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Breath analyzer for personalized monitoring of exercise-induced metabolic fat burning

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ABSTRACT

Obesity increases the risk of chronic diseases, such as type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases. Simple anthropometric measurements have time limitations in reflecting short-term weight and body fat changes. Thus, for detecting, losing or maintaining weight in short term, it is desirable to develop portable/compact devices to monitor exercise-induced fat burn in real time. Exhaled breath acetone and blood-borne β-hydroxybutyric acid (BOHB) are both correlated biomarkers of the metabolic fat burning process that takes place in the liver, predominantly post-exercise. Here, we have fabricated a compact breath analyzer for convenient, noninvasive and personalized estimation of fat burning in real time in a highly automated manner. The analyzer collects end-tidal breath in a standardized, user-friendly manner and it is equipped with an array of four low-power MEMS sensors for enhanced accuracy; this device presents a combination of required and desirable design features in modern portable/compact breath analyzers. We analyzed the exhaled breath (with our analyzer) and the blood samples (for BOHB) in 20 participants after exercise; we estimated the values of BOHB, as indication of the fat burn, resulting in Pearson coefficient *r* between the actual and predicted BOHB of 0.8. The estimation uses the responses from the sensor array in our analyzer and demographic and anthropometric information from the participants as inputs to a machine learning algorithm. The system and approach herein may help guide regular exercise for weight loss and its maintenance based on individuals' own metabolic changes.

1. Introduction

According to the World Health Organization, in 2016, 39 % of adults worldwide were overweight (pre-obese) and 13 % were obese [1]. This is a major public health concern, as obesity increases the risk of several chronic diseases, including diabetes mellitus, cardiovascular diseases, musculoskeletal disorders, and some cancers. An effective way to prevent and manage obesity includes to gradually lose weight and to maintain it in long term through a comprehensive approach, combining an energy intake reduction, an increase in physical activity and a change in lifestyle habits. However, the conventional way to evaluate obesity, predominantly by the body mass index (BMI), has limitations in reflecting changes (fat burning rates) occurring in the body in real time. There are ways to accurately measure these metabolic changes related to fat loss in real time, e.g., through venous β-hydroxybutyric acid (BOHB) and exhaled breath acetone. These two ketone biomarkers are the result of metabolic fat burning processes which is called lipolysis in the liver [2]. Increased ketones, ketosis, is related to weight loss [3]. Also, several researchers have found the correlation between these two ketones and their increased levels after exercise as a result of such metabolic processes [2,4,5]. Only acetone gets exhaled through the breath and collecting blood to measure BOHB is too invasive to perform regularly for

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at-home/gym monitoring, leaving the monitoring of breath acetone as an attractive option.

Conventional techniques to monitor breath acetone include gas chromatography coupled with mass spectroscopy [6–9], ion mobility [10,11] and laser absorption [12]. The main disadvantage of these sophisticated breath analysis techniques is their cost and lack of portability. Thus, there is a need for simple and miniaturized devices that allow the general public to conveniently monitor metabolic changes related to weight loss, especially those from exercise and/or diet monitoring. In this regard, metal oxide gas sensors have many advantages for this application due to their high sensitivity [13], low cost, low power consumption [14], low detection limit [14,15], fast response speeds [16], and small size [17]. However, there are challenges in the implantation of these gas sensors in a system for daily monitoring of exhaled breath. The human breath contains nearly 900 compounds (including acetone), which may pose a selectivity issue for acetone detection; also, these compounds may change depending not only on exercise but also on other factors [18]. In particular, besides physical activity [4–7], acetone levels may vary depending on diets [19], fasting status, and diseases (like diabetes mellitus for acetone) [20,21]. Given the complexity of exhaled human breath, many design features must be taken into consideration for a portable/compact breath analyzer based on metal oxides.

Several breath analyzers have been reported in research to sense exhaled breath acetone in portable or compact systems on-line [4,6,15,19,22], i.e., directly without storing the breath to maintain its authenticity. In general, these systems achieve their intended purpose for on-line acetone breath sampling and they incorporated many of the desirable design considerations. Specifically, the end-tidal breath, i.e., the breath containing endogenous volatile organic compounds (VOCs), is collected/sampled in most consulted systems; this is done to exclude the beginning of the exhaled breath that contains exogenous VOCs [4,15,19,22]. These systems also monitor the inlet pressure or control the flow of the breath (to a sensor chamber) for standardized, consistent sampling [4,15,19,22]. Few systems preferentially integrate sensors of various sensitivity characteristics in an array to enhance selectivity [6] or they couple other selectivity-enhancement mechanisms such as a gas chromatography column for the same purpose [15]. However, in spite of the features these systems have, each system lacks at least one of these desirable considerations. Therefore, it is the purpose of this research to incorporate in a single system all of the above-mentioned, desirable characteristics (Table S1). Additionally, it may be advantageous to use suitable data processing/machine learning techniques to account for inherent variabilities in the breath from participant to participant. In previous research, machine learning techniques have been used in exhaled breath analysis with an array of sensors [23] or with gas chromatography and mass spectroscopy techniques [24] to predict and diagnose liver diseases, cancers, asthma, and other conditions with high accuracy. To the best of our knowledge, this use of machine learning techniques has not been exploited before for compact/mobile fat burning monitoring. Thus, a compact breath analyzer coupled with machine learning techniques and the use of relevant demographic and anthropometric data show great promise.

