Clinical Therapeutics/Volume xxx, Number xxx, 2022

Original Research

An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation

Koichiro Shinozaki, MD, PhD[1,2,3]; Pey-Jen Yu, MD[4]; Qiuping Zhou, DO[5]; Hugh A. Cassiere, MD[6]; John Stanley, MHA, RT[6]; Daniel M. Rolston, MD, MSHPM[2,3]; Nidhi Garg, MD[2,7]; Timmy Li, PhD[2,3]; Jennifer Johnson, BA[3]; Kota Saeki, MEng[1,8]; Taiki Goto, MBE[9]; Yu Okuma, MD, PhD[1]; Santiago J. Miyara, MD, PhD[1]; Kei Hayashida, MD, PhD[1]; Tomoaki Aoki, MD, PhD[1]; Vanessa Wong, BS[1]; Ernesto P. Molmenti, MD[1,10]; Joshua W. Lampe, PhD[1,11]; and Lance B. Becker, MD, FAHA[1,2,3]

[1]The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York; [2]Department of Emergency Medicine, Zucker School of Medicine at Hofstra/Northwell, New York, New York; [3]Department of Emergency Medicine, North Shore University Hospital, Manhasset, New York; [4]Department of Cardiothoracic Surgery, North Shore University Hospital, Manhasset, New York; [5]Division of Critical Care Medicine of Emergency Medicine, Long Island Jewish Medical Center, New Hyde Park, New York; [6]Division of Critical Care Medicine, Department of Medicine, North Shore University Hospital, Manhasset, New York; [7]Department of Emergency Medicine, South Shore University Hospital, Bay Shore, New York; [8]Nihon Kohden Innovation Center, Cambridge, Massachusetts; [9]Nihon Kohden Corporation, Tokyo, Japan; [10]Department of Surgery, Medicine, and Pediatrics, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; and [11]ZOLL Medical, Chelmsford, Massachusetts

ABSTRACT

Purpose: To develop a system that is equivalent to the gold standard Douglas Bag (DB) technique for measuring oxygen consumption ($V\dot{}O_2$), carbon dioxide generation ($V\dot{}CO_2$), and respiratory quotient (RQ) and to validate its use in clinical settings.

Methods: This was a prospective, observational study conducted at a suburban, quaternary care teaching hospital. Healthy volunteers and patients 18 years or older who received mechanical ventilation were enrolled.

Findings: Data from 3 healthy volunteers and 7 patients were analyzed in this study. The interrater reliability between the automation device and DB methods were 0.999, 0.993, and 0.993 for $V\dot{}O_2$, $V\dot{}CO_2$, and RQ, respectively. In healthy volunteers, mean (SD) $V\dot{}O_2$, $V\dot{}CO_2$, and RQ measured by DB were 411 (100) mL/min, 288 (79) mL/min, and 0.70 (0.03) at high fraction of inspired oxygen (FiO_2) and 323 (46) mL/min, 280 (45) mL/min, and 0.85 (0.05) at normal FiO_2, respectively. $V\dot{}O_2$ was significantly higher ($P < 0.05$) and RQ was lower ($P < 0.01$) in the high FiO_2 group as compared to those in the normal FiO_2 group. Values measured by the automation system were 227 (31) mL/min, 141 (18) mL/min, and 0.62 (0.04) at high FiO_2 and 209 (25) mL/min, 147 (18) mL/min, and 0.70 (0.06) at normal FiO_2, respectively. RQ was significantly lower ($P < 0.05$) in the high FiO_2 group as compared to the normal FiO_2 group. We also successfully performed continuous and repeat measurements by using the device. The

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

longest measurement reached 12 hours 15 minutes, including 50 cycles of repeat measurements that are equivalent to the DB technique as described above.

Implications: We developed an automation system that enables repeat measurements of $V\dot{O}_2$, $V\dot{C}O_2$, and RQ, and the accuracy was equivalent to the DB technique. High FiO_2 may decrease RQ because of an increase in $V\dot{O}_2$. (*Clin Ther.* 2022;000:1–9.)

Keywords: carbon dioxide generation, Douglas bag, indirect calorimetry, oxygen consumption, respiratory quotient.

