and correlated their findings with COPD versus CHF and COPD versus normal subjects. The results were statistically significant with a receiver operating characteristic curve of 0.89 for COPD/CHF classification, and 0.98 for COPD/healthy classification. So far, most studies have been carried out offline for the extraction and analysis of the capnogram's features showing a strong correlation with obstructive lung diseases. Hence, the incorporation, implementation, and feasibility of these features while developing a real-time human respiration CO₂ measurement device are yet to be verified. This motivated us to develop a real-time, quantitative human respiration CO₂ measurement device with the disclosed features.

1.2. Available technology for the development of the CO₂ measurement device

The side- and mainstream techniques are used for the development of the CO₂ measurement device as a

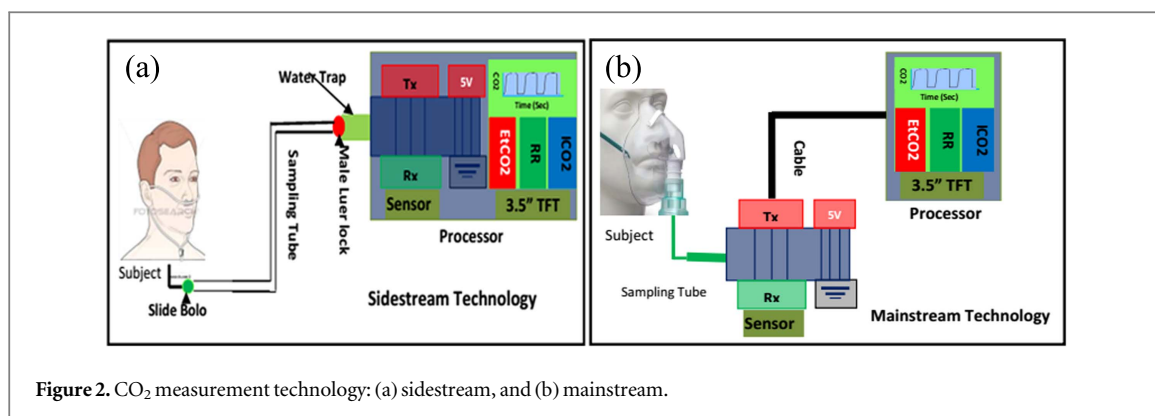


Figure 2. CO₂ measurement technology: (a) sidestream, and (b) mainstream.

function of time or volume, as illustrated in figures 2(a) and (b). In the sidestream technique, a CO₂ sensor is placed inside the main unit, away from the subject, to detect the CO₂ molecules. A mini pump aspirates the sample from the sampling tube at a sampling rate of 50–200 ml min⁻¹ which ensures the sidestream capnograph is reliable for both adults and children [10]. Hence, the sidestream technique has been found to be more convenient, simple and easy to sterilize compared with the mainstream technique. In addition, it can be used when a patient is in an unusual position [27, 28].

In contrast to the sidestream technique, a CO₂ sensor is placed between the endotracheal tube and the breathing circuit in the mainstream method. Hence it does not require a sampling tube, pump, motor, and scavenges. In addition, the mainstream capnograph has a faster response time, a simple mechanism and a more accurate sampling rate. However, mainstream CO₂ sensors are relatively expensive, heavy and require solid state sources, improved optics, and miniaturization [29]. Furthermore, the mainstream CO₂ sensor is heated above body temperature, about 40 °C, in order to prevent water vapor condensation, which may burn the patient's skin [29, 30]. Hence, we considered developing a time-based sidestream real-time CO₂ measurement device based on a non-dispersive infrared (NDIR) CO₂ sensor, which is considered to be the predominant form in a hospital setting [10].

1.3. Selection of infrared CO₂ sensor

Over the last few years, many NDIR CO₂ sensors, such as Sprint IR [3, 31], MG811 [32], COZIR [33], COMET [34], and MH410 [35], have been explored for the development of a respiration CO₂ measurement device. Of these, COMET is considered as the most suitable sensor due to its unique specifications (warm-up time, response time, weight, and output), as presented in table 1.

Table 1 illustrates that the warm-up time, response time, weight, and output range of the COMET CO₂ sensor is 2–15 s, 0.028 s, <7 g and 0%–13.8%, respectively. These specifications indicate that the COMET CO₂ sensor is highly selective and sensitive to CO₂ gas compared to other sensors.

Table 1. Comparison of the specifications of various NDIR CO₂ sensors used in the development of a CO₂ measurement device.

CO ₂ sensor	Warm-up time (s)	Response time (s)	Weight (g)	Reference
Sprint IR	<60	0.05	8	[3, 31]
MG811	300	<60	60	[32]
COZIR	<10	4–120	20	[33]
COMET	2–15	0.028	<7.0	[34]
MH410	90	<30	20	[35]

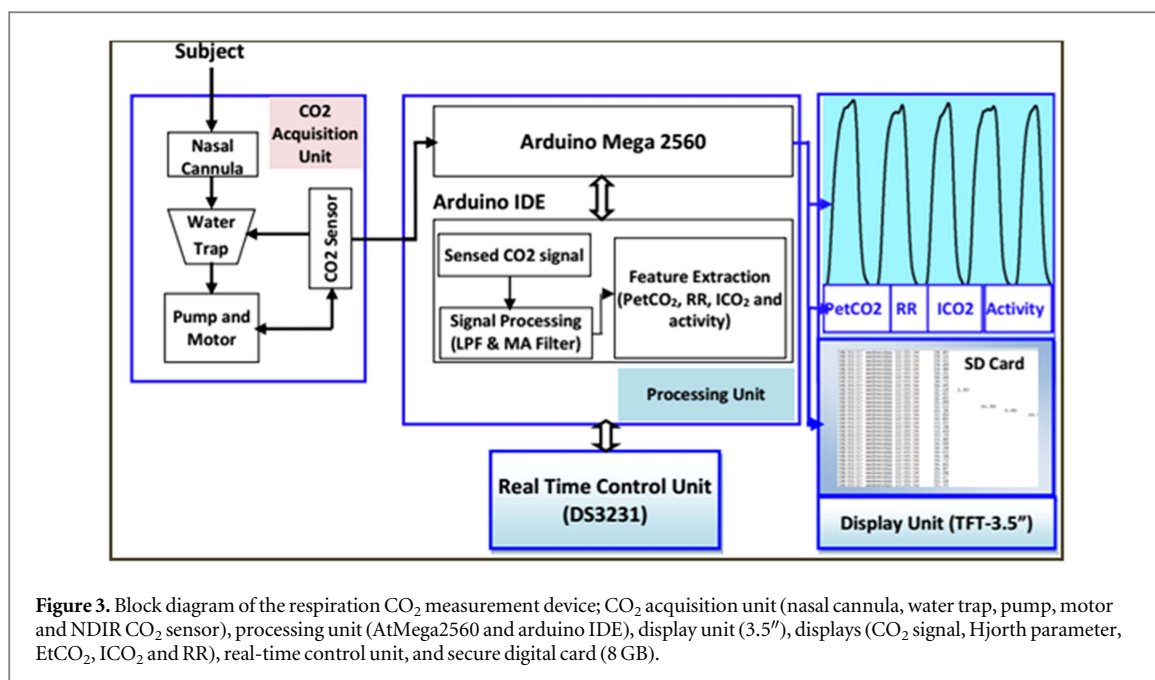
s = second.