In this work, we present a compact system with automatic breath sampling and a gas sensor array to provide with on-line, personalized exercise-induced metabolic values of BOHB based on the response of the sensors, health data of the participants and a recurrent neural networks (RNNs) algorithm. This system integrates the design considerations previously mentioned for a compact acetone breath analyzer. Specifically, we have developed an automatic on-line breath sampling assisted by CO_2-triggered valves and a pressure sensor for consistent end-tidal breath collection, an array of compact metal oxide sensors with various sensitivities for enhanced selectivity, and the use of RNNs to estimate the values of BOHB. Venous BOHB and breath tests (with our system) were taken at various times after exercise for 20 participants to monitor metabolic fat burn. The relation of venous BOHB and the responses of the sensors in the system to exhaled breath was established; based on the gas sensor responses and demographic and anthropometric health data from the participants, the values of BOHB could be estimated.

2. Experimental

2.1. Design of portable breath acetone analyzer

The breath analyzer is designed to only pass the end-tidal portion of the breath to a gas chamber in an automated flow sequence, aided by a series of valves, tubes, and a pump that help guide the exhaled breath. Specifically, for the automated breath sampling, the system monitors the pressure ($\geq$ 980 Pa) and CO_2 levels ($\geq$ 3 %); after meeting the specified threshold values for pressure and CO_2 concentration, the breath flow is switched from a bypass exhaust route to the gas chamber where the response of the sensors is recorded and transmitted to the computer. Three percent of CO_2 in the breath is considered end-tidal and the pressure is set to have sufficient breath in the flow [4]. An array of four commercial metal oxide sensors, with various sensitivity characteristics, are in the chamber to sense the breath. With this system, a person exhales through a mouthpiece on the device for approximately 10 s. In the past [25], we have performed preliminary tests of the sensors and the system to show selectivity and breath sampling capabilities. Table S1 shows a comparison of the design features for compact/portable breath acetone analyzers; as shown, our system combines the features described here.

2.2. Characterization of MEMS-type gas sensors

Four low-power commercial sensors are integrated into an array inside the breath analyzer; these sensors are named sensor #1–4 as follows: sensor #1 is TGS8100 from Figaro, Japan; sensor #2 is MiCS-6814 – NH_3; sensor #3 is MiCS-6814 – RED; and sensor #4 is MiCS-6814 – OX (Sensors #2∼#4 are from SGX Sensortech, Switzerland). In order to validate the response of the sensors to relevant concentrations of acetone and CO_2 (to test possible interferences), we conducted tests where the sensors were mounted on a standard gas chamber (outside the breath analyzer) and 2 ppm of acetone and 2 % of CO_2 were exposed to the sensors at a rate of 500 SCCM. These are concentrations similar to those present in exhaled breath. For this ex-situ experiment, a separate board was fabricated, shown in Fig. S1.

2.3. Participant selection criteria

The study conducted herein included a total of 20 participants. The participants were recruited voluntarily and the study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB B-2006/619–304). The participants are healthy adult male and female applicants aged between 22 and 43 years old with BMI of 22 kg/m^2 or higher. Because certain disease conditions [26] and diets [19] might be able to influence the levels of biomarkers in the blood and in the breath, participants taking medications for the following conditions were excluded: diabetes mellitus, hypertension, dyslipidemia or obesity. The individuals who were taking diuretics or steroids were also excluded. Furthermore, participants with the following history or conditions were excluded: excessive diet history (weight loss of more than 5 % within the last month), people with a history of malignant tumors within 5 years (excluding thyroid cancer), and pregnant women.

2.4. Design of exhaled breath experiments and exercise routine

Overall, the process for each participant consists of fasting (prior to the experiment), following a standard diet the day of the experiment, taking demographic survey and anthropometric measurements, performing the pedaling exercise, undergoing blood tests (to measure BOHB

and other metabolic markers), and taking breath samples with our breath analyzer (to measure exhaled acetone). Specifically, the participants fasted for more than 10 h prior to visiting the hospital, the standardized diet (1000 kcal) was provided at the hospital, which included sandwiches and drinks. The participants were surveyed and measured for demographic and anthropometric information such as sex, age, BMI, body fat, and others. The blood tests measure free fatty acids (FFA), acetoacetate, total ketones, and BOHB; these are related to the metabolic fat burning in the body. Subsequently, they followed the exercise routine consisting of 45 min of pedaling on a stationary bike at a top pedaling speed of 8 km/hr for men and 7 km/hr for women; the complete pedaling profile is shown in Fig. S2. This time of exercise has been reported as sufficient to induce an increase of fat burning related biomarkers [2,6]. To investigate changes in BOHB and breath acetone after the exercise intervention, the blood and breath sampling were performed immediately after exercise, 3 h after exercise and 6 h after exercise. Previous studies have reported significant changes in BOHB after 3 h of cessation of exercise [4,5].

2.5. Data analysis

The responses of the four sensors during breath analysis are defined as the resistance of the exhaled breath over the resistance in air, R_{breath}/R_{air}. The averaged response for all the participants of each of the four sensors, at each sampled time, is plotted against the averaged results for BOHB to show their relation. We estimated the values of BOHB for four participants after using the rest of participants' data as training set for RNN. Here, demographic and anthropometric information for each participant (BMI, sex, age, and body fat) were considered for the estimation.

