# Validity of the Lumen® hand-held metabolic device to measure fuel utilization in healthy young adults

**Kent A. Lorenz[1*], Shlomo Yeshurun[2], Richard Aziz[1], Julissa Ortiz-Delatorre[1], James R. Bagley[1], Merav Mor[2*], and Marialice Kern[1]**

[1]Exercise Physiology Laboratory, San Francisco State University, Department of Kinesiology, San Francisco, CA USA.

[2]Metaflow Ltd., Tel Aviv, Israel

*** Correspondence:**

Kent A. Lorenz

kalorenz@sfsu.edu

Merav Mor

merav@lumen.me

**Keywords:** Resting Metabolic Rate, Lumen®, ParvoMedics TrueOne® 2400, Validation, Respiratory Exchange Ratio, Metabolism, Fuel Utilization, Indirect Calorimetry

**Abstract**

*Objective:* To evaluate the validity of a novel hand-held device (Lumen®) for measuring metabolic fuel utilization in healthy young adults. *Background:* Metabolic carts measure the carbon dioxide produced and oxygen consumed from the breath in order to assess metabolic fuel usage (carbohydrates vs. fats). However, these systems are expensive, time-consuming, and only available in the clinic. A small hand-held device capable of measuring metabolic fuel via $CO_2$ was developed. *Approach:* Metabolic fuel usage was assessed in healthy participants (n = 33; age: 23.1 ± 3.9 y) via respiratory exchange ratio (RER) values from the "gold-standard" metabolic cart as well as $\%CO_2$ from the Lumen device. Measurements were performed at rest in two conditions, fasting, and after consuming 150 grams of glucose in order to determine changes in metabolic fuel. Major axis regression was performed as well as Bland-Altman plots and linear regressions to test for agreement between RER and Lumen $\%CO_2$. *Main results:* Both RER and Lumen $\%CO_2$ significantly increased after glucose intake compared with fasting conditions ($p < 0.0001$). Regression analyses and Bland-Altman plots revealed an agreement between the two measurements (mean bias = 3.505; limits of agreement = 2.784 - 4.226) with a fixed bias resulting from the nature of the different units. *Significance:* This study shows the validity of Lumen® to estimate metabolic fuel utilization in a comparable manner with the "gold-standard" metabolic cart, conveniently providing real-time metabolic information for users anywhere.

## 1 INTRODUCTION

Metabolic fuel is a well-known parameter which measures the body's fuel preference (carbohydrates vs. fats) for energy production. Respiratory quotient (RQ) is the ratio of carbon dioxide produced to oxygen consumed ($VCO_2/VO_2$) measured directly at the cellular level to estimate metabolic fuel utilization. However, this method requires the insertion of a catheter into the vein and artery for a blood sample or taking a tissue sample, which makes the RQ measurement invasive and infeasible outside of the laboratory (Brooks et al., 2019). With the use of a metabolic cart, an indirect measure of RQ can be made (indirect calorimetry). This is the respiratory exchange ratio (RER), which is currently the preferred method for determining metabolic fuel. Unlike RQ, RER measures the carbon dioxide produced ($VCO_2$) divided by the oxygen consumed ($VO_2$) from the breath (Benedict and Cathcart, 1913; Brooks et al., 2019). Both RQ and RER estimates the relative contribution of carbohydrate and lipids to overall energy expenditure (McClave et al., 2003). Though RER is not as invasive as the RQ, this method is time-consuming (taking up to 40 minutes) and is only available in laboratories as it requires professional technicians for both handlings and interpreting the system's output, which results on a very cumbersome and expensive technique.

As a result, metabolic carts are not used commonly for treatment or diagnostics purposes. Today, more than 10% of the US population suffer from diabetes, and it is estimated that over 80 million people in the US alone have prediabetes (Centers for Disease Control and Prevention, 2020). Metabolic flexibility (MF) is defined as the ability to easily switch between fuel sources when a glucose stimulant is introduced into the system (Goodpaster and Sparks, 2017). Metabolic inflexibility is a common feature of impaired fasting glycaemia and impaired glucose tolerance and is related to insulin resistance and type 2 diabetes (Færch and Vaag, 2011). Therefore, the development of a hand-held device that can be used by anyone, anytime, anywhere could be beneficial for those interested in their resting fuel utilization.