In addition, the sampling rate (100 samples per s) of the COMET is comparatively high and provides more precise and detailed analysis of the CO₂ signal. Hence, our developed CO₂ measurement device uses an NDIR CO₂ sensor equivalent to COMET [36] to acquire the CO₂ signal. The NDIR sensor absorbs the CO₂ molecules at a specific wavelength (4.3 μm) in the infrared region and follows Beer–Lambert law, as given in equation (1) [37–39]. This avoids any recompense when different concentrations of N₂O, O₂, anesthetic agents, and water vapor are present in the inspired and expired breath:

$$I = I_0 e^{-\alpha b t} \quad (1)$$

where I represents the intensity of the light hit on the detector ($W\ cm^{-2}$), I_0 is the considered intensity of the empty chamber ($W\ cm^{-2}$), α is the absorption coefficient ($cm^2\ mol^{-1}$), b is the concentration of CO₂ ($cm^2\ mol^{-1}$), and t is the length of the absorption path (cm).

Thus, for the first time, we report a real-time, and highly reliable human respiration CO₂ measurement device with the incorporation of a first order low-pass filter with a cut-off frequency ($f_c = 10\ Hz$) and a moving average filter (span, 8). In this paper, the complete research work is organized as follows. In section 2, we explain the technical details of the components used in our research study, followed by the computation and transmission processing algorithm, which includes feature extraction, the noise reduction method, and CO₂ data display as presented in the supplementary information (available online at stacks.iop.org/JBR/12/026003/mmedia). In section 3, we report the data



collection and recording procedures along with the statistical method used for the performance (reliability and relationship) evaluation of the device. In section 4, we present our results, followed by a discussion of the significance of the retrieved features, signal processing techniques, and performance of the developed device in section 5. Finally, in section 6, we conclude and outline the directions for future research in this area.

2. Material and methods

2.1. Overview of the human respiration CO₂ measurement device

Figure 3 shows a block diagram of the CO₂ measurement device. The device is comprised of four parts, namely a CO₂ acquisition unit, processing unit, real-time control (RTC) and a display unit. The CO₂ signal is acquired from the subjects through a sampling tube and is passed to a microcontroller unit for computation and transmission purposes. Further, the CO₂ signal and other parameters (EtCO₂, RR, ICO₂, and activity) are extracted and displayed on a thin film transistor (TFT) through serial communication. With this, EtCO₂ reflects the maximum CO₂ concentration of alveoli emptying last, RR is the rate at which breathing occurs, ICO₂ represents the amount of CO₂ concentration inhalation during breathing that provides information regarding the rebreathing of CO₂ which is caused due to an improper breathing circuit setup or a patient's unusual conditions, and activity is the first Hjorth's parameter that measures the mean power of each breath signal. The analysis considered the slopes of the curve, which shows a strong correlation with the CO₂ signal. The calculation of the activity is based on variance, hence the computational cost of this method is low compared to other methods. In

addition, data logging on an SD card is performed through an RTC which is controlled by a processing unit. The technical details of the components are explained in the supplementary information. In addition, the feature extraction and display processes of the CO₂ signal are presented in the supplementary information. Thereafter, the device performance is evaluated using statistical methods.

3. Performance evaluation of the proposed device

3.1. Data collection and recording procedures

In this study, a total of 22 healthy participants aged between 21 and 35, (12 females, 23.85 ± 4.02 ; 10 males, 29.81 ± 3.75) were recruited from the Faculty of Biosciences and Medical Engineering, Universiti Teknologi Malaysia (UTM) using random sampling [40], and the characteristic details of the participants are presented in table 2. An informed consent was obtained from all the participants before participating in the study. The data are presented in mean \pm SD unless otherwise specified.

All the participants were asked to sit comfortably in a chair with a backrest for 10 min and advised not to participate in strong physical activity to avoid any alteration in the EtCO₂, RR and activity values, as presented in figures 4(a) and 5(b), respectively. Then, the participants were instructed to breathe in and out through the nasal cannula in a normal, relaxed manner at their own pace. All the data (EtCO₂, RR, ICO₂ and activity) were recorded simultaneously for 2 min [41]. To check the reliability and validity of the developed device further, statistical methods were used.

Table 2. Characteristic details of healthy subjects ($n = 22$) presented by age and gender.

Age	Gender (n)	Age (Y)		Weight (Kg)		Height (m)		BMI (Kg m^{-2})	
		X	SD	X	SD	X	SD	X	SD
20–29	M (4)	25.75	2.75	72.75	9.91	1.68	0.03	25.67	3.20
	F (12)	22.58	1.97	55.89	8.93	1.56	0.06	22.87	3.26
30–35	M (5)	31.80	2.48	76.00	16.83	1.72	0.07	25.56	5.37
	F (1)	30.00	0.00	75.00	0.00	1.5	0.00	33.33	0.00

F = female, M = male, X = mean, SD = standard deviation, BMI = body mass index, Y = years, m = meter.

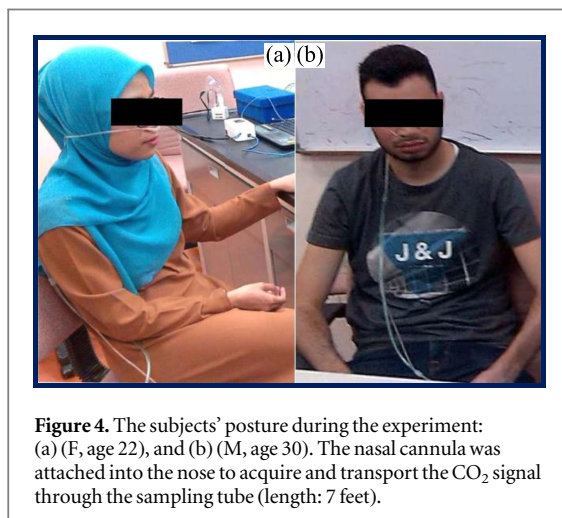


Figure 4. The subjects' posture during the experiment: (a) (F, age 22), and (b) (M, age 30). The nasal cannula was attached into the nose to acquire and transport the CO_2 signal through the sampling tube (length: 7 feet).