INTRODUCTION

Oxygen consumption ($V\dot{O}_2$) and carbon dioxide generation ($V\dot{C}O_2$) are important measures of metabolism in humans,[1,2] and the respiratory quotient (RQ), which is defined as the ratio of $V\dot{C}O_2$ to $V\dot{O}_2$, can be used as a clinical parameter of a patient's metabolism.[3] These measurements are widely used for patients with a variety of conditions, including postsurgery conditions,[1] shock,[4] pulmonary and cardiac diseases,[5] and critical illness requiring mechanical ventilation.[2,6,7] Indirect calorimetry is a noninvasive method of measuring metabolism in which $V\dot{O}_2$ and $V\dot{C}O_2$ are measured by concentrations of oxygen and carbon dioxide in inhalation and exhalation.[8–10] Because it is noninvasive, indirect calorimetry has been widely used in clinical settings[11,12] and translational research.[13–16] However, because of the lack of a gold standard, its accuracy has been questioned for a long time.[6,7,17]

One of the reference standards is the Douglas Bag (DB) collection technique that has been routinely used for >100 years.[17,18] The central focus of this method is the accuracy of gas concentrations in inhalation and exhalation. Errors of $V\dot{O}_2$, $V\dot{C}O_2$, and RQ are propagated when the concentrations of oxygen and/or carbon dioxide are uncertain, particularly when a higher oxygen concentration, such as 100% oxygen, is used.[10,16] The DB technique is a method using collection bags that contain a sample gas for a period to equilibrate the gas concentrations inside the bag. The DB technique becomes a gold standard, especially when measuring a gas concentration that changes dynamically over time. The concentrations of oxygen and carbon dioxide in exhalation have a dynamic change within a breath and are fluctuant every time. Therefore, the DB technique allows for reliable values when the accuracy of $V\dot{O}_2$, $V\dot{C}O_2$, and RQ is in need.[17]

Humidity is the other critical component that affects accuracy of the gas concentration in exhalation. Humidity not only affects the volume and concentration of a sample gas but can also interfere with the performance of gas sensors. We applied a method that reduced the humidity to approximately zero and measured the concentrations of oxygen and carbon dioxide in inhalation and exhalation of humans, who received mechanical ventilation. We first validated our method compared with the DB technique and developed an automation system to translate the measurements into a clinical setting. To the best of our knowledge, this is the first study that applied repeat measurements of $V\dot{O}_2$, $V\dot{C}O_2$, and RQ by using a method equivalent to the DB technique, and we report the results of continuous metabolic measurements in patients receiving mechanical ventilation.

MATERIALS AND METHODS

Study Design

This prospective, observational study was conducted at a suburban, quaternary care teaching hospital. Healthy volunteers and patients 18 years or older who received mechanical ventilation were enrolled. The study protocol was approved by the North Shore University Hospital Institutional Review Board. Informed consent for participation was obtained from volunteers, patients, or next of kin before the procedures. If a patient did not hold a capacity for consent or did not have a legally authorized representative or next of kin, the patient was enrolled with waived consent. We excluded patients whose positive end-expiratory pressure was >10 cm H_2O owing to a predicted gas leak from the mechanical ventilation circuit. Our method and calculation algorithm enabled measurements of $V\dot{O}_2$,

Accepted for publication September 5, 2022
https://doi.org/10.1016/j.clinthera.2022.09.004
0149-2918/$ - see front matter

$V^{\cdot}CO_2$, and RQ at a variety range of fraction of inspired oxygen (FiO_2)[19]; therefore, no upper limit was made on an FiO_2 setting of the mechanical ventilation.

DB COLLECTION

Ten minutes were given to all patients and volunteers for acclimating to the apparatus before starting a measurement. For the measurements of $V^{\cdot}O_2$, $V^{\cdot}CO_2$, and RQ, inhalation and exhalation were separately collected, and the concentrations of oxygen and carbon dioxide were measured. A commercially available gas analyzer (GF-210R Multi-Gas Module, Nihon Kohden Corporation) was used. The gases were sampled from a mechanical ventilator (AVEA ventilator, CareFusion). Healthy volunteers breathed via mechanical ventilator through a sealed face mask or a mouthpiece plus nose clip. We provided enough time for the volunteers to rely on the ventilator and to breathe through the ventilator circuit. The sample gases (inhalation and exhalation) were collected into 2 bags (4 L, polyvinylidene fluoride gas collection bag, Cole-Parmer, and 50 L, polyvinyl chloride gas collection bag, Harvard Apparatus, respectively). Because the inhalation gas was a mixture gas of air and oxygen, the humidity of inhalation was zero. However, because the exhalation included humidity generated from individuals, to reduce the humidity level, we placed the 50-L bag in a freezer and lowered the temperature of exhalation gas to $<-20°C$. The humidity of the collected gas, when it went into the gas analyzer, became ab underdetectable level. The humidity was measured for each experiment by a hygrometer (Ebro TFH620 Compact Thermohygrometer, Cole-Parmer) that was attached to the gas analyzer. Ventilation settings of the patients and volunteers, including a minute ventilation volume of exhalation, inhalation to exhalation ratio, leak rate, and bias flow, were recorded simultaneously with the gas collection. A bias flow of the ventilator circuit was adjustable at a range of 0.4 to 5.0 L/min. A default setting of the bias flow was 2.0 L/min, and so most cases had the bias flow at 2.0 L/min. A detailed calculation algorithm for $V^{\cdot}O_2$, $V^{\cdot}CO_2$, and RQ is described in eAppendix I.