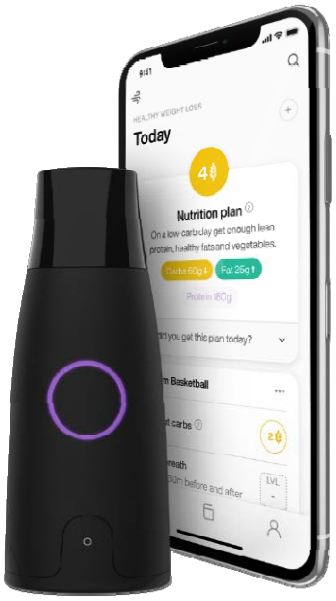


**Figure 1.** The Lumen® device and application

Metaflow Ltd. developed Lumen®, a novel metabolic fuel utilization breathalyzer that is a personalized hand-held device that provides metabolic status in real-time (Figure 1). The device measures indirect metabolic fuel dynamics via a $CO_2$ sensor and a flow meter, using a unique breathing maneuver and sophisticated algorithms. In this sense, Lumen is making personal, at home metabolic tracking available outside of research labs in order to change the way we approach weight loss, fitness and healthy nutrition decision making. This methodology is based on the fact that carbohydrate oxidation produces more carbon dioxide, relative to the consumption of oxygen, than fat oxidation. The unique breath maneuver enables quantifying those changes in $CO_2$ production allowing the user to estimate their metabolic state.

Pilot studies previously performed by Lumen (unpublished) showed the potential of Lumen to measure metabolic fuel usage accurately (in response to diet and exercise), and in a comparable manner with the "gold standard" metabolic cart. In this study, we set to evaluate whether the Lumen measurement is in agreement with the metabolic cart (RER) in healthy participants pre- and post-glucose consumption at rest and assess the difference between the

measurements.

## 2 METHODS

*Participants*

Forty-two healthy volunteers reported to the Exercise Physiology Laboratory in the Department of Kinesiology at San Francisco State University to participate in this study. To be included in the study, participants must have been between the ages of 18-45 years old; had a BMI less than 30 kg/m$^2$; not participated in high intensity aerobic exercise more than 3 days per week; not have any cardiovascular, pulmonary, and/or metabolic diseases; and must have an Apple or Android smartphone. If participants did not meet any of these criteria they were asked not to participate in the study. This study was approved by the University's Institutional Review Board for Human Subjects, and written informed consent was obtained from each participant before testing.

*Study Design*

Participants were recruited and their height and weight measured using a stadiometer and Seca scale (Seca, Hamburg, Germany). If they met the BMI criteria, they were provided their own Lumen device which was labeled with an identification number. Subsequently, the participants synchronized their Lumen device to their smartphone's corresponding application. Once synchronized, the participants practiced the Lumen breathing technique which was used for the remainder of the study. After the participant demonstrated competence in using the Lumen device, the participant took the device home where they used it for a minimum of 30 sessions, consisting of 3 breaths per session. After the minimum amount of breath sessions were met, participants were scheduled for the measurement day. The participants visited the metabolic laboratory between 07:00 a.m. and 11:00 a.m. after a 12-h fast and abstaining from any form of physical activity (other than walking) prior to completing the ventilated, open-circuit indirect calorimetry measurement.

On measurement day, participants arrived in a fasted state and blood glucose levels were measured from a sterile finger prick blood sample using a glucometer (OneTouch, LifeScan Inc. Milpitas, CA). They then completed two sessions of Lumen breaths (5-minute break between each session), and then laid supine on a padded examination table. A rigid plastic canopy with a comfortable, flexible seal was placed over their head and torso (for RER measurement). Once they finished the metabolic cart measurement, they moved back to a chair, and after relaxation were asked to complete another two sessions of Lumen breaths. Once finished, they were asked to drink 150 grams of glucose solution (separated in 3 drinks with 20 minutes intervals between each). After 45 minutes from the intake of the first drink (5 minutes after finished), their glucose levels were reassessed, and the subjects repeated the same procedure performed in the fasting state. Subjects were removed from the analysis if they were unable to finish all glucose drinks.

*Metabolic cart*

RER was analyzed using a calibrated TrueOne® 2400 metabolic cart (ParvoMedics, Murray, UT, USA). This system uses a paramagnetic oxygen analyzer and infrared carbon dioxide analyzer with a Rudolph heated pneumotach. The Parvo Medics system's pneumotach was warmed up for a minimum of 60 minutes each day before testing began in order to ensure accurate readings. The gas analyzers, flow rate, and volume were calibrated as per manufacturer's recommendations. To ensure quality control

between participants, gas analyzers were calibrated to < 0.1% standard gas and flow rate and volume were calibrated to ≤ 3% error. The ambient temperature was kept between 22 and 26°C, and humidity was maintained at roughly 60%. Once calibration was complete, the metabolic hood was placed over the participant's head and was tucked in around the head and torso area in order to ensure no air was escaping the hood. The participants were required to lay awake, and VE, $VCO_2$, $VO_2$ parameters were expressed as 30-s averages. For analysis purposes, the steady-state definition (denoted SS) was based on variations in the $VO_2$ and $VCO_2$ of ≤ 5% CV over a period of five consecutive minutes. Inability to meet this criterion resulted in removal from the analysis.