3. Results and discussion

3.1. The fabricated compact breath acetone analyzer

Fig. 1 shows an overview of the device and the strategy for BOHB estimation in this work. The fabricated, compact breath analyzer, shown in Fig. 1(a), has dimensions of 21 cm × 21 cm × 8 cm and weighs 1.3 kg. Once the operation is started (Fig. (1b)), the end-tidal breath is guided to the sensor array automatically (by pressure and CO_2 monitoring). As shown in Fig. 1(c), the collected sensor responses are used for quantitative estimation of BOHB. Fig. 1(c) (ii) depicts the increase/decrease in resistance of the sensors with distinct sensitivity characteristics. Given that multiple interfering gases/vapors (such as humidity, ethanol, etc.) may be present in the breath at the same time, the use of sensors with various sensitivity characteristics in an array is beneficial [6]; for example, machine learning or other statistical techniques be applied to distinguish the variations attributable to acetone alone. With our breath analyzer, we combine the design considerations in several research [4,6, 15,19,22], i.e., for an on-line breath analyzer that is highly automated, with standardized sampling, and one that incorporates a sensor array (Table S1).

Fig. 2 describes in more details the configuration and operation of the fabricated device. Fig. 2(a) shows a see-through schematic of the analyzer while Fig. 2(b) shows a diagram of operation, highlighting the flow sequence of the sampled breath. It is worth noting that the sampler, the detachable part with the mouthpiece, has a filter to remove larger humid particles and the sampler tube is heated to maintain constant temperature. As shown in Fig. 2(a), the exhaled breath travels in the following order: through a filter in the detachable part (to help reduce humidity), the pressure and CO_2 sensors, the gas measurement module (containing the gas-sensing array), and finally through the exhaust (aided by the pump). This sequence is represented by the green-dotted line in Fig. 2(b); before this described sequence takes place, the initial flow of breath (blue-dotted line) bypasses the gas chamber (until the CO_2 levels sensed are greater than 3 %).

The process of breath collection takes approximately 10 s; this includes the time taken by the participant to exhale inside the device (while checking until the pressure and CO_2 levels are acceptable as indicated on the device), and it includes the time taken by the analyzer to guide and capture this end-tidal breath inside the gas chamber in the device (using its values and the pump). The system records the resistance changes of the sensors in the array before and after the breath is captured; all sensor signals stabilize in less than 100 s and recover in

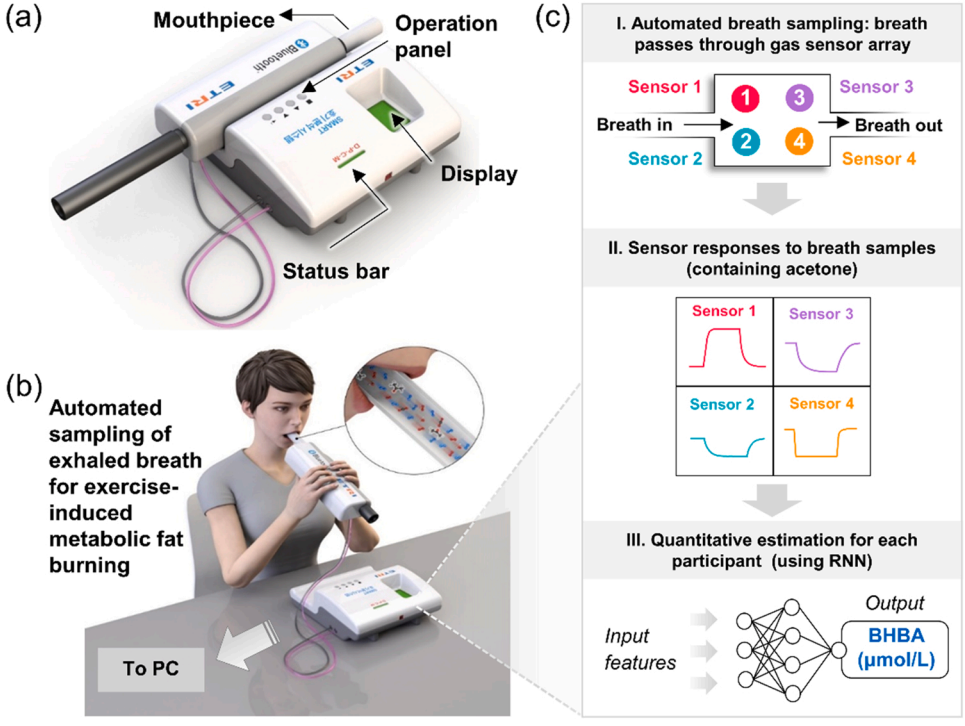

Fig. 1. Overview of the breath analysis system and strategy for BOHB estimation. (a) Isometric view of the breath analyzer. (b) Schematic representation of the system during operation (breath intake). (c)(i) the breath is guided to the sensor chamber with the four metal oxide sensors. (ii) Typical response of the sensors inside the system during breath sampling; each sensor shows a response different in magnitude or direction. (iii) The response is recorded and then used to estimate BOHB with the use of RNN.