A 4-L clear-soft bag was used for the collection of the inhalation gas, and a 50-L polyvinyl chloride bag was used for the exhalation gas. Both materials were known to exert low permeability to oxygen, carbon dioxide, and humidity. A sampling adaptor was inserted inside the ventilator circuit to collect the inhalation gas. The connector was placed 4 in from a Y piece connector attached to the patient's endotracheal tube or volunteer's face mask. The inhalation gas was collected to the bag by opening a valve, and a cross clump was used to adjust the gas flow. The goal of a flow rate was 200 to 300 mL/min, and it was adjusted by monitoring the ventilator. We titrated the flow based on a leak rate that did not exceed 3% of the minute ventilation volume, which was normally 7 to 10 L/min. All connections were tightly sealed, and the leakage was confirmed zero before the gas collection. Therefore, the detected leakage was only for the collection of inhalation to the bag. We collected the exhalation gas by connecting the bag directly to the exhaust port of the mechanical ventilator, meaning we collected the whole exhalation gas over a period when a volunteer or patient was breathing. The valves of the collection bags for inhalation and exhalation were opened simultaneously, and the gases were collected for approximately 5 to 7 minutes until the bags were 80% filled. The temperature, humidity, and atmospheric pressure were recorded during the gas collection.

Automation System

The DB collection method is the gold standard; however, it allows for a point measurement. Because of an unmet need for continuous and repeat measurements, we developed an automation system that follows the same methodologic principle of the aforementioned DB collection technique. The same gas analyzer was used to measure the concentrations of oxygen and carbon dioxide. The measurement was performed at the bedside, which enabled a real-time and continuous collection of data. The sampling adaptor was inserted inside the ventilator circuit to collect the inhalation gas. The connector was placed 4 in from a Y piece connector attached to the patient's endotracheal tube or the volunteer's face mask. The inhalation gas was collected at a flow rate of 200 mL/min. The flow was regulated by the gas analyzer. A dehumidification device (DHU-1000 Dehumidification Unit, Nihon Kohden Corporation) was set in conjunction with the gas analyzer: the dehumidification unit was intended for use in dehumidifying a sample gas. This unit included switching valves to select a gas sample from inhalation or exhalation. A 100-mL mixing chamber was attached to the exhaust port. This chamber was

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

engineered for partial sampling of exhalation that is equivalent to the whole-gas collection technique, and its performance was validated in a separate setting of experiments (eAppendix II). eAppendix II includes (1) validation data for a system response time, (2) sensor accuracy of gas concentrations, (3) the performance of mixing chamber, and (4) the calculation algorithm of our automation system.

Calculations and Analysis

Fio_2, fraction of expired oxygen (Feo_2), fraction of inspired carbon dioxide ($Fico_2$), fraction of expired carbon dioxide ($Feco_2$), in-circuit humidity and temperature in the dehumidification device, and ambient pressure and temperature around the mechanical ventilator circuit were measured. A minute ventilation volume of exhalation (V_E), inhalation to exhalation ratio, and bias flow setting were recorded from the mechanical ventilator. For the automation system, Feo_2 and $Feco_2$ were calculated from the gas concentrations measured at the ventilator exhaust port. The gas concentrations of inhalation and exhalation were measured alternately, and the duty cycle was 15 minutes. The inhalation gas was measured for the first 6 minutes of the duty cycle, and the exhalation was for the next 9 minutes. During the inhalation phase, the initial 4 minutes of the data were disregarded, and the latter 2 minutes of the data were averaged as Fio_2 and $Fico_2$. A valve switched the sampling port from inhalation to exhalation; the initial 4 minutes of the data for exhalation were disregarded, and the last 5 minutes of the data were used as Feo_2 and $Feco_2$. The data were collected every 1 minute during the exhalation phase, and the total 5 measurements were averaged. If there was a significant change in Fio_2 within a duty cycle, the value was excluded from our analysis. The time series of Fio_2 was calculated from the values of pre- and post- Fio_2. The equations used in this study are as follows:

$$R = V_I/V_E \quad (1)$$

$$Vo_2 = V_I \times Fio_2 - V_E \times Feo_2 \quad (2)$$

$$Vco_2 = V_E \times Feco_2 - V_I \times Fico_2 \quad (3)$$

where V_I is a minute ventilation volume of inspiration and V_E is that of expiration. $Fico_2$ is zero because the inspiration gas does not contain CO_2. The RQ, $\dot{V}O_2$, and $\dot{V}CO_2$ are then transformed to the following equations:

$$Vo_2 = (R \times Fio_2 - Feo_2) \times V_E \quad (4)$$

$$Vco_2 = Feco_2 \times V_E \quad (5)$$

$$RQ = Vco_2/Vo_2 \quad (6)$$

R is generally derived from a transformation of the Haldane equation with the assumption that nitrogen is neither produced nor retained by the body and that no gases are present other than oxygen, carbon dioxide, and nitrogen.[20] Because the denominator includes Fio_2 and it goes to zero as Fio_2 increases to 1.0, R increases to an infinite number when Fio_2 is 1.0. Therefore, the Haldane transformation limits Fio_2 generally up to 0.6. This is a significant limitation in critical care medicine in which patients normally require higher Fio_2. Therefore, we developed a method for measuring R and sought the number of R by using our rodent model.[19] Our results suggest that R was not 1.0, and so V_I was not equal to V_E. Although our result was in line with the concept of the Haldane transformation suggesting $V_I \neq V_E$, the data from our report supported that R might be a constant in lieu of a dependent variable affected by Fio_2. Our results from the rodent model indicate that the mean (SD) R was 1.0081 (0.0017) at an Fio_2 of 0.3 and 1.0092 (0.0029) at an Fio_2 of 1.0. In this study, we determined human R as 1.0097 calculated from the values obtained from previous human studies[20,21] and determined it as 1.0097 in this study (Appendix III).

Statistical Analysis

We reported data as means (SDs), and descriptive statistics were used. The values were reported as standard temperature and pressure and dry (STPD). The *t* test was used for comparison between the 2 groups. Interrater reliability was evaluated by the intraclass correlation coefficient. Prism for Mac, version 9 (GraphPad Software) and SPSS, version 27 (IBM Corp) were used for statistical analysis, and $P < 0.05$ was considered statistically significant.

RESULTS

Automation System is DB Equivalent

Figure 1 shows the repeat measurements of $\dot{V}O_2$, $\dot{V}CO_2$, and RQ collected from healthy volunteers.

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

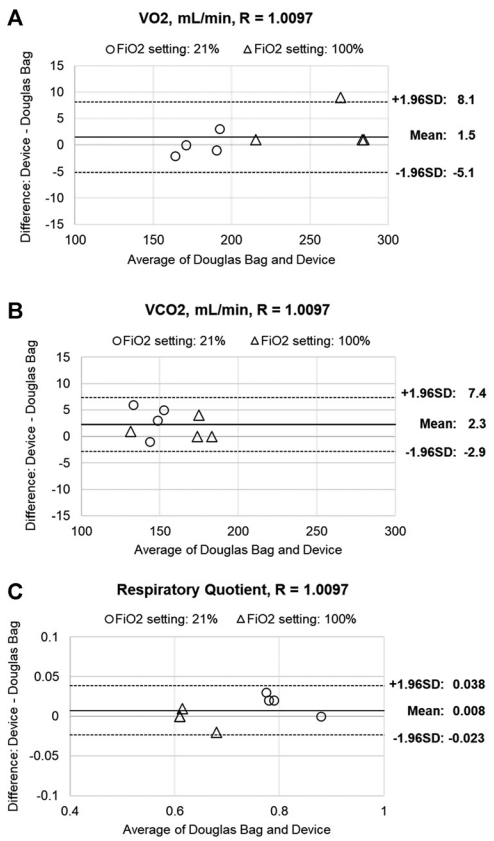

Figure 1. Repeat mean (SD) measurements of oxygen consumption ($V^{\cdot}o_2$), carbon dioxide generation ($V^{\cdot}co_2$), and RQ collected from healthy volunteers. Values were obtained by the automation system and compared with those obtained by the Douglas Bag (DB) method. After approximately 10 minutes of acclimating time for participants, we performed the DB gas collections simultaneously with the automation system. The duty cycle of the automation system was 15 minutes, which was divided into 6 and 9 minutes for inhalation and exhalation, respectively. Inhalation and exhalation gas collections by the DB technique were synchronized with those by the automation device. R indicates the volume ratio of inhalation to exhalation. (A) $V^{\cdot}o_2$ at standard temperature and pressure and dry (STPD). (B) $V^{\cdot}co_2$ at STPD. (C) RQ. DB and device measurements were paired and repeated twice for each participant (n = 2) at 2 different fraction of inspired oxygen (Fio_2) settings.

Values were obtained by the automation system and compared with those obtained by the DB method. The Bland-Altman plots support excellent agreement between the 2 methods. $V^{\cdot}o_2$ ranged from 164 to 193 mL/min at an Fio_2 of 0.21 and 215 to 285 mL/min at an Fio_2 of 1.00. The mean (SD) difference between the methods was 1.5 (6.6), which was not considered significant (within 3%). The $V^{\cdot}co_2$ ranged from 133 to 153 mL/min at an Fio_2 of 0.21 and 131 to 183 mL/min at an Fio_2 of 1.00. The mean (SD) difference between the methods was 2.3 (5.1), which was not considered significant (within 5%). The RQ ranged from 0.78 to 0.88 at an Fio_2 of 0.21 and 0.61 to 0.68 at an Fio_2 of 1.00. The mean (SD) difference between the methods was 0.008 (0.030), which was not considered significant (within 4%). The interrater reliability of these 2 methods on $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ was 0.999, 0.993, and 0.993, respectively. Overall, these data indicate that $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ are interchangeable between the 2 methods.