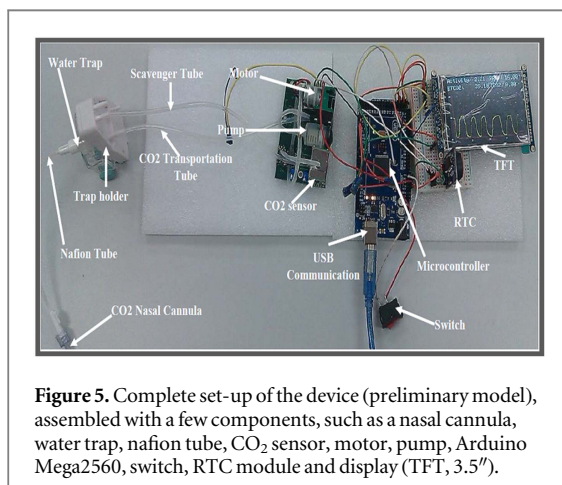


Figure 5. Complete set-up of the device (preliminary model), assembled with a few components, such as a nasal cannula, water trap, nafion tube, CO_2 sensor, motor, pump, Arduino Mega2560, switch, RTC module and display (TFT, 3.5").

3.2. Statistical method for performance (reliability and validity) analysis

A repeated measures design was adopted to examine the inter- and intra-rater reliability of the device for a CO_2 signal, EtCO_2 , RR, and activity. The reliability studies were carried out by certified researchers of the Good Clinical Practice on different occasions in compliance with the UTM Health Center's ethical clearance standard. Reliability analysis helps to confirm whether the output is consistent or not when the test is performed by the same or different users with dissimilar times. In addition, it is believed that a device cannot be valid until it is reliable [42]. Hence, in this study, we have examined both the reliability and

validity of the newly developed device. To test the validity, data were recorded using a standard capnograph device (CapnostreamTM²⁰ Model CS08798) and the developed respiration CO_2 measurement device for each subject for 2 min.

For this, descriptive statistics (mean and standard deviation) of the CO_2 signal, EtCO_2 , RR, and Hjorth's parameter (activity) were calculated for all participants, both male and female. Further, the normality distribution of each feature was analyzed with respect to each measurement. For this, the skewness and kurtosis, z -values and Shapiro–Wilk p -values were calculated for a dependent variable to verify the normality of the data for both males and females. The z -value ($-1.96 \leq z \leq 1.96$) and Shapiro–Wilk p -value ($p > 0.05$) were considered statistically significant [43–47].

Further, the intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) were used to quantify the inter- and intra-rater reliability. In addition, to verify the level of absolute reliability and sensitivity, SEM and SDD were calculated using equations (2) and (3), respectively [48, 49]. The convention of Rosner was adopted to describe the strength of the ICCs ($\text{ICC} < 0.40$ = poor reliability; $0.40 \leq \text{ICC} < 0.75$ = fair to good reliability, and $\text{ICC} \geq 0.75$ = excellent reliability) [50, 51]. Further, the outputs of both devices were compared using Bland–Altman analysis and the acceptable limit was set at $\pm 10\%$ for CO_2 , EtCO_2 , and RR values, respectively [52]. Additionally, the Pearson correlation coefficient was calculated to determine the relationship between the features. Statistical analysis was performed using SPSS (SPSS 23.0 for Windows) and the significance was set at $p < 0.05$. The results are presented in section 4:

$$\text{SEM} = \text{SD} \times (\sqrt{1 - \text{ICC}}), \quad (2)$$

$$\text{SDD} = 1.96 \times \sqrt{2} \times \text{SEM}, \quad (3)$$

where, SD is the standard deviation and ICC represents the intraclass correlation coefficient value.

4. Result

4.1. Real-time human respiration CO_2 measurement device

We report a real-time quantitative and user-operable human respiration CO_2 measurement device based on

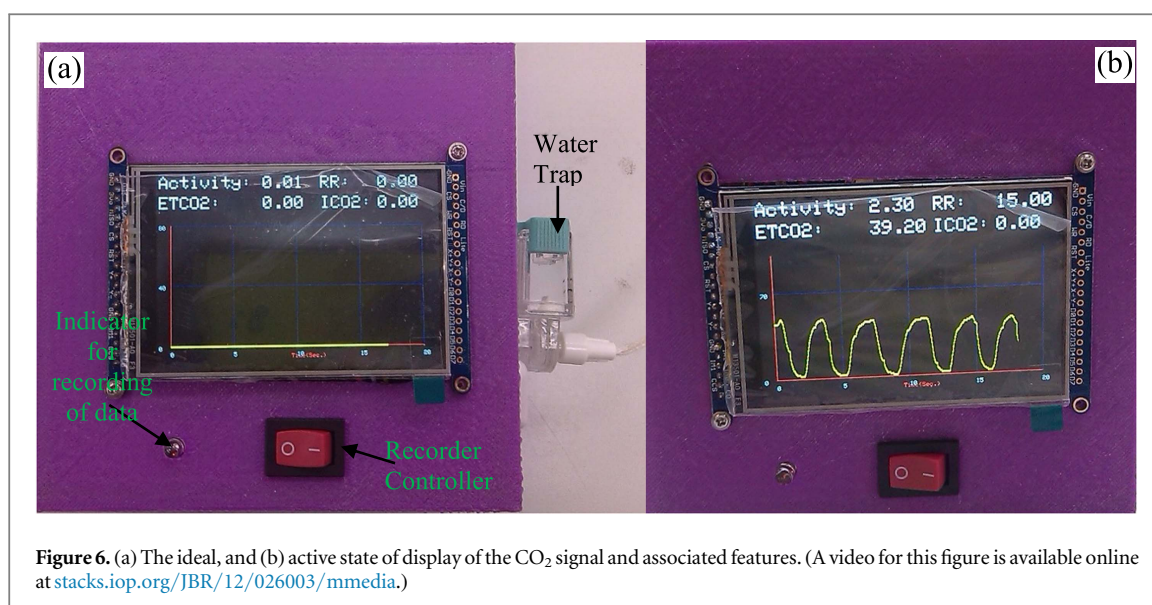


Figure 6. (a) The ideal, and (b) active state of display of the CO₂ signal and associated features. (A video for this figure is available online at stacks.iop.org/JBR/12/026003/mmedia.)

sidestream technology that can be used inside and outside a hospital setting. In addition, LPF (fc, 10) and MAF (span, 8) were employed in order to reduce noise and to provide a smooth CO₂ signal. This helped in extracting specific and precise features from the CO₂ signal. A preliminary model (the internal arrangement of components) of the device is presented in figure 5.