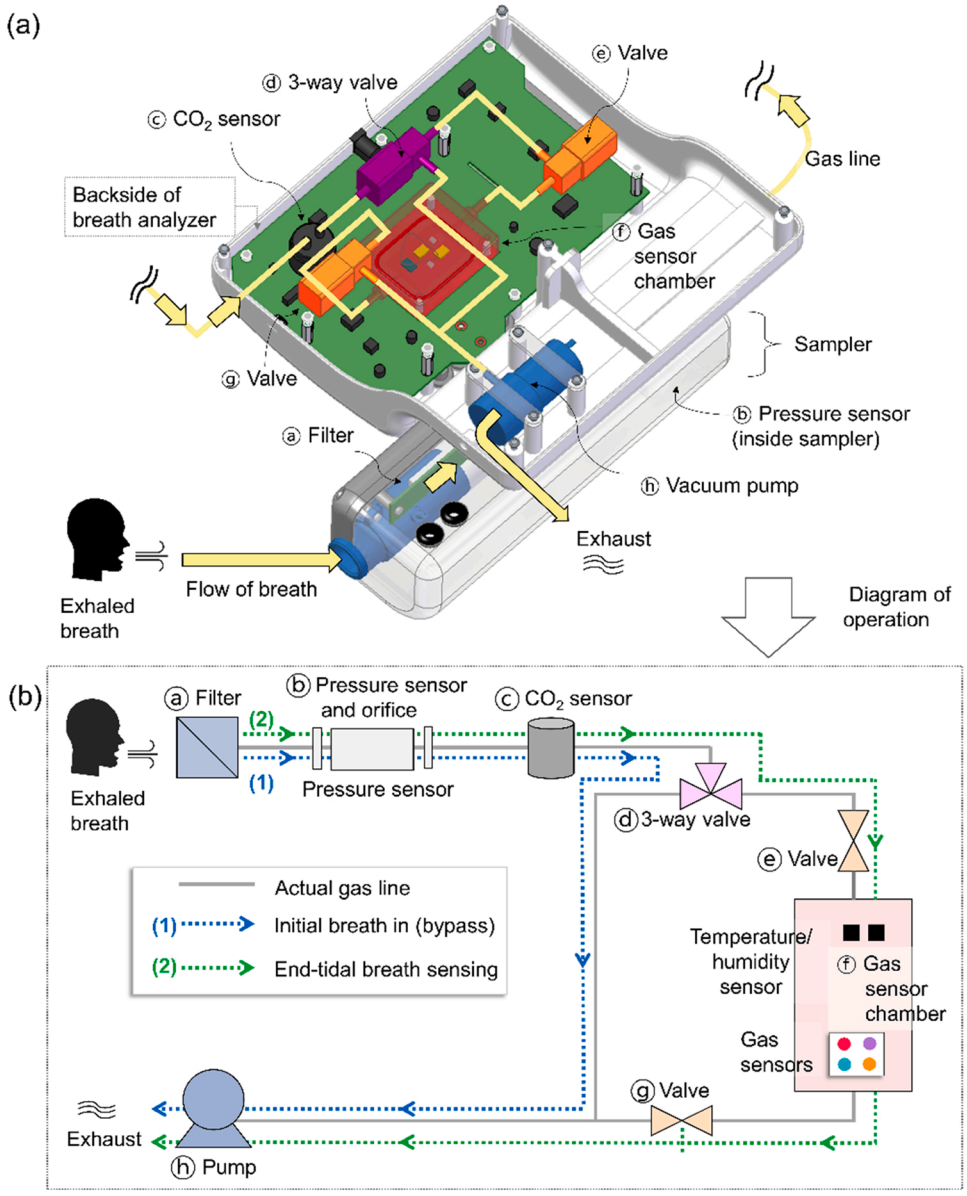

Fig. 2. Description of the breath analyzer and its operation. (a) Three-dimensional model of the system (viewed from backside), showing the layout of the physical components as they are arranged inside the breath analyzer along with the flow of breath from the intake to the exhaust. (b) Diagram of operation of the breath analyzer. After initiated, the system checks for pressure and CO_2 levels and guides the breath to exhaust initially (blue-dotted line); after the pressure and level of CO_2 is sufficient, the end-tidal breath is passed to the gas sensor chamber and the response is recorded (green-dotted line). The order of the letter bullets next to the name of each component (ⓐ through ⓗ), consistent in both parts (a) and (b) of this figure, follow the flow of the collected breath as it passes through the analyzer.

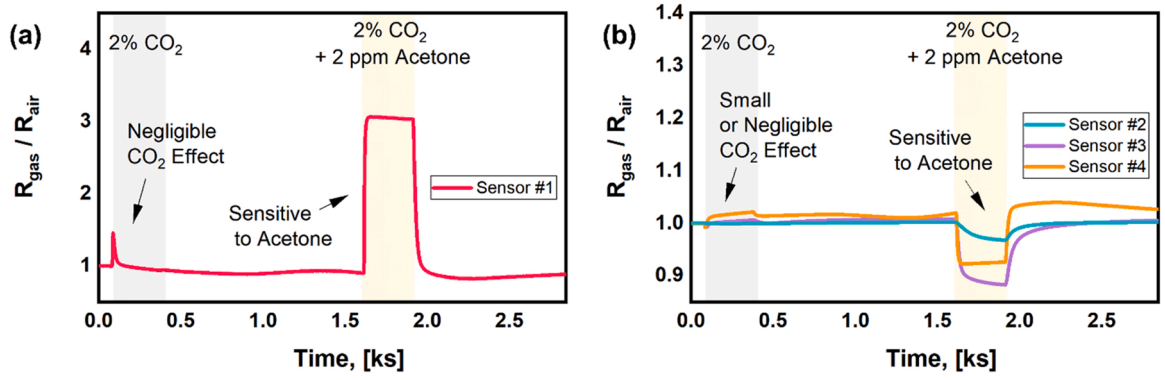

Fig. 3. Transient response curves of sensors in the array to relevant concentrations of CO_2 and acetone gases, i.e., comparable to concentrations found in human breath; the time is shown in kiloseconds (ks). (a) Response of sensor #1 (TGS 8100 sensor from Figaro, Japan). (b) Responses of Sensor #2 (MiCS-6814 – NH_3); Sensor #3 (MiCS-6814 – RED); and Sensor #4 (MiCS-6814 – OX). Sensors #2–4 are from SGX Sensortech, Switzerland. These four commercial gas sensors in an array show small or negligible interference from CO_2 and various sensitivity characteristics to acetone gas.

similar timing. The automated procedure, from breath collection to recovery, takes approximately 6 min. In future work, we aim to shorten this total time by reducing the dimensions of most components in the system and making them more compact; this is expected to minimize the dead volume and increase the response speed.