Effects of High Fio_2 on $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ

Figure 2 reports the effects of high Fio_2 investigated in 3 healthy volunteers, 4 patients after open heart surgery, and 3 patients in a medical intensive care unit. High Fio_2 was defined as and Fio_2 >0.5, and data were collected from individuals whose $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ were measured at both settings of high and normal Fio_2. In healthy volunteers, mean (SD) $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ were measured by the DB method as 411 (100) mL/min, 288 (79) mL/min, and 0.70 (0.03) at high Fio_2 and 323 (46) mL/min, 280 (45) mL/min, and 0.85 (0.05) at normal Fio_2, respectively. Statistically significant differences were found in $V^{\cdot}o_2$ ($P < 0.05$) and RQ ($P < 0.01$). Mean (SD) values measured by the automation system were 227 (31) mL/min, 141 (18) mL/min, and 0.62 (0.04) at high Fio_2 and 209 (25) mL/min, 147 (18) mL/min, and 0.70 (0.06) at normal Fio_2, respectively. A significant difference was found only in RQ ($P < 0.05$). These results suggest that high Fio_2 lowers RQ.

Continuous and Repeat Metabolic Measurements

We performed continuous and repeat metabolic measurements by the automation system device (Figure 3). The measurements in an intensive care unit patient lasted for 12 hours 15 minutes, and 50 cycles of repeat measurements were successfully completed. The mean (SD) $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ over time were