In this preliminary study, we preferred to extract EtCO₂, RR, ICO₂, and the Hjorth parameter (activity) due to the unfussiness and ease of implementation of the algorithm (see the supplementary information) and displayed all the parameters onto the TFT along with the CO₂ signal. These parameters (EtCO₂, RR, and ICO₂) were exhibited for each breath whereas Hjorth's parameter (activity) was measured for every breath and the mean of two consecutive breaths was displayed. With this, EtCO₂ reveals the maximum amount of CO₂ which exits the alveolus and increases during a blockage in the air track when the subjects do not adequately eject CO₂ during expiration, RR displays the breathing pattern that may increase or decrease depending on the subject's severity of gasping efficiency, and ICO₂ reveals the rebreathing of CO₂ gas. Figures 6(a) and (b) indicate the ideal and active state, respectively, of the display where the horizontal axis denotes the time, ranging from 0–20 s, and the vertical axis indicates expired CO₂, ranging from 0–80 mmHg.

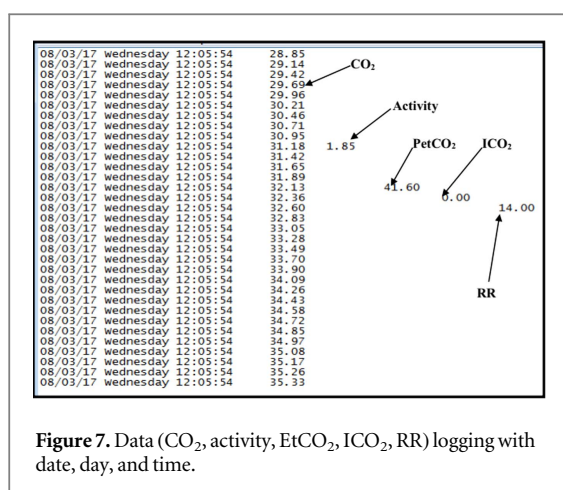
Figure 6(a) shows the retrieved features and the CO₂ signal to be zero ('0'), as the nasal cannula was not subjected to testing. Figure 6(b) shows the CO₂ signal and associated features for a healthy subject (e.g. EtCO₂, 39.20 mmHg; RR, 15 bpm; ICO₂, 0.00 and activity, 2.30) as soon as the sample line is fastened. There was a sweep in the CO₂ signal after 19.98 s due to a loss of 0.02 s when starting from the beginning. Additionally, the obtained parameters and CO₂ signal were saved onto an SD card (8 GB) through an RTC unit (DS3231), as presented in figure 7. With this, each

data point was saved inside a folder with respect to date, day, and time with a delay of 10 ms, providing an easy method of accessing the subject's information in the future. The code for each folder has a designated ID containing the current date. In this, the saving procedure was controlled by a mechanical switch that saves the data. With every press, a new file was generated according to the hour, minute, and second of the day, depending upon the need of the subject or observer. Further, we have discussed the performance of the filter and device in subsequent sections.

4.2. Implementation of filters

A 10 Hz FIR low-pass filter was applied to limit the bandwidth and remove the upper-frequency components of the CO₂ signal. Figure 8(a) shows raw (red dash line) and filtered (blue dot point) CO₂ signals. This clearly shows that CO₂ signals fall within 10 Hz. A further moving average filter (span, 8) was applied to provide smooth CO₂ signals in order to avoid any imprecision while extracting the features. In addition, it also removed random noise while preserving the sharp step response, making it the foremost, optimal filter for a time domain programmed signal. Figure 8(b) shows the raw (red line) and smoothed CO₂ signal (blue line) for five consecutive breaths, extracted from a 2 min recorded signal. The raw CO₂ signal seems to be noisy, disturbed and has an irregular shape that may provide an inaccurate result, whereas the filtered signal appears very smooth and crisp, with regular shapes and a resolution of more than 99.10% of the raw CO₂ signal.

In addition, the correlation coefficient was calculated for each CO₂ signal after filtering (low pass and moving average) for a justified cut-off frequency and span width, respectively. For example, the correlation coefficient for one of the subject's signals after a low



pass and moving average filter was 1.000 and 0.9910672, respectively.

4.3. Performance evaluation (reliability and validity)

Further, the developed device was tested on 22 healthy subjects, in order to ascertain the reliability, validity and relationship of each feature. The recording procedures have been explicated in section 3. The result revealed that the mean and SD values of EtCO₂, RR and activity were 39.57 ± 2.91 mmHg, 17.00 ± 2.33 bpm, and 1.69 ± 0.45 , respectively, whereas the ICO₂ was 0.00 mmHg for all the healthy subjects, as presented in figure 9. Further, the normality distribution of the data was verified using skewness and kurtosis, z -values and Shapiro–Wilk p -values. Our findings demonstrate that each feature shows little skewness and kurtosis for both males and females, but it does not differ significantly from normality. Hence, we assume that our data are approximately normally distributed in terms of skewness and kurtosis. Besides, Shapiro–Wilk p -values are found above 0.05 for each feature for both males and females. Therefore, we maintained a null hypothesis, and in terms of the Shapiro–Wilk test, we assume that data are approximately normally distributed. Thus, the inter- and intra-rater reliability test was assessed based on ICC, SEM and SDD, and the validity was assessed using Bland–Altman plot analysis, whereas a relationship was established using Pearson correlation coefficients (r).

4.3.1. Reliability analysis

The inter- and intra-rater reliability test was conducted on two dissimilar occasions by two observers. The ICC values (95% CI), SEM and SDD of inter- and intra-rater reliability for all the parameters are summarized in tables 3 and 4, respectively.