*Lumen*

During the measurement day, subjects took 2 sessions of 3 Lumen breaths before each metabolic cart measurement and 2 more after the metabolic cart measurement. Each Lumen session consisted of a breathing technique where participants inhaled steadily through the Lumen device followed by a 10 second hold of breath followed by a long steady exhale through the Lumen device. Each breath was separated by a 15 second rest period to allow the participant to relax. Each session was separated by a 5-minute rest period before the participant could begin their next session. Exclusion criteria included $\%CO_2 > 6$ or < 3, inhale volume > 3 liters, or inhale duration < 3 seconds.

*Statistical Analyses*

In order to evaluate the changes after glucose intake, two-tailed paired t-test was performed in order to compare blood glucose levels, RER levels, and Lumen %CO2 before and after glucose intake.

Major axis regression ('Deming's method') was performed in order to compare RER of the metabolic cart and $\%CO_2$ from the Lumen device (Brace, 1977). As RER and %CO2 are in different units, the analysis is identical to ordinary least product regression, which is the most suitable analysis for comparison between two methods of measurement (Ludbrook, 2010). Moreover, Bland-Altman plot was created to demonstrate limits of agreement, together with a linear regression to test the distribution of error terms to identify if any systematic bias existed within Lumen and RER measures. In addition, a simple linear regression was performed to determine the ability to predict Lumen values from the gold-standard value of RER.

Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software Inc., LA Jolla, CA). The threshold for significance was set at $p < 0.05$.

## 3 RESULTS

From the original fifty-four subjects recruited, only forty-two healthy volunteers were measured in the study (Figure 2). However, thirty-three were used for the final analysis, as nine were removed since they failed to meet the inclusion criteria as detailed in the methods section: one subject was unable to consume all glucose drinks, in three subjects there was inability to find 5 min with CV < 5% in RER, and in five subjects, results from the Lumen device could not be interpreted (Figure 2). Characteristics of the final participants are presented in Table 1.