3.2. Gas tests of sensor array

As mentioned in the experimental part of this work, we have tested the commercial sensors to breath-relevant concentrations of acetone and CO_2 in a standard chamber and printed circuit board (Fig. S1). Fig. 3 shows that all four sensors show more reactivity in the presence of a small concentration of acetone (2 ppm) compared to a large concentration of carbon dioxide (2 %), which is beneficial for breath analysis. It can also be seen that each sensor shows different reactivity (response) to the same concentration of acetone (as expressed schematically in Fig. 1 (c) (ii)). The different reactivity of each sensor to the same gaseous environment is also seen during breath analysis. This feature (of various sensitivity characteristics) can be exploited for pattern identification and quantification of VOCs present in the breath.

As expected, the commercial sensors shown herein also show different reactivity to other gases. Preliminary demonstration of the device in this work [25] shows that the combination of these sensors in an array can identify, through principal component analysis (PCA), various VOCs (ethanol, acetone and formaldehyde (HCHO)) in simulated breath samples. For practical applications, as many VOCs can be exhaled based on numerous factors (diet/fasting, diseases, exercise, etc.), it is necessary to apply other approaches beyond controlled lab tests with simulated breath. These approaches include: the use of array of sensors, advanced analytical tools, and validation with a gold standard measurement of fat burning during exercise (such as blood tests for BOHB). Previous research has seen the needs to incorporate these approaches. More specifically, most portable breath analyzers use one sensor [4,15,19,22]; however, as an example, other previous research has shown that by using two sensors, in a portable breath analyzer, it is possible to compensate for the effect of another common VOCs in breath (ethanol) while measuring acetone [6]. These results support the use of the sensors in an array and highlight their potential when used with a machine-learning algorithm due to the sensors' various sensitivity values for the same gas and for different gases.

3.3. Population study

Detailed information for the clinical profile (demographic, anthropometric, and blood data) of each of the 20 participants is shown in the Table 1. The same number of female and male participants took part in the experiment with an average age of 29.9 ± 5.6 years. The BMI of the participants ranged from 22.5 kg/m^2 to 35.6 kg/m^2, i.e., from healthy normal weight to obese. In literature, age, body fat, and weight have been shown to negatively correlate with BOHB increases post-exercise [27]. In our study, despite the limited sample size, we observed similar tendencies in Table 1 (although with notable exceptions), such as the younger participants (#9, 14, 19 and 20) showing greater changes of BOHB post-exercise. We also observed that participants with the highest BMIs (obese participants) showed little changes of BOHB post-exercise (participants #8 and 18), consistent with previous studies which reported lower metabolic fat burning in obese individuals [2,6]. Given their relation in metabolic processes [5], the fatty acids and ketone bodies showed positive correlations with BOHB: FFA (Pearson's $r = 0.57$), acetoacetate ($r = 0.93$), and total ketone ($r = 0.99$) (all $p < 0.05$) (Table 1). It is expected that when used in combination of breath acetone data, and specially in larger samples, sex, age, BMI or body fat, can help estimate the changes in BOHB post-exercise. Particularly, this kind of data has been used in other research for the prediction of disease incidence and diagnosis when coupled with machine learning techniques [28,29]; we look to extend this kind of approach to fat burning monitoring through exhaled breath hereinafter.

3.4. Analysis of exhaled breath after exercise

Previous studies have shown that significant increases in both breath acetone and BOHB start to take place after moderate exercise routines in the hours following the cessation of the exercise [2,4,5,30], i.e., consistent with the metabolic processes whereby the body burns fat as a result of the exercise. As acetone and BOHB are correlated, several research have used venous BOHB as validation of the exhaled breath sensor output (or gas chromatography) [2,4,5]. In our study, we have performed similar approach by measuring blood BOHB and breath

Table 1
Demographic, anthropometric, and clinical profile of all participants in the experiment and the change of BOHB and other markers (from the end of exercise to 6 h thereafter). The summary of all 20 participants is shown in the last row. The ratio of male to female participants is 1:1.

Demographics			Anthropometric and body composition		Blood analysis (change from cessation of exercise to 6 hr thereafter)			
Participant number	Sex [M/F]	Age [year]	BMI [kg/m^2]	Body fat [%]	Δ (FFA) [μmol/L]	Δ (Aceto-acetate) [μmol/L]	Δ (Total ketone) [μmol/L]	Δ (BOHB) [μmol/L]
# 1	M	27	26.5	30.2	590	104	455	351
# 2	M	27	23.2	15.7	139	9	71	62
# 3	F	34	24.8	37.9	245	35	213	178
# 4	F	38	26.1	37.2	5	29	196	167
# 5	F	32	32.0	41.4	208	119	463	344
# 6	M	28	24.2	21.6	498	93	397	304
# 7	M	31	24.3	30.8	-105	-22	-51	-29
# 8	M	27	35.6	35.7	103	-13	-44	-31
# 9	F	24	29.7	42.0	365	90	359	269
# 10	F	35	25.0	37.0	-98	-1	30	31
# 11	M	43	22.6	23.0	492	8	91	83
# 12	M	31	27.9	23.0	105	44	241	197
# 13	F	37	23.6	39.0	576	77	336	259
# 14	F	24	28.2	19.8	25	15	143	128
# 15	M	28	23.8	26.7	327	52	266	214
# 16	M	33	25.0	26.0	591	35	199	164
# 17	F	26	23.3	36.4	155	25	117	92
# 18	M	28	35.2	31.0	29	12	76	64
# 19	F	22	22.5	36.8	146	73	342	269
# 20	F	22	23.0	32.7	85	74	374	300
Mean		**29.9**	**26.3**	**31.2**	**224.1**	**42.9**	**213.7**	**170.8**
Standard Deviation		**5.6**	**4.0**	**7.7**	**220.7**	**39.6**	**154.1**	**115.3**