In our study, for inter-rater reliability, the ICC ranged from 0.88–0.96 with an average (95% CI 0.83–0.97); SEM and SDD values ranged from 0.23–1.80 and 0.65–4.99, respectively. For intra-rater reliability, the obtained ICC ranged from 0.78–0.96

with an average (95% CI 0.72–0.95); SEM and SDD values ranged from 0.38–1.58 and 1.07–4.39, respectively. The obtained ICC values for both reliabilities were greater than 0.8, except the activity (intra-rater ICC, 0.783) which revealed that the developed device is highly reliable for all the measured parameters. In addition, the SDD and SEM values were found to be lower than 5% for all the measured parameters, revealing the high level of absolute reliability and sensitivity, i.e. measurement error was low and accuracy was high. Therefore, one or more observers can use the device and its features for the measurement of a CO₂ signal with little variation, demonstrating the device's ease of use.

4.3.2. Validation of the device and its features

The precision of the device was verified using a Bland–Altman plot by comparing data obtained from the developed device and standard capnography (CapnostreamTM²⁰ model CS08798). Figures 10(a) and (b), 11(a) and (b) and 12(a) and (b) show Bland–Altman plots, generated for CO₂, EtCO₂, and RR measurements respectively. The plots display a data point for each subject, where the x -coordinate is the average of the two device measurements and the y -coordinate is the difference between the measurements as a percentage of the average. The 95% limit of agreement between the mean differences for CO₂, EtCO₂ and RR from standard capnography and the readings from our device were 1.8 mmHg and -1.2 mmHg (9.03% and -6.09%), 2.42 mmHg and -3.10 mmHg (6.24% and -7.99%) and 1.47 bpm and -1.04 bpm (8.51% and -5.94%), respectively. It also revealed that the mean differences from the actual values are closer to zero with bias inaccuracy for CO₂, EtCO₂, and RR, which were 0.30 mmHg (1.47%), -0.34 mmHg (-0.87%) and 0.21 bpm (1.28%), respectively. Thus, the robustness of the developed device in measuring different parameter values (CO₂, EtCO₂ and RR) with the same performance is guaranteed compared with standard capnography.

4.3.3. Relationship between EtCO₂, RR, and activity

The reason for establishing this relationship is that the study conducted by Kesten *et al* [9], Nagurka *et al* [19], Kassabian *et al* [20], Azab *et al* [21], Guthrie *et al* [18], Brown *et al* [7] and Kean *et al* [11], reported that during asthmatic and CHF attacks, RR increases whereas EtCO₂ and Hjorth's parameter (activity) decreases. However, to the best of our knowledge, to date, no study has been performed combining all these parameters in correlation with cardiorespiratory conditions due to a lack of evidence. Hence, to verify the findings, we performed bivariate correlation analysis between these parameters to assess the relationship between EtCO₂, RR, and activity. The relationship between EtCO₂, RR, and activity is shown in figures 13(a), (b). Figure 13(a) shows that EtCO₂ and RR ($r = -0.70$, $N = 22$ and $p = 0.000$) are negatively

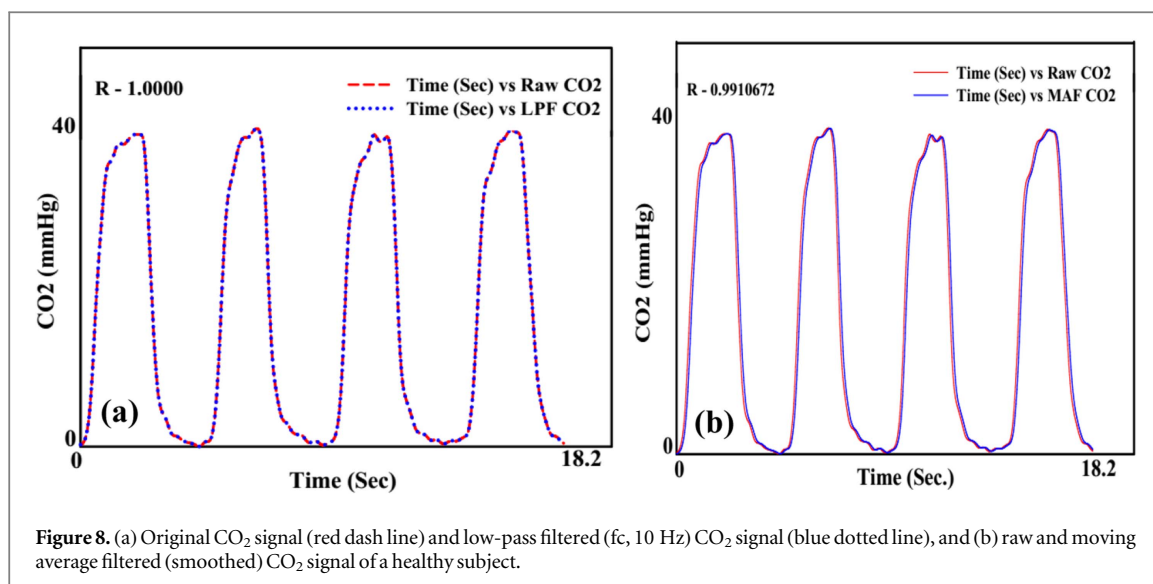


Figure 8. (a) Original CO₂ signal (red dash line) and low-pass filtered (fc, 10 Hz) CO₂ signal (blue dotted line), and (b) raw and moving average filtered (smoothed) CO₂ signal of a healthy subject.

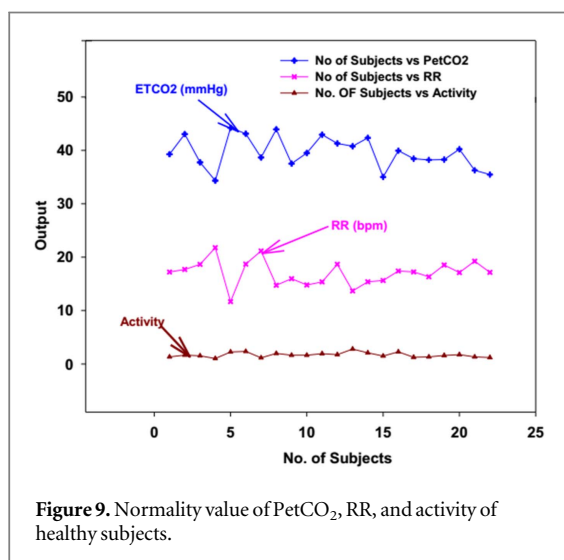


Figure 9. Normality value of PetCO₂, RR, and activity of healthy subjects.

Table 3. Features extracted from the CO₂ signal for a 2 min recording and reliability test ($n = 22$).