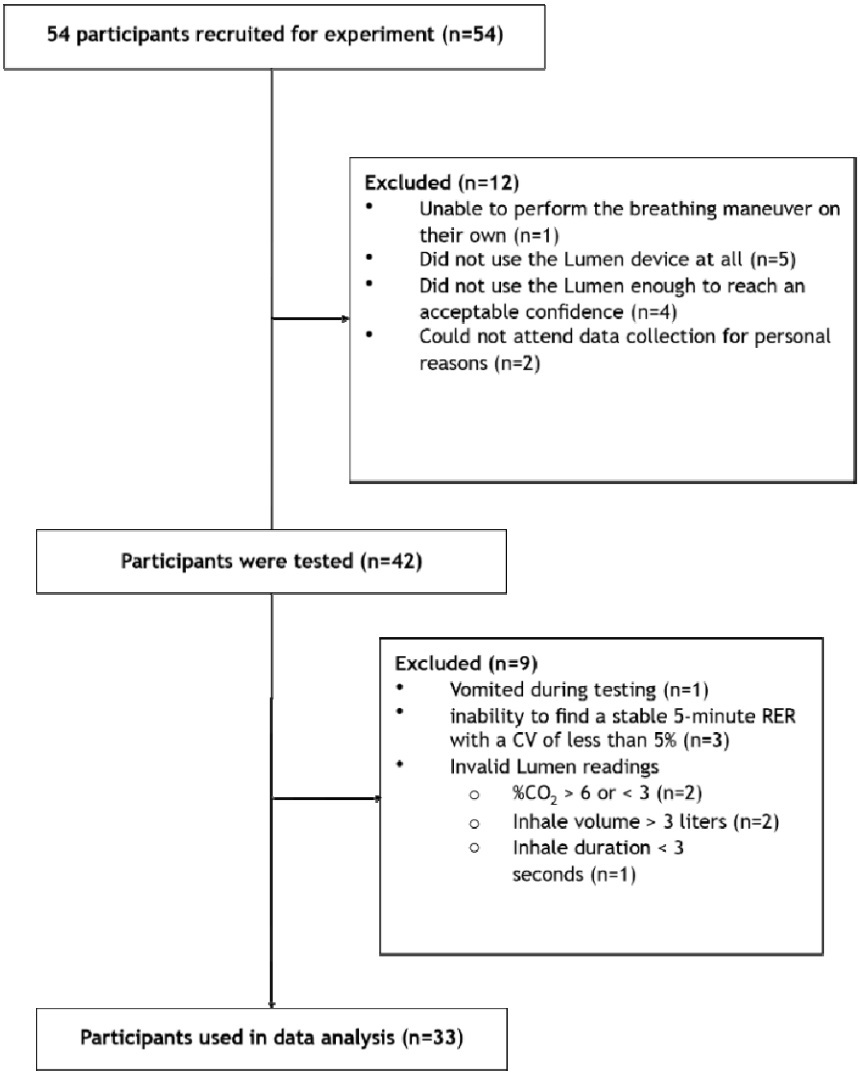


**Figure 2.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

**Table 1. Descriptive statistics of study's participants.**

| Gender | Count | Age (years) | Weight (kg) | Height (cm) | BMI (kg/m2) |
|---|---|---|---|---|---|
| Male | 17 | 24.0 ± 3.0 | 73.7 ± 10.2 | 171.7 ± 7.8 | 24.9 ± 2.5 |
| Female | 16 | 22.3 ± 4.5 | 59.1 ± 6.4 | 160.9 ± 5.5 | 22.9 ± 2.6 |
| Total | 33 | 23.1 ± 3.9 | 66.2 ± 11.1 | 166.1 ± 8.6 | 23.9 ± 2.7 |

Data are presented as mean ± SD.

As expected, blood glucose levels increased from 90.6 ± 9.2 mg/dL to 145.2 ± 25.3 mg/dL as a result of glucose intake ($t_{(32)}$ = 11.04, $p$ < 0.0001; Figure 3A). RER levels were also elevated from 0.787 ± 0.043 to 0.876 ± 0.053 in response to glucose ($t_{(32)}$ = 10.84, $p$ < 0.0001; Figure 3B). Moreover, Lumen %$CO_2$ concentrations significantly rose from 4.2 ± 0.4 to 4.48 ± 0.34 as well ($t_{(32)}$ = 5.978, $p$ < 0.0001; Figure 3C).

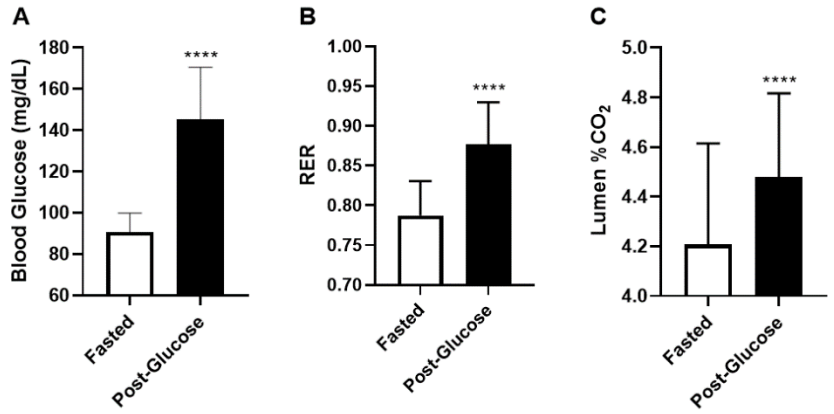


**Figure 3.** Increased levels of (A) blood glucose, (B) RER, (C) Lumen %CO2, after glucose intake. Data is presented as mean ± SD. ****p < 0.0001. n = 33 for each condition.

In order to look for agreement between RER units from the metabolic cart and %$CO_2$ from Lumen, reduced major axis regression was performed (Ludbrook, 1997). It revealed a significant relationship between RER and Lumen %$CO_2$ ($F_{(1,63)}$ = 18.54, $p$ < 0.0001, y = 6.111x - 0.7445; Figure 4), with a fixed but not proportional bias, as expected from the nature of the different units (x-intercept = 0.1218).

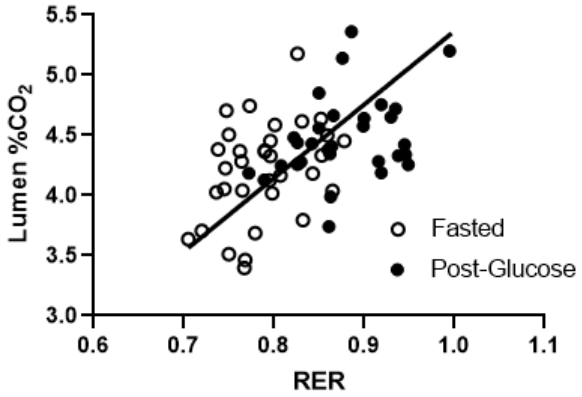


**Figure 4.** Reduced major axis regression of RER from the metabolic cart and Lumen's %CO2 measurements for metabolic activity. n = 33 for each condition.