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

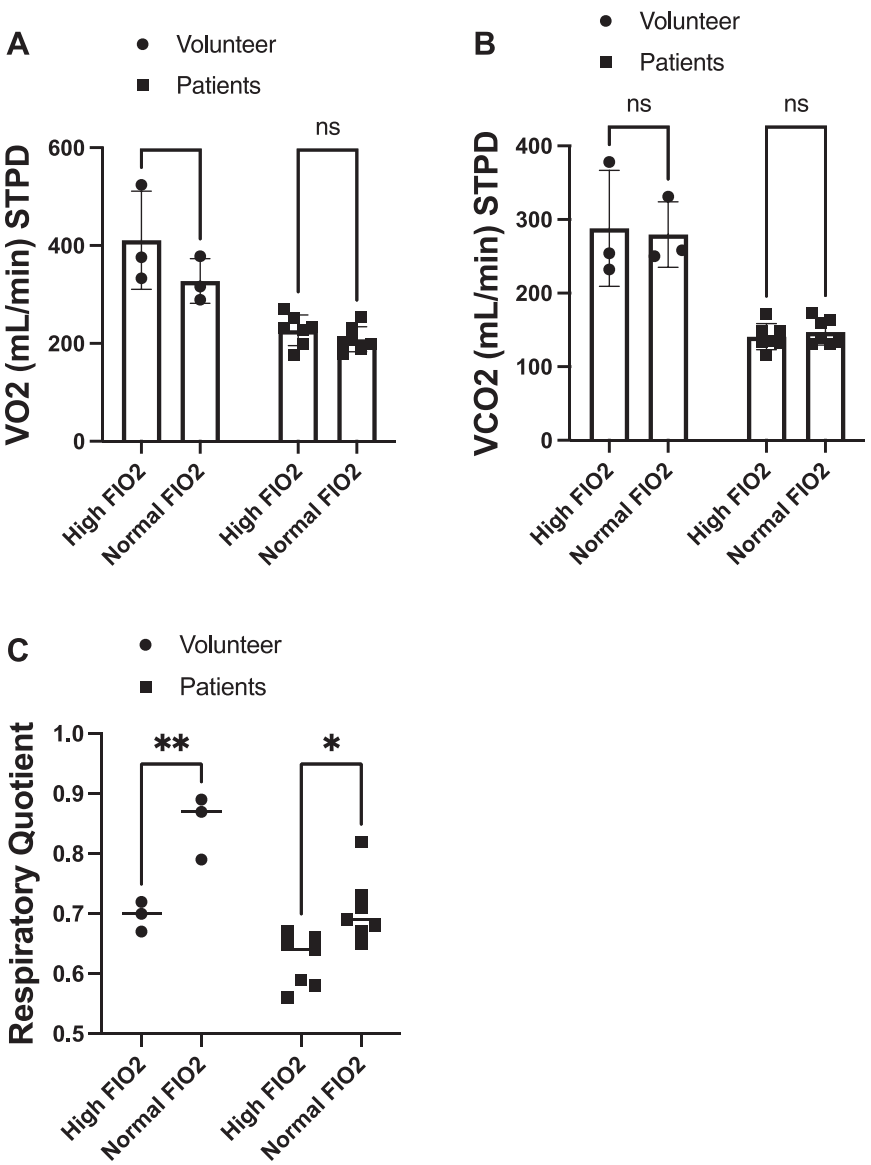

Figure 2. Effects of high fraction of inspired oxygen (Fio_2) investigated in 3 healthy volunteers, 4 patients after open heart surgery, and 3 patients in a medical intensive care unit. High Fio_2 lowers the respiratory quotient (RQ). High Fio_2 was defined as > 0.5 and normal as ≤ 0.5. (A) Oxygen consumption ($\dot{V}o_2$) at standard temperature and pressure and dry (STPD). (B) Carbon dioxide generation ($\dot{V}co_2$) at STPD. (C) RQ. n = 3 in healthy volunteers and n = 7 in postsurgical and intensive care unit patients. Measurements were paired with 2 different Fio_2 settings. Number are expressed as mean (SD). $^{*}P < 0.05$; $^{**}P < 0.01$.

189 (8.7) mL/min at STPD, 133 (4.6) mL/min at STPD, and 0.71 (0.027), respectively. $\dot{V}o_2$, $\dot{V}co_2$, and RQ ranged from 168 to 210 mL/min at STPD, 122 to 143 mL/min at STPD, and 0.63 to 0.77, respectively. The Fio_2 setting was 0.6 at the beginning and was titrated down to 0.3 after 6 cycles of the measurements. These data support the capability of repeat measurements of $\dot{V}o_2$, $\dot{V}co_2$, and RQ by the automation system; however, it is logistically impossible if the traditional DB technique is applied.

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

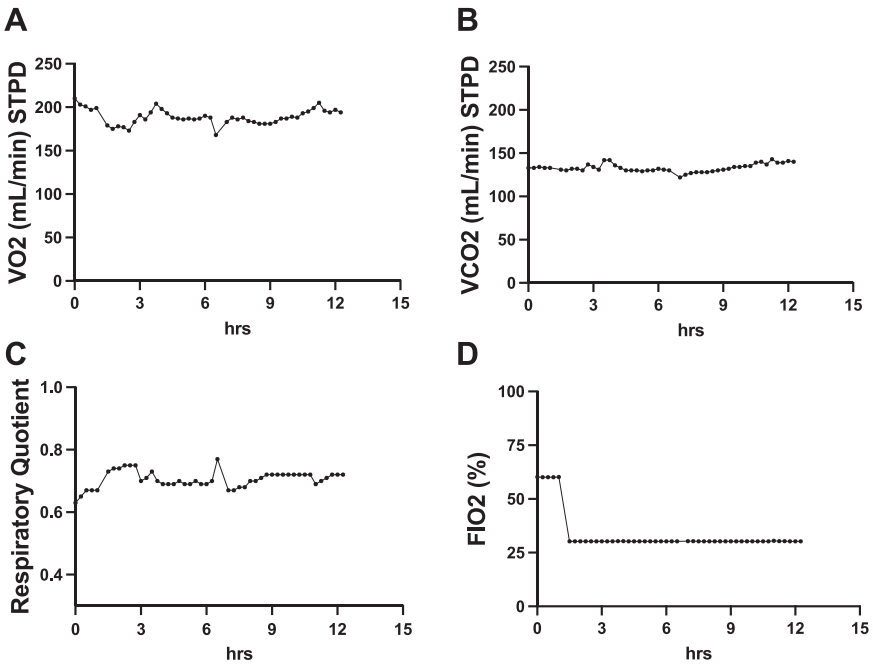

Figure 3. Continuous and repeat metabolic measurements by the automation system device. (A) Case with the continuous measurements of oxygen consumption ($V^{\cdot}o_2$), carbon dioxide generation ($V^{\cdot}co_2$), and respiratory quotient (RQ). The measurements were repeated automatically by our device and lasted for 12 hours 15 minutes, including 50 cycles of the measurements. (A) $V^{\cdot}o_2$ at standard temperature and pressure and dry (STPD). (B) $V^{\cdot}co_2$ at STPD. (C) RQ. (D) Fraction of inspired oxygen (Fio_2).

DISCUSSION

We developed a system for measuring Fio_2, Feo_2, and $FeCo_2$ in individuals receiving mechanical ventilation. These gas concentrations are critical elements to seeking accurate values of $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ. The accuracy of our system was equivalent to the gold standard method—DB collection technique. In addition, our automation system allows for continuous and repeat measurements as opposed to the DB technique that limits the number of experiments.

