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, PhD1,2,3; Pey-Jen Yu, MD4; Qiuping Zhou, DO5; Hugh A. Cassiere, MD6; John Stanley, MHA, RT6; Daniel M. Rolston, MD, MSHPM2,3; Nidhi Garg, MD2,7; Timmy Li, PhD2,3; Jennifer Johnson, BA3; Kota Saeki, MEng1,8; Taiki Goto, MBE9; Yu Okuma, MD, PhD1; Santiago J. Miyara, MD, PhD1; Kei Hayashida, MD, PhD1; Tomoaki Aoki, MD, PhD1; Vanessa Wong, BS1; Ernesto P. Molmenti, MD1,10; Joshua W. Lampe, PhD1,11; and Lance B. Becker, MD, FAHA1,2,3

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

ABSTRACT

Purpose: To develop a system that is equivalent to the gold standard Douglas Bag (DB) technique for measuring oxygen consumption (\(V_{O_2}\), carbon dioxide generation (\(V_{CO_2}\)), 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 intrarater reliability between the automation device and DB methods were 0.999, 0.993, and 0.993 for \(V_{O_2}\), \(V_{CO_2}\), and RQ, respectively. In healthy volunteers, mean (SD) \(V_{O_2}\), \(V_{CO_2}\), 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 (Fi\(_{O_2}\)) and 323 (46) mL/min, 280 (45) mL/min, and 0.85 (0.05) at normal Fi\(_{O_2}\), respectively. \(V_{O_2}\) was significantly higher (\(P < 0.05\)) and RQ was lower (\(P < 0.01\)) in the high Fi\(_{O_2}\) group as compared to those in the normal Fi\(_{O_2}\) group. Values measured by the automation system were 227 (31) mL/min, 141 (18) mL/min, and 0.62 (0.04) at high Fi\(_{O_2}\) and 209 (25) mL/min, 147 (18) mL/min, and 0.70 (0.06) at normal Fi\(_{O_2}\), respectively. RQ was significantly lower (\(P < 0.05\)) in the high Fi\(_{O_2}\) group as compared to the normal Fi\(_{O_2}\) group. We also successfully performed continuous and repeat measurements by using the device. The
Clinical Therapeutics

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 $V'\text{O}_2$, $V'\text{CO}_2$, and RQ, and the accuracy was equivalent to the DB technique. High FiO$_2$ may decrease RQ because of an increase in $V'\text{O}_2$. (Clin Ther. 2022;000:1-9.) © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

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

INTRODUCTION

Oxygen consumption ($V'\text{O}_2$) and carbon dioxide generation ($V'\text{CO}_2$) are important measures of metabolism in humans, and the respiratory quotient (RQ), which is defined as the ratio of $V'\text{CO}_2$ to $V'\text{O}_2$, can be used as a clinical parameter of a patient’s metabolism. These measurements are widely used for patients with a variety of conditions, including postoperative conditions, shock, pulmonary and cardiac diseases, and critical illness requiring mechanical ventilation. Indirect calorimetry is a noninvasive method of measuring metabolism in which $V'\text{O}_2$ and $V'\text{CO}_2$ are measured by concentrations of oxygen and carbon dioxide in inhalation and exhalation. Because it is noninvasive, indirect calorimetry has been widely used in clinical settings and translational research. However, because of the lack of a gold standard, its accuracy has been questioned for a long time.

One of the reference standards is the Douglas Bag (DB) collection technique that has been routinely used for >100 years. The central focus of this method is the accuracy of gas concentrations in inhalation and exhalation. Errors of $V'\text{O}_2$, $V'\text{CO}_2$, 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. 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 $V'\text{O}_2$, $V'\text{CO}_2$, and RQ is in need.

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 $V'\text{O}_2$, $V'\text{CO}_2$, 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$_2$O owing to a predicted gas leak from the mechanical ventilation circuit. Our method and calculation algorithm enabled measurements of $V'\text{O}_2$, $V'\text{CO}_2$, and RQ.
V\textsubscript{\textsuperscript{\textacuteslash}CO\textsubscript{2}} and RQ at a variety range of fraction of inspired oxygen (Fi\textsubscript{O\textsubscript{2}})\textsuperscript{19}; therefore, no upper limit was made on an Fi\textsubscript{O\textsubscript{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\textsubscript{\textsuperscript{\textacuteslash}O\textsubscript{2}}, V\textsubscript{\textsuperscript{\textacuteslash}CO\textsubscript{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\textsubscript{\textsuperscript{\textacuteslash}O\textsubscript{2}}, V\textsubscript{\textsuperscript{\textacuteslash}CO\textsubscript{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-M mixing chamber was attached to the exhaust port. This chamber was
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 \((\text{eAppendix II})\). 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**