Features	Inter-rater, ICC (95% CI)	Intra-rater, ICC (95% CI)
PeCO ₂	0.957 (0.895–0.982)	0.920 (0.809–0.967)
EtCO ₂	0.963 (0.909–0.985)	0.968 (0.924–0.987)
RR	0.888 (0.732–0.953)	0.862 (0.673–0.942)
Activity	0.922 (0.810–0.968)	0.783 (0.484–0.909)

PeCO₂ = exhaled carbon dioxide; EtCO₂ = partial end-tidal carbon dioxide; RR = respiratory rate; CI = confidence interval; ICC = intraclass correlation coefficient; n = number of healthy subjects.

correlated. The figure shows a simple scatter regression graph which reveals that as EtCO₂ increases, RR tends to decrease, and the data points are in line with the regression line, revealing that both have a moderately strong linear association. Figure 13(b) shows that EtCO₂ and activity ($r = 0.85$, $N = 22$ and $p = 0.000$) are positively correlated. EtCO₂ and activity both increase simultaneously. Additionally, the values of EtCO₂ and activity are very near the line, specifying a

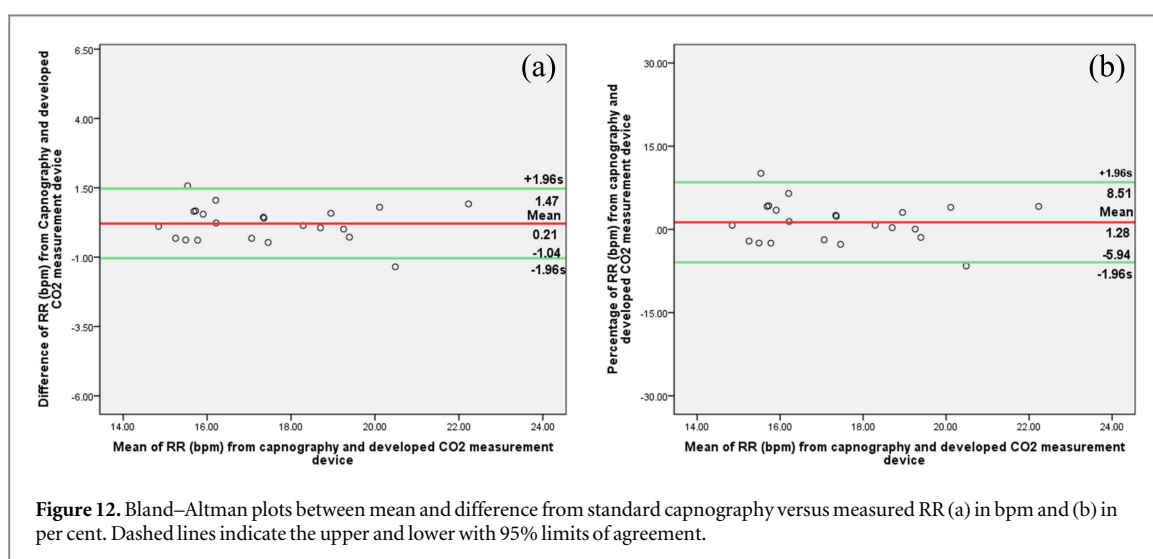
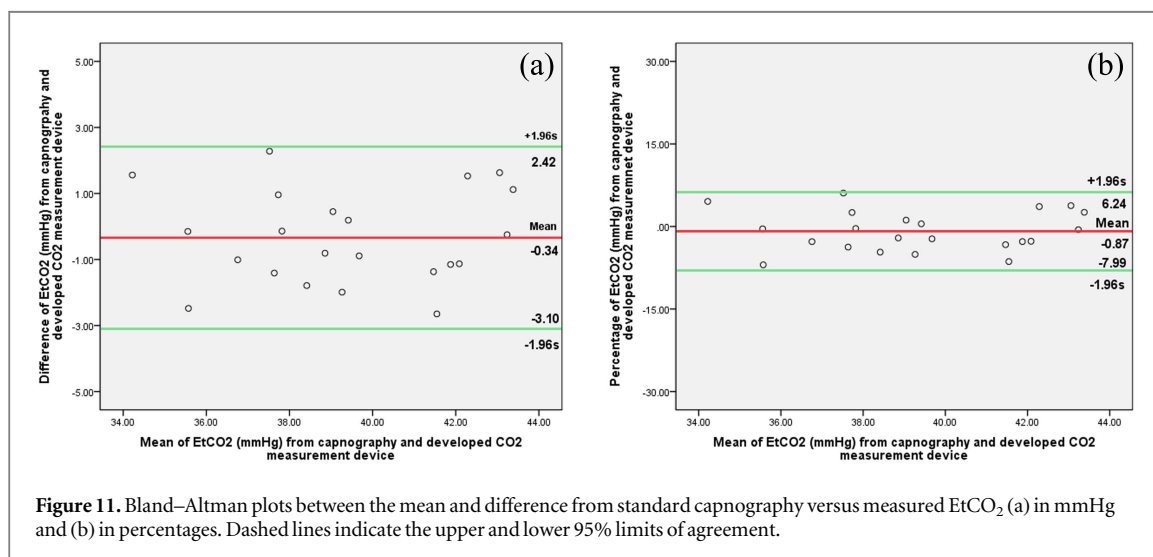
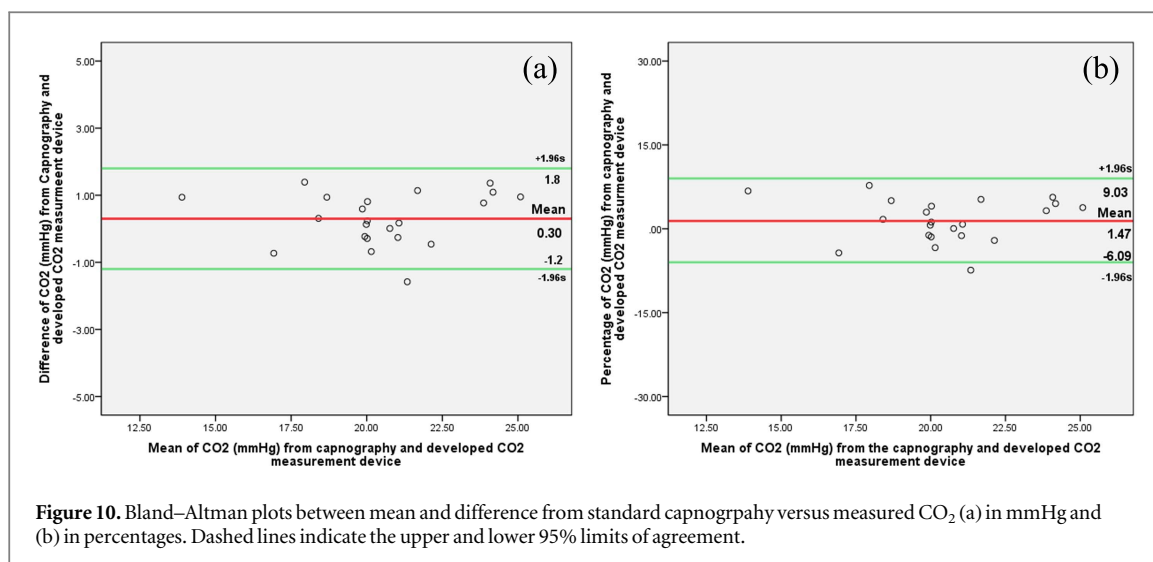
Table 4. The standard error of measurement (SEM) is stated in millimeters of mercury (mmHg) and breath per minute (bpm), respectively for PeCO₂, EtCO₂, and RR. The small detectable difference (SDD) is dimensionless.