acetone immediately after exercise, 3 h later and 6 h later. In addition, in contrast to other studies reported in literature, we have used an array of sensors to better capture the biological information in the breath; the results of the blood and breath sampling are shown in Fig. 4 for 20 participants. Concretely, Fig. 4(a) shows the sampling schedule for blood test and exhaled breath; samples are taken immediately after exercise, 3 h later and 6 h later. Fig. 4(b) shows the average results of the BOHB values for all participants at the different times after exercise; as expected, BOHB values increase over time after exercise cessation and the standard deviation error bars show that there are variabilities from participant to participant because of the different metabolisms in individuals, consistent with previous observations [4,5]. Fig. 4(c) through Fig. 4(f) show the average response of each gas sensor in the array versus the average results of the BOHB values for all participants at eat time. Noteworthy, Fig. 4(b) ~ Fig. 4(f) show linear fits of the data to show the trends of responses over time. As acetone is a reducing gas and giving that the concentration of breath acetone increases over time after exercise, the response of sensor #1 (Fig.4(c)) increases while the response for sensors #2 ~ #4 (Fig. 4(d) ~ 4(f)) decreases. In Fig. 4, the magnitude of the Pearson coefficient *r* for the sensors varies from 0.71 to 0.99. This may indicative that overall acetone levels influence the sensors differently. Additionally, the lower Pearson coefficient values in some sensors may arise from interferences of other VOCs or lower selectivity to acetone. These variations in sensor responses are also beneficial as they may contain information (for the array as a whole) that may help with compensation [6] or when using machine-learning algorithms, as will be discussed hereinafter.