A Bland-Altman plot was done to discuss limit of association (Giavarina, 2015) between RER and Lumen %$CO_2$. Bland-Altman plots are used to calculate the level of agreements between two measures by studying the mean difference between measurements and constructing limits of agreement (Bland and Altman, 1986). Bland-Altman analysis revealed a mean difference between RER units and Lumen %$CO_2$ of 3.505 with 95% limits of agreement from 2.784 to 4.226 (Figure 5). Since the Lumen device always

provides a measurement that is numerically greater than RER, Lumen measurements with smaller values should produce smaller differences and larger Lumen values will produce larger differences. However, the slope of the line indicates this bias is consistent across the range of Lumen and RER values. To test the bias in measurements a regression of difference (Lumen $\%CO_2$ – RER) scores on average ((Lumen $\%CO_2$ + RER)/2) values was performed. Simple linear regression showed that bias was consistent, with a significant model effect ($F_{(1,63)} = 721$, $p < 0.0001$, $R^2 = 0.9196$).

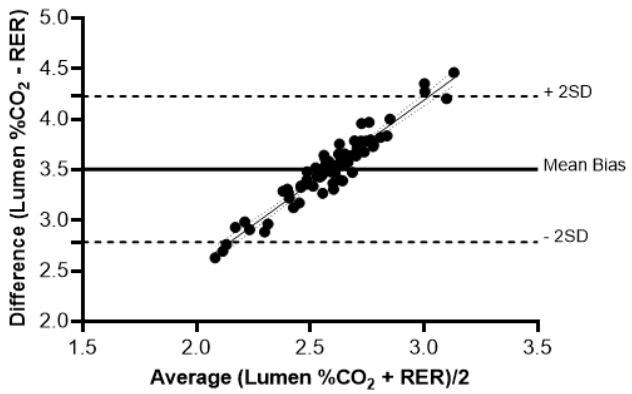


**Figure 5.** Bland-Altman analysis with simple linear regression. The solid line represents the mean bias between the Lumen %CO2 and RER. The upper and lower dashed lines represent the 95% confidence intervals (±2 SD) from the mean bias. Linear regression line: y = 1.646*x - 0.7472. n = 33 for each condition.

To determine the ability of RER to predict Lumen $\%CO_2$, an OLS regression was performed to estimate Lumen values from RER measures, with the assumption that RER is an accurate measure. With RER as the independent variable, we used simple linear regression to predict Lumen $\%CO_2$, and a significant model effect was present ($F_{(1,63)} = 18.54$, $p < 0.0001$, $R^2 = 0.2274$; Figure 6). The RER parameter estimate indicated that for every one-unit increase in RER, a 2.914-unit increase ($SE = 0.6767$) in Lumen $\%CO_2$ is expected. However, since a full unit increase in RER is not a plausible outcome, this parameter estimate can be interpreted similarly by saying a 0.1-unit increase in RER (e.g., 0.7 to 0.8) will produce a 0.2914-unit increase in Lumen $\%CO_2$.

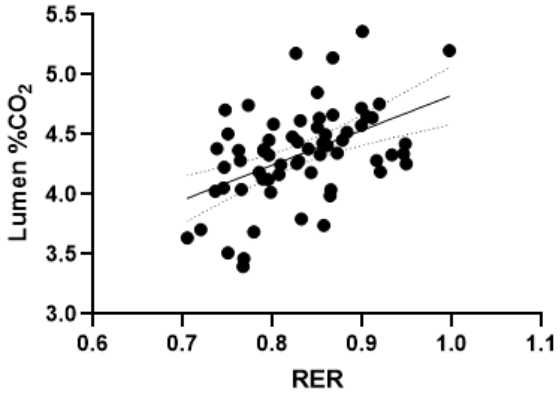


**Figure 6.** Ordinary least squared regression of RER as the independent variable and Lumen as the dependent variable. n = 33 for each condition.

## 4 DISCUSSION

This study evaluated the capability of the Lumen device to assess changes in the body's metabolic fuel utilization, as compared to the gold standard, indirect measurement using a metabolic cart in healthy young adults. Our results show that Lumen %$CO_2$ levels are in agreement with RER values from the metabolic cart, which correspond to relative changes in metabolic fuel utilization.