The volume ratio of inhalation to exhalation defined as R in this study was the key to comparing the values of $V^{\cdot}o_2$ and RQ among different Fio_2 settings. Measuring the small differences between V_I and V_E presents a significant technical difficulty. Therefore, V_I is commonly calculated by using the Haldane transformation, which unfortunately limits the use of Fio_2 up to 0.6, which made it impossible to compare these values between Fio_2 0.21 and 1.0. Assuming V_I equals V_E and ignoring this small difference eliminate the concern. However, failure to account for this small difference can erroneously decrease $V^{\cdot}o_2$ by 17%[10] if V_I is actually not equal to V_E and the error propagates even more as higher Fio_2 is used. The adequacy of the Haldane transformation[20] supports that V_I is not likely equal to V_E. Therefore, the effect of high Fio_2 on $V^{\cdot}o_2$ and RQ became an unanswered question.

The oxygen metabolism at high Fio_2 has not been well described because of the lack of a reliable method. Lodato[22] reported decreased $V^{\cdot}o_2$at normobaric hyperoxia in dogs measured by the Fick method. However, Chapler et al[23] found no effect of hyperoxia on $V^{\cdot}o_2$. A limited utility of the Fick method has been discussed because of its technical complexity.[24] Moreover, a major missing piece of this method is $V^{\cdot}co_2$ or RQ, which is paramount in metabolic studies. Lauscher et al[25] used indirect calorimetry, and their $V^{\cdot}o_2$data were in line with that reported by Lodato.[22] They measured $V^{\cdot}o_2$, $V^{\cdot}co_2$, and RQ by a manufactured indirect calorimetry, which used an adopted Haldane algorithm; however, it has

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

not been published anywhere, which caused concern that the algorithm might not be validated by actual measurements.

Therefore, we have developed a method for measuring the small differences between V_I and V_E.[19] Our results from the rodent model indicate that R ranged from a mean (SD) 1.0081 (0.0017) to 1.0092 (0.0029) at Fio_2 0.3 and 1.0, respectively. V_I was actually not equal to V_E. Although our result was in line with the concept of the Haldane transformation supporting $V_I \neq V_E$, our data indicate that R might be a constant in lieu of a dependent variable affected by Fio_2. In this study, we determined human R as 1.0097, which was within a good agreement with the numbers from our rat model, but this was calculated from the values from previous human studies.[20,21] and determined it as 1.0097, which was in agreement with the numbers obtained from our rat model. Our current work indicates that high Fio_2 increased $\dot{V}o_2$ (Figure 2), which was consistent with the finding from rats.[19,26] Lang et al[27] evaluated the effect of high Fio_2 by using the Wasserman prediction that was calculated from weight and exercise load (watts). Their data also indicate that high Fio_2 could increase $\dot{V}o_2$ and decrease RQ.

Our automation system allows for continuous and repeat measurements of $\dot{V}o_2$, $\dot{V}co_2$, and RQ, which is unfortunately impossible if the traditional DB technique is used. We do not know yet the value of continuous measurements of $\dot{V}o_2$, $\dot{V}co_2$, and RQ in critical care patients who receive mechanical ventilation, but it is important to first establish the accurate measurement. Further studies may warrant a test to validate the usefulness of the measurements, with accuracy and reliability equivalent to the DB technique.

CONCLUSIONS

We developed an automation system that enables repeat measurements of $\dot{V}o_2$, $\dot{V}co_2$, and RQ. High Fio_2 may increase $\dot{V}o_2$ and further decrease RQ. Critical metabolic indicators are widely used in a variety of clinical settings, and the gold standard method warrants the development of an unexplored field of science.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.09.004.

REFERENCES

1. Gump FE, Kinney JM, Price Jr JB. Energy metabolism in surgical patients: oxygen consumption and blood flow. *J Surg Res*. 1970;10:613–627.
2. Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, Kushner R, Schmidt GA, Wood LD. Effect of cooling on oxygen consumption in febrile critically ill patients. *Am J Respir Crit Care Med*. 1995;151:10–14.
3. McClave SA, Lowen CC, Kleber MJ, McConnell JW, Jung LY, Goldsmith LJ. Clinical use of the respiratory quotient obtained from indirect calorimetry. *JPEN J Parenter Enteral Nutr*. 2003;27:21–26.
4. Siegel JH, Fabian M, Smith JA, Kingston EP, Steele KA, Wells MR, Kaplan LJ. Oxygen debt criteria quantify the effectiveness of early partial resuscitation after hypovolemic hemorrhagic shock. *J Trauma*. 2003;54:862–880 discussion 880.
5. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126:2261–2274.
6. Sundstrom M, Tjader I, Rooyackers O, Wernerman J. Indirect calorimetry in mechanically ventilated patients: a systematic comparison of three instruments. *Clin Nutr*. 2013;32:118–121.
7. Graf S, Karsegard VL, Viatte V, Heidegger CP, Fleury Y, Pichard C, Genton L. Evaluation of three indirect calorimetry devices in mechanically ventilated patients: which device compares best with the Deltatrac II((R))? a prospective observational study. *Clin Nutr*. 2015;34:60–65.
8. Matarese LE. Indirect calorimetry: technical aspects. *J Am Diet Assoc*. 1997;97:S154–S160.
9. da Rocha EE, Alves VG, da Fonseca RB. Indirect calorimetry: methodology, instruments and clinical application. *Curr Opin Clin Nutr Metab Care*. 2006;9:247–256.
10. Branson RD, Johannigman JA. The measurement of energy expenditure. *Nutr Clin Pract*. 2004;19:622–636.
11. Soussi S, Vallee F, Roquet F, Bevilacqua V, Benyamina M, Ferry A, Cupaciu A, Chaussard M, De Tymowski C, Boccara D, Mimoun M, Chaouat M, Anstey J, Mebazaa A, Legrand M. Measurement of oxygen consumption variations in critically ill burns patients: are the Fick method and indirect calorimetry interchangeable? *Shock*. 2017;48:532–538.
12. Hensel M, Kox WJ. Increased intrapulmonary oxygen consumption in mechanically ventilated patients with