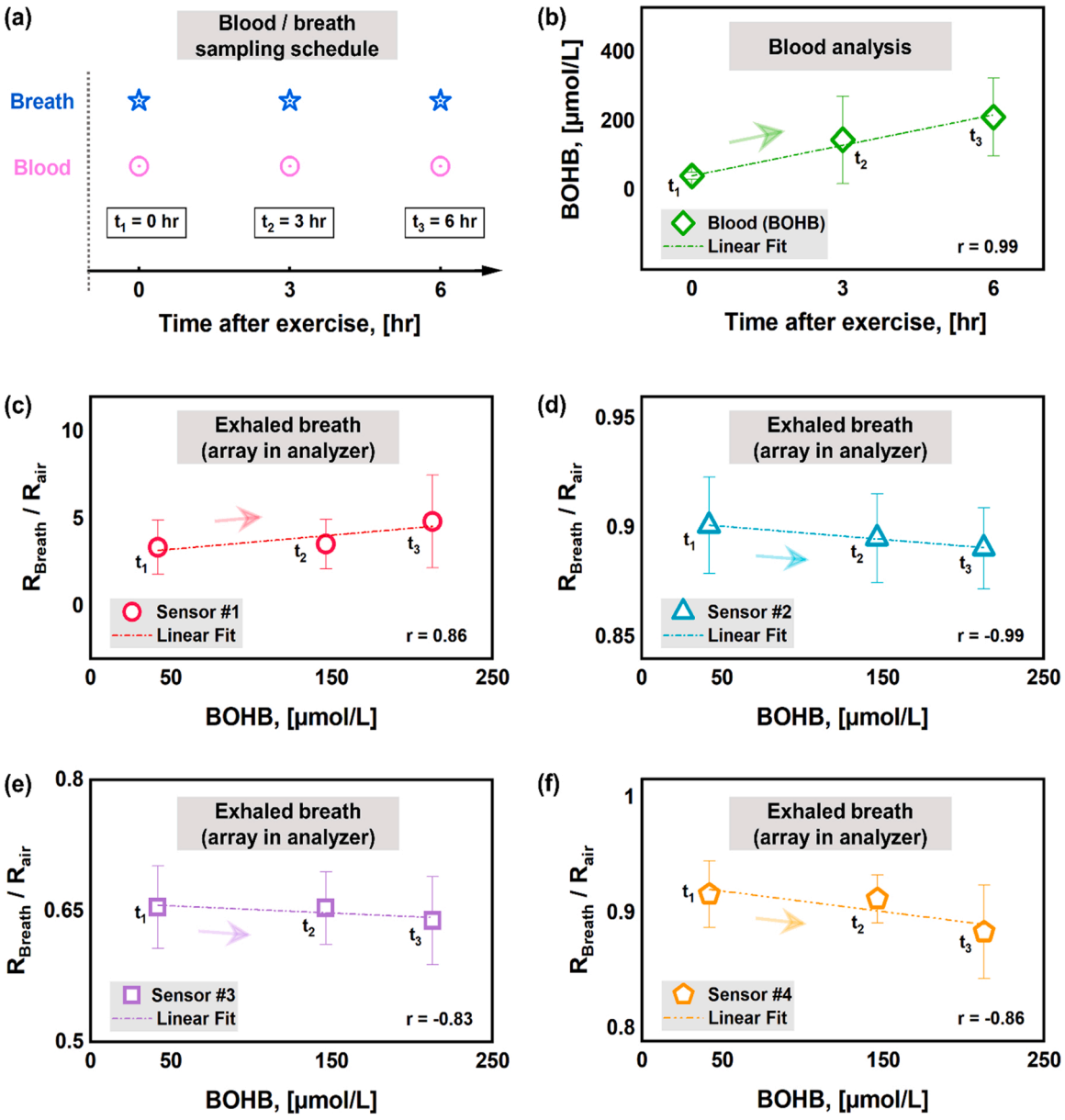

Fig. 4. Average values of BOHB and gas sensor responses (from exhaled breath) for all 20 participants (n = 20) at different times after exercise. (a) Time schedule of blood sampling (for BOHB) and exhaled breath (gas sensor array). (b) Average values of BOHB at different times after exercise; BOHB increases over time after exercise due to the metabolic fat burning process of the participants. Average responses R_{breath}/R_{air} vs BOHB for (c) sensor #1, (d) sensor #2 (e) sensor #3, and (f) sensor #4. The sensor #1 experiences an increase in response over time (after exercise) while sensors #2–4 experience a decrease, consistent with an increase in acetone from fat burning.

3.5. Estimation of BOHB for different excise times

Ultimately, for monitoring an individual's fat burning process after exercise, a personalized estimation of the BOHB is desired based on the gas sensor data and other participant-specific data. Besides the output of the gas sensors in Fig. 4, several readily available factors from each participant (demographic and anthropometric data, as in Table 1) have an effect on fat burning and they may also provide valuable information in tandem with the sensor data [2,5,6,27]. Fig. 5 shows an example of such strategy for BOHB values estimation. As shown in Fig. 5(a), we input the gas sensor responses of the exhaled breath, along with demographic and anthropometric information from the participants, to a RNN algorithm for regression; here, we obtain BOHB values as an output (indicator of fat burned). To implement this technique, the distribution of the data set is as follows: 80 % of the data was used for learning and 20 % for testing (validation). In Fig. 5(b), we see the feature impact of each input value; the information provided by the sensors and the participant-specific information in the breath analyzer contribute to the regression output as indicated by the values of their coefficients. As shown, the results in Fig. 5(b) (and in Fig. 5(c)) do not include sensor #1 as an input feature. Following a filter feature selection method, the data from the four original constituent sensors in the array were analyzed for collinearity, given that high multicollinearity amongst the constituent sensors deteriorates the prediction accuracy (or output error for regression) of the machine learning algorithm. It was found that the VIF (Variance Inflation Factor) for sensor #1 is greater than 10, which indicates that the multicollinearity of this sensor with other sensors is high; thus, sensor #1 was removed for better prediction results. Fig. 5(c) shows the predicted vs ground truth values of BOHB in the test set; the Pearson coefficient r between the actual and predicted BOHB of the model (participants in learning set) is 0.8 and for the test set is 0.75 ($p < 0.05$). Despite the obtained r value between 0.75 and 0.8 in Fig. 5 (c), the plot shows some scattering, which leaves room for improvement; this can be attributed to the relatively small sample size, i.e., the number of participants and breath samples collected [31]. In future work, with the goal of improving the predictive performance of the model, the sample size will be increased by recruiting more participants and collecting more breath samples per participant; additionally, the number of sensors will be increased and other transient features (such as rise time and shape of the transient curves) will be used.

The fabricated compact breath analyzer can help guide/adjust exercise routines (interventions) for effective weight management in real time, analogous to the use of BOHB in the past to guide exercise routines [27] but with the added noninvasive advantage of the former. The predicted, increased levels of BOHB have several meanings with respect to the breakdown of stored fat. Although, in literature, evidence is based upon nutritional conditions rather than exercise itself, ketosis with BOHB helps the metabolic status with improved muscle strength and insulin sensitivity [3]. We expect that the application of the approach reported herein to a wider and more diverse population may help train and establish a database where compact/portable systems may account more accurately for the complex nature of the exhaled breath volatilome. In addition, while the potential for personalized fat burning monitoring has been demonstrated here with a focus on personalized