Both Lumen %$CO_2$ and RER showed significant increases in their levels, as a result of glucose intake in healthy individuals at rest (Figure 3). These results were expected as cells using carbohydrates as fuel produce more carbon dioxide relative to the oxygen consumption than cells metabolizing fat. The ratio between the $CO_2$ production and the $O_2$ consumption in this process is known as respiratory quotient (RQ) or RER. RQ/RER changes depending on the energy source of the cell (carbohydrate vs. fat), and the two are commonly used interchangeably (Benedict and Cathcart, 1913; McClave et al., 2003; Brooks et al., 2019). In resting conditions, oxygen consumption does not change dramatically (Spurr et al., 1988; Green, 2011), meaning that subject's changes in the RQ will generally be represented by changes in $CO_2$ production. This understanding is the basic principle underlying Lumen's approach which enables it to track changes metabolic fuel utilization. Therefore, it was important to make sure that the participants in this study were at rest before taking their measurements.

Major axis regression revealed an agreement between RER and Lumen %$CO_2$ in two metabolic states (Figure 4). The Bland-Altman plot showed a mean bias of 3.505, with a significant linear model of difference scores compared to mean values, which enabled the investigators to understand the agreement between the two methods despite measuring in different units (Figure 5). These results demonstrated the capability of Lumen to provide comparable results to the metabolic cart in assessing the metabolic fuel utilization. This is due to several sophisticated algorithms in the backlog of the device's application, including the breath holding technique, which enables it to achieve a single and accurate measurement of the $CO_2$ production (Tsoukias et al., 1998).

Evidence suggests that the assessment of RER can be a benefit for multiple conditions, such as nourishing, diabetes prevention, weight management, physical activity, and healthy lifestyle (Ferrannini, 1988; Ramos-Jiménez et al., 2008). It has previously been shown that RER could be a prognostic marker of weight loss and a predictor of weight gain (Zurlo et al., 1990; Valtueña et al., 1997). Moreover, minute-by-minute RER corresponded directly to intensity of exercise, and slopes of RER were different in response to different dietary treatments (Gribok et al., 2016). However, although RER is currently the preferred method for determining metabolic fuel, it is a costly, time consuming, uncomfortable and an impractical tool for assessing metabolic activity over time and for real time decisions. In contrast, the Lumen device is small, relatively cheap, mobile, specific to the user, delivers the outcome immediately to the user and enables taking real time decisions.

In healthy subjects, normal physiology is characterized by diurnal oscillations in whole-body RER which is the reflection of a metabolically flexible state in which mitochondria switches from carbohydrate to fat oxidation according to dietary intake and also to the demand of different metabolic states, like fasting or high-intensity workouts (Hurni et al., 1982; Malin et al., 2013). Kelly and collogues in 1999 discovered that there was a difference in metabolic fuel utilization (fat and glucose) between healthy non-diabetic patients and obese non-diabetic patients. They termed the ability to respond or adapt to conditional changes in metabolic demand as metabolic flexibility (MF) (Kelley et al., 1999).

MF is the capacity to switch from predominantly lipid oxidation and high rates of fatty acid uptake during fasting conditions to the suppression of lipid oxidation and increased glucose uptake, oxidation, and storage under insulin-stimulated conditions (Kelley and Mandarino, 2000). Galgani, Moro and Ravussin (2008), showed a negative correlation (r=-0.41) between resting RER and MF, illuminating high MF individuals have a lower resting RER, and those that are metabolically inflexible, have a higher resting RER (Galgani et al., 2008). Today, it is believed that MF is a precondition for developing insulin resistance. RER at a fasting state and in response to glucose loading can be used to diagnose people with insulin resistance in the early stages (Galgani et al., 2008).Due to the association of MF as a precursor to the development of type 2 diabetes, researchers have found common mechanistic links between those that are metabolically inflexible and those that are obese and or have developed type 2 diabetes (Ukropcova et al., 2007; Malin et al., 2013; Begaye et al., 2020). A decrease in the ability to utilize fat and glucose stems from changes in muscle fiber type, decreased mitochondrial function, and dysregulation of fat storage and transportation (Muoio, 2014; Smith et al., 2018). In order to achieve improved metabolic health, Lumen adapts daily macronutrients recommendations according to the users fasting measurements and generates a specific recommendation for achieving better metabolic flexibility.

**Limitations**

This study is the first to show agreement between Lumen %$CO_2$ and RER. However, it is important to note that participants in this study were relatively young (mean age: 22.4 y) and healthy, which can be unrepresentative of other groups. Results from the metabolic cart can be altered with increasing age (Riera and Dillin, 2015). Therefore, future studies will need to examine whether RER levels correspond to Lumen levels in older subjects and those with metabolic conditions (e.g., pre-diabetes and type 2 diabetes). Furthermore, the results from the simple linear regression predicting Lumen %$CO_2$ using RER values, suggest that while there is measurement agreement between the Lumen %$CO_2$ and RER, the proportion of explained variance remains low. Thus, Lumen can be seen to be an effective instrument for monitoring relative, individual changes in metabolic responses (within-subject consistency), rather than a substitute for laboratory-grade RER measurements (between-subject precision).