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004

pneumonia. *Am J Respir Crit Care Med*. 1999;160:137–143.
13. Musch TI, Bruno A, Bradford GE, Vayonis A, Moore RL. Measurements of metabolic rate in rats: a comparison of techniques. *J Appl Physiol (1985)*. 1988;65:964–970.
14. van Klinken JB, van den Berg SA, van Dijk KW. Practical aspects of estimating energy components in rodents. *Front Physiol*. 2013;4:94.
15. Yo K, Yu YM, Zhao G, Bonab AA, Aikawa N, Tompkins RG, Fischman AJ. Brown adipose tissue and its modulation by a mitochondria-targeted peptide in rat burn injury-induced hypermetabolism. *Am J Physiol Endocrinol Metab*. 2013;304:E331–E341.
16. Even PC, Nadkarni NA. Indirect calorimetry in laboratory mice and rats: principles, practical considerations, interpretation and perspectives. *Am J Physiol Regul Integr Comp Physiol*. 2012;303:R459–R476.
17. Black C, Grocott MP, Singer M. Metabolic monitoring in the intensive care unit: a comparison of the Medgraphics Ultima, Deltatrac II, and Douglas bag collection methods. *Br J Anaesth*. 2015;114:261–268.
18. Shephard RJ. A critical examination of the Douglas bag technique. *J Physiol*. 1955;127:515–524.
19. Shinozaki K, Okuma Y, Saeki K, Miyara SJ, Aoki T, Molmenti EP, Yin T, Kim J, Lampe JW, Becker LB. A method for measuring the molecular ratio of inhalation to exhalation and effect of inspired oxygen levels on oxygen consumption. *Sci Rep*. 2021;11:12815.
20. Wilmore JH, Costill DL. Adequacy of the Haldane transformation in the computation of exercise VO2 in man. *J Appl Physiol*. 1973;35:85–89.
21. Herron JM, Saltzman HA, Hills BA, Kylstra JA. Differences between inspired and expired minute volumes of nitrogen in man. *J Appl Physiol*. 1973;35:546–551.
22. Lodato RF. Decreased O2 consumption and cardiac output during normobaric hyperoxia in conscious dogs. *J Appl Physiol (1985)*. 1989;67:1551–1559.
23. Chapler CK, Cain SM, Stainsby WN. The effects of hyperoxia on oxygen uptake during acute anemia. *Can J Physiol Pharmacol*. 1984;62:809–814.
24. Stock MC, Ryan ME. Oxygen consumption calculated from the Fick equation has limited utility. *Crit Care Med*. 1996;24:86–90.
25. Lauscher P, Lauscher S, Kertscho H, Habler O, Meier J. Hyperoxia reversibly alters oxygen consumption and metabolism. *Sci World J*. 2012;2012:410321.
26. Okuma Y, Becker LB, Hayashida K, Aoki T, Saeki K, Nishikimi M, Shoaib M, Miyara SJ, Yin T, Shinozaki K. Effects of post-resuscitation normoxic therapy on oxygen-sensitive oxidative stress in a rat model of cardiac arrest. *J Am Heart Assoc*. 2021;10:e018773.
27. Lang S, Herold R, Kraft A, Harth V, Preisser AM. Spiroergometric measurements under increased inspiratory oxygen concentration (Fio_2): putting the Haldane transformation to the test. *PLoS One*. 2018;13:e0207648.

Address correspondence to: Koichiro Shinozaki, MD, PhD, Department of Emergency Medicine, Zucker School of Medicine at Hofstra/Northwell, The Feinstein Institutes for Medical Research, 350 Community Dr, Manhasset, NY 11030. E-mail: shino@gk9.so-net.ne.jp.

Please cite this article as: K. Shinozaki et al., An Automation System Equivalent to the Douglas Bag Technique Enables Continuous and Repeat Metabolic Measurements in Patients Undergoing Mechanical Ventilation, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.09.004