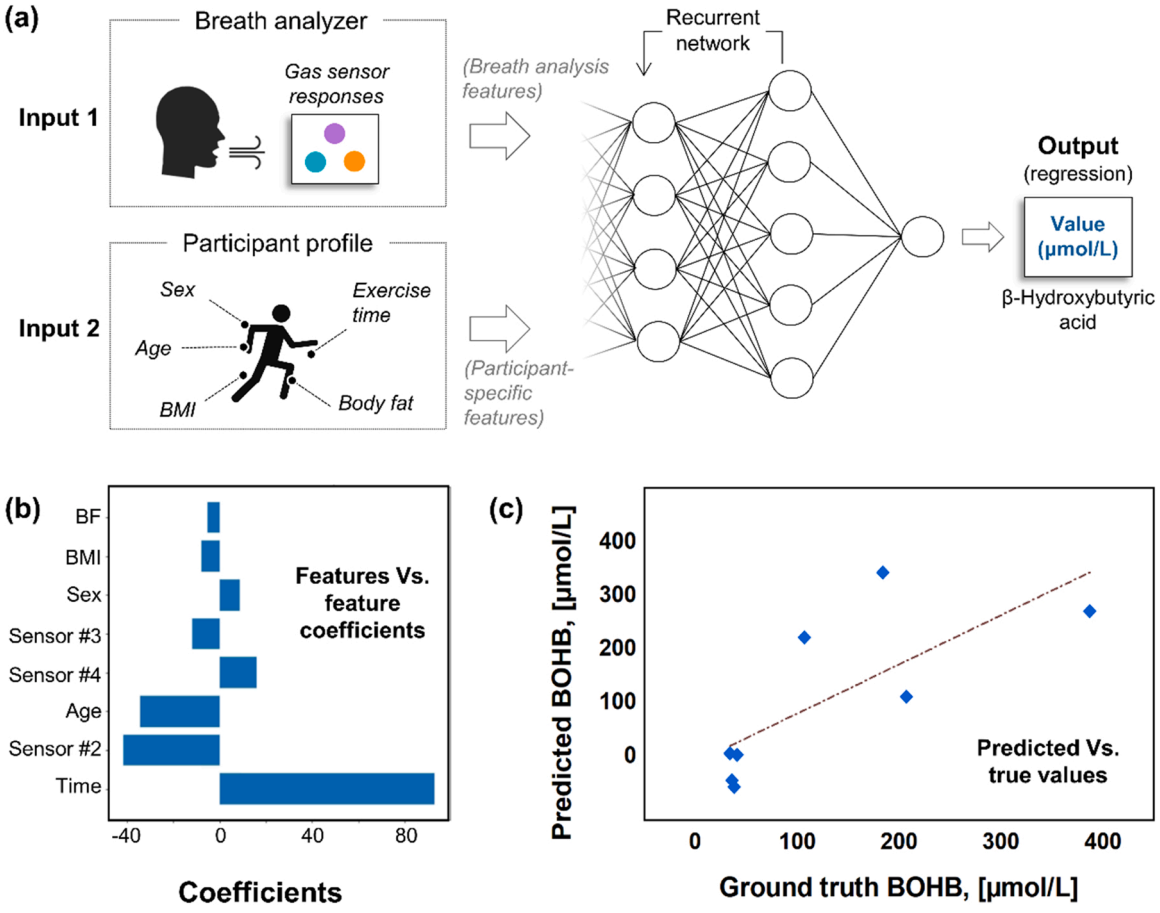

Fig. 5. Machine learning strategy and results. (a) Machine learning architecture to estimate BOHB values (output) based on responses of the sensors in the array and demographic and anthropometric information from the participants (inputs). (b) Feature coefficients for each of the variables, showing their contributions for the trained model; BF is body fat. (c) Predicted values of BOHB (out of algorithm) vs ground truth values (from blood samples); the Pearson coefficient r between the actual and predicted BOHB of the model (learning set) is 0.8 and the r of the test set is 0.75 ($p < 0.05$).

healthcare, another promising application is that of performance sports and creational fitness training [30]. On the other hand, there is also room for improvement in the device. While the analyzer reported herein has smaller dimensions than most comparable analyzers surveyed [4,19, 22], the size could be further reduced [6,15]; in this regard, our ongoing and future work focuses on maintaining and/or improving the various performance parameters of the device while reducing it to a handheld size. Additionally, in terms of practical uses, we will study the effects of interfering factors such as diet and diseases to expand the target users and usability of the system.

Besides the field of metal oxide-based breath analyzers, as discussed in this work, another emerging research direction is that of wearable, self-powered sensors for breath analysis [32–34] based on piezoelectricity and triboelectricity; this emerging field has shown promising results for flexible arrays of sensors to detect various biomarkers [32], and for nanomaterial-based sensors to detect exhaled breath Oxygen [33]. We anticipate that in the future, the complex task of breath analysis will incorporate, besides advanced analytical techniques, the integration of different transduction mechanisms in multi-transduction arrays (such as chemiresistive metal oxides and piezoelectric devices) for enhanced discrimination capabilities given that each transduction can provide distinct sensing signals relevant to the physiochemical properties of a gas [35].

4. Conclusion

In conclusion, we have fabricated and tested a compact breath analyzer for real-time, personalized monitoring of fat burning induced by physical exercise; the breath sampling requires only approximately 10 s of exhaled breath and the sampling is highly automated. The fabricated system incorporates a combination of several design considerations for modern compact/portable breath analyzers, including, the collection of end-tidal breath systematically and the use of an array of 4 gas sensors of various selectivity characteristics to better capture the complex biological information contained in human breath. As a key biomarker to reflect exercise-induced fat burning in real time, we measured BOHB after exercise in 20 participants. We found that the predicted BOHB was highly correlated with the actual BOHB measured in blood, resulting in 0.8 of correlation coefficient *r*. In our approach, we used the response of the sensors in the array and demographic and anthropometric data as inputs to a RNN for the estimation. We anticipate that the advantages of our fabricated system (standardized and automated breath sampling, use of an array, etc.) and the approach followed for estimation (combined use of several inputs with machine learning) could help advance the field of personalized fat burning monitoring systems for encouraging physical exercise in the general public.

CRediT authorship contribution statement

Dionisio V. Del Orbe: Formal analysis, Data curation, Writing – original draft, Visualization. **Hyung Ju Park:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Myung-Joon Kwack:** Methodology, Software, Investigation, Data curation. **Hyung-Kun Lee:** Conceptualization, Formal analysis, Writing – review & editing. **Do Yeob Kim:** Investigation, Methodology. **Jung Gweon Lim:** Formal analysis, Software. **Inkyu Park:** Writing - Review & Editing, Supervision. **Minji Sohn:** Investigation, Resources. **Soo Lim:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Dae-Sik Lee:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.snb.2022.132192.

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