In addition, our results show high peak of blood glucose levels 45 minutes after glucose intake (5 minutes after the third drink), whereas both RER and Lumen %$CO_2$ showed moderate despite significant increase in levels. Therefore, it is possible that the metabolic cart and Lumen measurements were performed too early, before their peak can be observed, since the glucose intake has not been fully metabolized yet (Eyth et al., 2019).

**Conclusions**

In summary, Lumen® can provide valid information regarding an individual's metabolic state. This corresponds with results from metabolic cart, but unlike the metabolic cart, can be performed anywhere and by anyone, without the need for a special clinic, equipment, and technicians. Lastly, the capability of taking these measurements continuously, can provide numerous insights about the metabolic state of an individual, as well the additional valuable information for our scientific knowledge about metabolic flexibility and nutrition.

**Conflict of Interest**

SY and MM are employees of Metaflow Ltd., and contributed to the design and analysis of the study as well as the preparation of the manuscript. The other authors declare that they have no competing interests.

**Ethics Statement**

This study was approved by the University's Institutional Review Board for Human Subjects, and written informed consent was obtained from each participant before testing.

**Author Contributions**

KAL analyzed the data and prepared the manuscript

SY analyzed the data and prepared the manuscript

RA coordinated the project and collected the data

JO coordinated the project and collected the data

JRB reviewed and edited the manuscript

MM conceived, designed, and supervised the study as well as reviewed and edited the manuscript

MK conceived, designed, and supervised the study as well as reviewed and edited the manuscript

All authors approved the manuscript before submission

**Funding**

This work was supported by Metaflow Ltd.

**Abbreviations**

RQ - Respiratory Quotient

RER - Respiratory Exchange Ratio

MF – Metabolic Flexibility

**Acknowledgements**

We would like to thank the participants for their time in taking part in this study, and the Lumen® team for their support.

## 5 REFERENCES


Begaye, B., Vinales, K. L., Hollstein, T., Ando, T., Walter, M., Bogardus, C., et al. (2020). Impaired metabolic flexibility to high-fat overfeeding predicts future weight gain in healthy adults. *Diabetes* 69, 181–192. doi:10.2337/db19-0719.

Benedict, F. G., and Cathcart, E. P. (1913). *Muscular Work, a Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine.* Carnegie institution of Washington.

Bland, M. J., and Altman, D. G. (1986). Statistical Methods for Assessing Agreement Between Two Methods of Clinical Measurement. *Lancet* 327, 307–310. doi:10.1016/S0140-6736(86)90837-8.

Brace, R. A. (1977). Fitting straight lines to experimental data. *Am. J. Physiol.* 233.

Brooks, G. A., Fahey, T. D., and Baldwin, K. M. (2019). *Exercise physiology: human bioenergetics and its applications.* Independently Published.

Centers for Disease Control and Prevention (2020). National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States. *US Dep. Heal. Hum. Serv.*, 2020.

Eyth, E., Basit, H., and Smith, C. J. (2019). *Glucose Tolerance Test*. StatPearls Publishing.

Færch, K., and Vaag, A. (2011). Metabolic inflexibility is a common feature of impaired fasting glycaemia and impaired glucose tolerance. *Acta Diabetol.* 48. doi:10.1007/s00592-010-0245-x.

Ferrannini, E. (1988). The theoretical bases of indirect calorimetry: A review. *Metabolism* 37, 287–301. doi:10.1016/0026-0495(88)90110-2.

Galgani, J. E., Moro, C., and Ravussin, E. (2008). Metabolic flexibility and insulin resistance. *Am. J. Physiol. - Endocrinol. Metab.* 295, 1009–1017. doi:10.1152/ajpendo.90558.2008.

Giavarina, D. (2015). Understanding Bland Altman Analysis. *Biochem. Medica* 25, 141–51. doi:10.11613/BM.2013.003.

Goodpaster, B. H., and Sparks, L. M. (2017). Metabolic Flexibility in Health and Disease. *Cell Metab.* 25. doi:10.1016/j.cmet.2017.04.015.

Green, J. A. (2011). The heart rate method for estimating metabolic rate: Review and recommendations. *Comp. Biochem. Physiol. - A Mol. Integr. Physiol.* 158, 287–304. doi:10.1016/j.cbpa.2010.09.011.

Gribok, A., Leger, J. L., Stevens, M., Hoyt, R., Buller, M., and Rumpler, W. (2016). Measuring the short-term substrate utilization response to high-carbohydrate and high-fat meals in the whole-body indirect calorimeter. *Physiol. Rep.* 4. doi:10.14814/phy2.12835.