\(\text{FiO}_2\), fraction of expired oxygen (\(\text{FeO}_2\)), fraction of inspired carbon dioxide (\(\text{FiCO}_2\)), fraction of expired carbon dioxide (\(\text{FeCO}_2\)), 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, \(\text{FeO}_2\) and \(\text{FeCO}_2\) 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 \(\text{FiO}_2\) and \(\text{FiCO}_2\). 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 \(\text{FeO}_2\) and \(\text{FeCO}_2\). 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 \(\text{FiO}_2\) within a duty cycle, the value was excluded from our analysis. The time series of \(\text{FiO}_2\) was calculated from the values of pre- and post- \(\text{FiO}_2\). The equations used in this study are as follows:

\[
R = \frac{V_I}{V_E} \quad (1)
\]

\[
V_{O_2} = V_I \times \text{FiO}_2 - V_E \times \text{FeO}_2 \quad (2)
\]

\[
V_{CO_2} = V_E \times \text{FeCO}_2 - V_I \times \text{FiCO}_2 \quad (3)
\]

where \(V_I\) is a minute ventilation volume of inspiration and \(V_E\) is that of expiration. \(\text{FiCO}_2\) is zero because the inspiration gas does not contain \(\text{CO}_2\). The RQ, \(V_{O_2}\), and \(V_{CO_2}\) are then transformed to the following equations:

\[
V_{O_2} = (R \times \text{FiO}_2 - \text{FeO}_2) \times V_E \quad (4)
\]

\[
V_{CO_2} = \text{FeCO}_2 \times V_E \quad (5)
\]

\[
\text{RQ} = \frac{V_{CO_2}}{V_{O_2}} \quad (6)
\]

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. Because the denominator includes \(\text{FiO}_2\) and it goes to zero as \(\text{FiO}_2\) increases to 1.0, R increases to an infinite number when \(\text{FiO}_2\) is 1.0. Therefore, the Haldane transformation limits \(\text{FiO}_2\) generally up to 0.6. This is a significant limitation in critical care medicine in which patients normally require higher \(\text{FiO}_2\). Therefore, we developed a method for measuring R and sought the number of R by using our rodent model. 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 \(\text{FiO}_2\). Our results from the rodent model indicate that the mean (SD) R was 1.0081 (0.0017) at an \(\text{FiO}_2\) of 0.3 and 1.0092 (0.0029) at an \(\text{FiO}_2\) of 1.0. In this study, we determined human R as 1.0097 calculated from the values obtained from previous human studies 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 \(V_{O_2}\), \(V_{CO_2}\), and RQ collected from healthy volunteers.
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. $V'\text{O}_2$ 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 $V'\text{CO}_2$ 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 intrarater reliability of these 2 methods on $V'\text{O}_2$, $V'\text{CO}_2$, and RQ was 0.999, 0.993, and 0.993, respectively. Overall, these data indicate that $V'\text{O}_2$, $V'\text{CO}_2$, and RQ are interchangeable between the 2 methods.

**Effects of High FiO$_2$ on $V'\text{O}_2$, $V'\text{CO}_2$, 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 $V'\text{O}_2$, $V'\text{CO}_2$, and RQ were measured at both settings of high and normal FiO$_2$. In healthy volunteers, mean (SD) $V'\text{O}_2$, $V'\text{CO}_2$, 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 $V'\text{O}_2$ ($P < 0.05$) 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) $V'\text{O}_2$, $V'\text{CO}_2$, and RQ over time were...
Figure 2. Effects of high fraction of inspired oxygen (Fio₂) investigated in 3 healthy volunteers, 4 patients after open heart surgery, and 3 patients in a medical intensive care unit. High Fio₂ lowers the respiratory quotient (RQ). High Fio₂ was defined as > 0.5 and normal as ≤ 0.5. (A) Oxygen consumption (V’o₂) at standard temperature and pressure and dry (STPD). (B) Carbon dioxide generation (V’co₂) 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 Fio₂ 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. V’o₂, V’co₂, 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 Fio₂ 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 V’o₂, V’co₂, and RQ by the automation system; however, it is logistically impossible if the traditional DB technique is applied.
DISCUSSION

We developed a system for measuring FiO₂, FeO₂, and FeCO₂ in individuals receiving mechanical ventilation. These gas concentrations are critical elements to seeking accurate values of V'O₂, V'CO₂, 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'O₂ and RQ among different FiO₂ settings. Measuring the small differences between V₁ and Vₑ in a significant technical difficulty. Therefore, V₁ is commonly calculated by using the Haldane transformation, which unfortunately limits the use of FiO₂ up to 0.6, which made it impossible to compare these values between FiO₂ 0.21 and 1.0. Assuming V₁ equals Vₑ and ignoring this small difference eliminate the concern. However, failure to account for this small difference can erroneously decrease V'O₂ by 17% \(^{10}\) if V₁ is actually not equal to Vₑ and the error propagates even more as higher FiO₂ is used. The adequacy of the Haldane transformation\(^ {20}\) supports that V₁ is not likely equal to Vₑ. Therefore, the effect of high FiO₂ on V'O₂ and RQ became an unanswered question.

The oxygen metabolism at high FiO₂ has not been well described because of the lack of a reliable method. Lodato\(^ {22}\) reported decreased V'O₂ at normobaric hyperoxia in dogs measured by the Fick method. However, Chapler et al\(^ {23}\) found no effect of hyperoxia on V'O₂. 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'CO₂ or RQ, which is paramount in metabolic studies. Lauscher et al\(^ {25}\) used indirect calorimetry, and their V'O₂ data were in line with that reported by Lodato. They measured V'O₂, V'CO₂, and RQ by a manufactured indirect calorimetry, which used an adopted Haldane algorithm; however, it has
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 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 $V^O_2$ (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 $V^O_2$ and decrease $RQ$.

Our automation system allows for continuous and repeat measurements of $V^O_2$, $V^CO_2$, and $RQ$, which is unfortunately impossible if the traditional DB technique is used. We do not know yet the value of continuous measurements of $V^O_2$, $V^CO_2$, 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 $V^O_2$, $V^CO_2$, and $RQ$. High $FiO_2$ may increase $V^O_2$ 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**

12. Hensel M, Kox WJ. Increased intrapulmonary oxygen consumption in mechanically ventilated patients with...


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.