SEM and SDD ($n = 22$), respiration CO ₂ measurement device			
Features	Rater	SEM	SDD
PeCO ₂	Inter-rater	1.08	3.00
	Intra-rater	1.42	3.94
EtCO ₂	Inter-rater	1.80	4.99
	Intra-rater	1.58	4.39
RR	Inter-rater	1.49	4.13
	Intra-rater	1.54	4.28
Activity	Inter-rater	0.23	0.65
	Intra-rater	0.38	1.07

strong linear relationship. Thus, the finding reveals that there is a moderately strong relationship between EtCO₂, RR, and activity. Hence a concurrent measurement of these parameters may possibly help health care professionals to evaluate the patient's cardiopulmonary status.

5. Discussion

To date, no studies have reported the incorporation of both a noise reduction algorithm and newly introduced features in correlation with cardiopulmonary assessment in real time. An earlier study presented a side-stream capnograph which measured EtCO₂, RR and a capnogram. However, the device was complex and the computation cost was high due to the microcontroller (AtMega 8535) and display (128 × 64), as the data could not be saved [29]. Our developed device measures the features EtCO₂, RR, CO₂ and the newly introduced feature, activity, and is displayed on a high resolution TFT (320 × 480). Additionally, it can save the data onto



an SD card via RTC which is mounted with a TFT. We extracted these features in agreement with earlier studies [9–11, 18–21, 53], since these can be used as indices when evaluating the cardiorespiratory condition

at a preliminary or extreme level. The research conducted by Kesten *et al* [9], Azab *et al* [21], Guthrie *et al* [18], Nagurka *et al* [19], Kean *et al* [11], Langhan *et al* [53], and Lamba *et al* [8] suggested that the

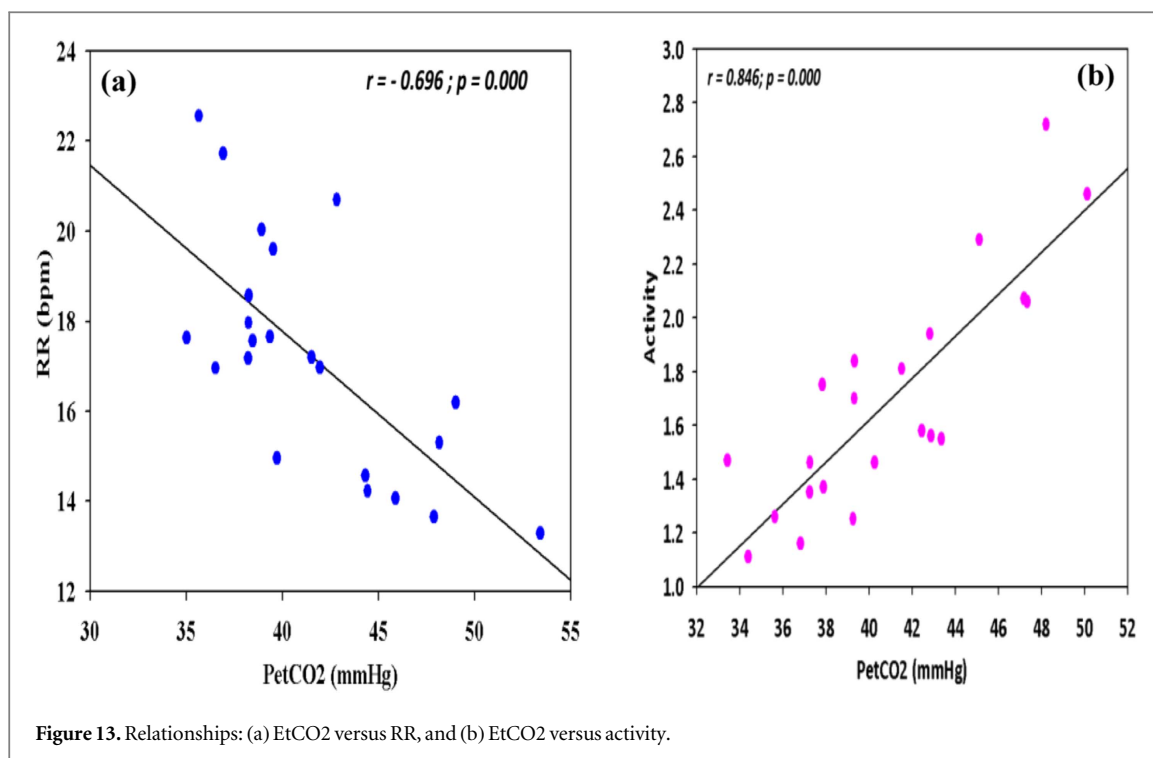


Figure 13. Relationships: (a) EtCO₂ versus RR, and (b) EtCO₂ versus activity.

measurement of these parameters can help observers to evaluate the obstruction level in the air passage of patients. Kean *et al* also reported that the computation of a new feature (activity) for one breath is capable of discriminating asthmatic and non-asthmatic conditions with an AUC (0.8951) and p -value (<0.0001). Further we verified the normality range of each feature based on earlier studies, and findings revealed that the data were in the normal range [53, 54].

Further, a noise reduction algorithm (LPF and MAF) was implemented in real time in order to smooth the shape of the CO₂ signal, helping to extract precise features. LPF was applied in agreement with an earlier study to limit the bandwidth of the signal [55]. The application of two earlier advised 13-span filters for MAF [10, 25, 56] to smooth the signal was tested, and a loss of data of more than 4.9% was found. Hence in our study we apply an optimum span 8 for high resolution (99.1%) compared with previous studies. Further, the consistency of each feature was verified based on relative and absolute reliability analysis [48, 57].