Hurni, M., Burnand, B., Pittet, P., and Jequier, E. (1982). Metabolic effects of a mixed and a high-carbohydrate low-fat diet in man, measured over 24 h in a respiration chamber. *Br. J. Nutr.* 47, 33–43. doi:10.1079/bjn19820006.

Kelley, D. E., Goodpaster, B., Wing, R. R., and Simoneau, J. A. (1999). Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. *Am. J. Physiol. - Endocrinol. Metab.* 277. doi:10.1152/ajpendo.1999.277.6.e1130.

Kelley, D. E., and Mandarino, L. J. (2000). Fuel selection in human skeletal muscle in insulin resistance: A reexamination. *Diabetes* 49, 677–683. doi:10.2337/diabetes.49.5.677.

Ludbrook, J. (1997). Comparing measurment methods. *Clin. Exp. Pharmacol. Physiol.* 24, 193–203.

Ludbrook, J. (2010). Linear regression analysis for comparing two measurers or methods of measurement: But which regression? *Clin. Exp. Pharmacol. Physiol.* 37, 692–699. doi:10.1111/j.1440-1681.2010.05376.x.

Malin, S. K., Haus, J. M., Solomon, T. P. J., Blaszczak, A., Kashyap, S. R., and Kirwan, J. P. (2013). Insulin sensitivity and metabolic flexibility following exercise training among different obese insulin-resistant phenotypes. *Am. J. Physiol. - Endocrinol. Metab.* 305, 1292–1298. doi:10.1152/ajpendo.00441.2013.

McClave, S. A., Lowen, C. C., Kleber, M. J., McConnell, J. W., Jung, L. Y., and Goldsmith, L. J. (2003). Clinical use of the respiratory quotient obtained from indirect calorimetry. *J. Parenter. Enter. Nutr.* 27, 21–26. doi:10.1177/014860710302700121.

Muoio, D. M. (2014). Metabolic inflexibility: When mitochondrial indecision leads to metabolic gridlock. *Cell* 159, 1253–1262. doi:10.1016/j.cell.2014.11.034.

Ramos-Jiménez, A., Hernández-Torres, R. P., Torres-Durán, P. V., Romero-Gonzalez, J., Mascher, D., Posadas-Romero, C., et al. (2008). The Respiratory Exchange Ratio is Associated with Fitness Indicators Both in Trained and Untrained Men: A Possible Application for People with Reduced Exercise Tolerance. *Clin. Med. Circ. Respirat. Pulm. Med.* 2, CCRPM.S449. doi:10.4137/ccrpm.s449.

Riera, C. E., and Dillin, A. (2015). Tipping the metabolic scales towards increased longevity in mammals. *Nat. Cell Biol.* 17, 196–203. doi:10.1038/ncb3107.

Smith, R. L., Soeters, M. R., Wüst, R. C. I., and Houtkooper, R. H. (2018). Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. *Endocr. Rev.* 39, 489–517. doi:10.1210/er.2017-00211.

Spurr, G. B., Prentice, A. M., Murgatroyd, P. R., Goldberg, G. R., Reina, J. C., and Christman, N. T. (1988). Energy expenditure from minute-by-minute heart-rate recording: Comparison with indirect calorimetry. *Am. J. Clin. Nutr.* 48, 552–559. doi:10.1093/ajcn/48.3.552.

Tsoukias, N. M., Tannous, Z., Wilson, A. F., George, S. C., Nikolaos, M., Tannous, Z., et al. (1998). Single-exhalation profiles of NO and CO 2 in humans: effect of dynamically changing flow rate. *J. Appl. Physiol.* 85, 642–652.

Ukropcova, B., Sereda, O., De Jonge, L., Bogacka, I., Nguyen, T., Xie, H., et al. (2007). Family history of diabetes links impaired substrate switching and reduced mitochondrial content in skeletal muscle. *Diabetes* 56, 720–727. doi:10.2337/db06-0521.

Valtueña, S., Salas-Salvadó, J., and Lorda, P. G. (1997). The respiratory quotient as a prognostic factor in weight-loss rebound. *Int. J. Obes.* 21, 811–817. doi:10.1038/sj.ijo.0800480.

Zurlo, F., Lillioja, S., Puente, A. E. D., Nyomba, B. L., Raz, I., Saad, M. F., et al. (1990). Low ratio of fat to carbohydrate oxidation as predictor of weight gain: Study of 24-h RQ. *Am. J. Physiol. - Endocrinol. Metab.* 259. doi:10.1152/ajpendo.1990.259.5.e650.