The relative reliability indicates the amount of any changes in the measurement of healthy subjects in each feature measurement, and clarifies, by actual differences, the true value of the attribute being quantified. We found that the ICC value for the inter-rater test was 0.88–0.96; this demonstrates that 88%–96% of the quantity deviation was due to inconsistency in the true value of the measured attribute and 12%–4% to random inter-subject variability. For the intra-rate test, ICC was 0.78–0.96; this demonstrates that the 78%–96% measurement difference was owing to the changeability in the true value of the measured

characteristic, and 22%–4% to chance in the intra-subject variability. Since ICC values of more than 0.7% are acceptable in clinical settings, the developed device may provide useful information for diagnostic and classification purposes in cardiopulmonary patients.

In the absolute analysis, the SEM provides an approximation of the error size of each feature and indicates the absolute reliability [48], whereas SDD reveals the sensitivity of the changes in the measured value [48]. Both the SEM and SDD values collectively disclose a change in the index, reflecting the reliability of the indicators [58]. The lower SEM and SDD demonstrate the greater reliability in the accuracy and precision of the measured values. Further, when the SEM value is less than 10% of the average measured or the highest measured score, the quantify error is small, and thus the measurement is reliable [58]. We found that SEM and SDD activity was 0.38% and 1.07% respectively for the intra-rater test, but 0.23% and 0.65% for the inter-rater test compared with other features with less than 5%. Thus, the findings reveal that 68% of the repeat measurements are likely to fall within ± 1.80 (maximum, SEM) of the true value for each parameter, in agreement with earlier studies [59, 60]. Further, the precision of the developed device is discussed by comparing the output with standard capnography (CapnostreamTM²⁰ Model CS08798) from Oridion.

From figures 10(a) and (b), 11(a) and (b) and 12(a) and (b), it can be seen that some outliers are observed in the CO₂ and EtCO₂ measurements; however, most of the data points fall within the limits of agreement. In addition, SD values were found close to each other with an average value of approximately 5%.

Accordingly, the difference between the measurements of the device for any subject is supposed to be $\pm 10\%$ relative to the bias. Thus, these results show that the differences between both devices measurements are within an acceptable range. Hence, the Bland–Altman plots reveal a reasonable consistency between the measurements of the developed and existing capnography device. Thus, the developed device is capable of providing valid and robust measurements. Hence, it is considered to be a valid monitoring device that can be used as an alternative to a standard capnography device for clinical and home monitoring purposes. Further, a relationship was established using Pearson's coefficient as a proof of hypothesis regarding the correlation between EtCO₂, RR and activity during obstructive lung diseases [9, 61].

We found that EtCO₂ and RR are negatively correlated with ($r = -0.7$); this reveals that there is a 70% chance of an increase in the RR value during the initial stage of a blockage in the wind pipe, and EtCO₂ values decrease, which concurs with the statement from Kesten *et al* [9], and English [61]. Additionally, EtCO₂ and activity are positively correlated with ($r = 0.85$) each other and have an 85% probability of an increase in activity with an increase in EtCO₂ values. Hence concurrent measurement of these parameters possibly may help health care professionals to evaluate the patient's cardiopulmonary status. In the next section, the strengths and limitations of the device are discussed.

5.1. Device strengths and limitations

The developed device is small in size (12.50 cm \times 13 cm \times 8 cm), light weight (650 g) and user operable. Hence it can be used by health care professionals in their work place setting, as well as in emergency settings, unlike traditional capnography, in order to evaluate the cardiorespiratory condition. Further, it can be used by individuals who have been affected by cardiorespiratory disorders in their home or work place, and data can be recorded and sent to health professionals via a simple mail transfer protocol. Further, it does not require any special skills or training in order to operate the device, in contrast to existing devices.

In addition, the developed device is incorporated with a noise reduction algorithm that eliminates random noise while preserving the sharp step response during CO₂ data recording, unlike existing devices. Another novel feature of the device is that it estimates Hjorth's parameter (activity) from each breath cycle considering the slope of the CO₂ signal; hence it may be useful for providing obstructive lung disease information, in contrast to existing capnography. In addition, capnography is not only used in ICU to confirm endotracheal intubation, assessment of cardiac output, and the detection of gastric tubes inadvertently

placed in the trachea, but it can also be used to identify and assess obstructive lung diseases such as COPD, asthma, and CHF because of changes in the characteristics of the CO₂ waveform. Further, existing capnography devices only measure the maximum and minimum amount of CO₂ and RR from each breath cycle, which does not involve an analysis of the slope of the resultant CO₂ signal and is unable to provide clear information about the ventilation and perfusion status of the lung. Hence, the incorporation of these features are an added advantage that may be useful in recognizing and assessing cardiorespiratory status more efficiently compared with existing devices. On the other hand, the developed device has limitations which warrant caution. The device only saves the measured features (CO₂, EtCO₂, RR, ICO₂, and activity) but cannot transfer data to remotely located physicians providing care to a patient either in hospital or elsewhere. Finally, the atmosphere pressure and temperature values should be set as per the location in the sketch to avoid false respiration CO₂ readings while using the sensor.

6. Conclusion and future work

We developed a non-invasive, highly reliable, precise, and user operable real-time human respiration CO₂ measurement device based on sidestream technology that measures expired CO₂. The developed device displays the quantified features such as EtCO₂, RR, ICO₂, activity, and CO₂ signal on a small and single screen (TFT), hence minimizing the size of the device. In addition, this is the first device which has been incorporated with low-pass (fc, 10 Hz) and moving average filters (span, 8) after signal conversion (analog-to-digital) that reduces the total computation cost and provides a sharp and smooth CO₂ signal. The developed device has been tested successfully on 22 subjects in order to ascertain the reliability, validity and relationship of the features. The findings revealed that the inter- and intra-rater mean of each parameter was more than 0.75 and mean differences \pm standard deviations for a set limit were 0.30 ± 0.77 mmHg, -0.34 ± 1.41 mmHg and 0.21 ± 0.64 bpm for CO₂, EtCO₂ and RR, which demonstrate that the developed device can be used in a clinical setting. The developed device also enabled frequent measurements of the features over a continuous period of time, and delivered accurate and reproducible readings that are not limited by inter- or intra-observer variability. We also found that the features are strongly correlated, and concurrent measurements may assist the physician in assessing cardiopulmonary conditions. In the future, a performance evaluation of the developed device will be carried out on asthma patients.

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Disclosures

The authors declare no conflict of interest.

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