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Abstract

Introduction: The international ICALIC initiative aims at developing a new indirect calorimeter according to the needs of the clinicians and researchers in the field of clinical nutrition and metabolism. The project initially focuses on validating the calorimeter for use in mechanically ventilated acutely ill adult patient. However, standard methods to validate the accuracy of calorimeters have not yet been established. This paper describes the procedures for the in-vitro tests to validate the accuracy of the new indirect calorimeter, and defines the ranges for the parameters to be evaluated in each test to optimize the validation for clinical and research calorimetry measurements. Methods: Two in-vitro tests have been defined to validate the accuracy of the gas analyzers and the overall function of the new calorimeter. 1) Gas composition analysis allows validating the accuracy of O2 and CO2 analyzers. Reference gas of known O2 (or CO2) concentration is diluted by pure nitrogen gas to achieve predefined O2 (or CO2) concentration, to be measured by the indirect calorimeter. O2 and CO2 concentrations to be tested were [...]
Methods to validate the accuracy of an indirect calorimeter in the in-vitro setting

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Methods: Two in-vitro tests have been defined to validate the accuracy of the gas analyzers and the overall function of the new calorimeter.

1) Gas composition analysis allows validating the accuracy of O2 and CO2 analyzers. Reference gas of known O2 (or CO2) concentration is diluted by pure nitrogen gas to achieve predefined O2 (or CO2) concentration, to be measured by the indirect calorimeter. O2 and CO2 concentrations to be tested were determined according to their expected ranges of concentrations during calorimetry measurements.

2) Gas exchange simulator analysis validates O2 consumption (VO2) and CO2 production (VCO2) measurements. CO2 gas injection into artificial breath gas provided by the mechanical ventilator simulates VCO2. Resulting dilution of O2 concentration in the expiratory air is analyzed by the calorimeter as VO2. CO2 gas of identical concentration to the fraction of inspired O2 (FiO2) is used to simulate identical VO2 and VCO2. Indirect calorimetry results from publications were analyzed to determine the VO2 and VCO2 values to be tested for the validation.

Results: O2 concentration in respiratory air is highest at inspiration, and can decrease to 15% during expiration. CO2 concentration can be as high as 5% in expired air. To validate analyzers for measurements of FiO2 up to 70%, ranges of O2 and CO2 concentrations to be tested were defined as 15–70% and 0.5–5.0%, respectively.

The mean VO2 in 426 adult mechanically ventilated patients was 270 ml/min, with 2 standard deviation (SD) ranges of 150–391 ml/min. Thus, VO2 and VCO2 to be simulated for the validation were defined as 150, 250, and 400 ml/min.

Conclusion: The procedures for the in-vitro tests of the new indirect calorimeter and the ranges for the parameters to be evaluated in each test have been defined to optimize the validation of accuracy for clinical and research indirect calorimetry measurements. The combined methods will be used to validate the accuracy of the new indirect calorimeter developed by the ICALIC initiative, and should become the standard method to validate the accuracy of any future indirect calorimeters.

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Keywords:
Indirect calorimetry
Validation
In-vitro
Gas exchange simulation

Summary

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1. Introduction

Indirect calorimetry allows to determine the patients energy needs and tailor the prescription of nutrition [1,2]. Indirect calorimeters measure energy expenditures of patients by breath gas analysis, based on the principle that the volumes of oxygen consumption (VO₂) and carbon dioxide production (VCO₂) correspond to energy expenditure [1]. The accuracy of the calorimeters depends on accuracy of the analyzers to measure O₂ and CO₂ concentrations and flow of breaths gas [1,3], and of the overall performance of the indirect calorimeter to combine the measurements by the analyzers to derive VO₂ and VCO₂ [1]. However, recent validations of indirect calorimeters have been conducted as comparisons of measurements between different indirect calorimeters [4,5], and very few studies have focused on the intrinsic accuracy of the calorimeter [6,7].

An international academic initiative (the ICALIC project) aims at developing a new indirect calorimeter designed according to the needs of the clinicians and researchers in the field of nutrition and metabolism [1]. Although the new calorimeter is designed for use in both mechanically ventilated and non-ventilated subjects, the initial phase of the study will focus on the challenging task of validating this new device for use in mechanically ventilated patients in the adult intensive care unit (Clinicaltrials.gov: NCT02796430). In-vitro tests were planned in order to validate the accuracy per se of the new indirect calorimeter before the clinical trial. However, an extensive literature search has revealed that standard methods to validate the accuracy of indirect calorimeters in mechanically ventilated patients have not been established until now. Therefore, we sought to define the comprehensive methods to validate the accuracy of an indirect calorimeter to be suitable for clinical and research use in the mechanically ventilated setting. As a result, two in-vitro tests have been proposed to validate the accuracy of the analyzers and the resulting VO₂ and VCO₂ measurements of the new calorimeter: — Gas composition analysis aims to validate the O₂ and CO₂ analyzers; — Gas exchange simulation analysis aims to validate the measurements of VO₂ and VCO₂ using the CO₂ injection technique [8] in the mechanically ventilated setting.

This paper describes the procedures of the in-vitro tests, and defines the critical ranges for the parameters to be evaluated in each test to enable the comprehensive validation of accuracy for the new indirect calorimeter developed by the ICALIC initiative to be suitable for clinical and research use.

2. Materials and methods

2.1. Gas composition analysis

2.1.1. Procedures

Gas composition analysis aims at validating the accuracy of the O₂ and CO₂ analyzers. A very simple and widely used method was adopted to build a precision gas mixing system to provide gas mixtures of predefined O₂ or CO₂ concentrations by diluting O₂ (99.9%) gas (or CO₂ gas; 1% or 5%) with nitrogen (N₂; 99.9%) gas, to be measured by the new indirect calorimeter (Fig. 1). Two precision flow controllers (EL-FLOW® F-201CV-500, Bronkhorst®, Germany) are used to regulate the flows of O₂ or CO₂ gas and N₂ gas simultaneously, to precisely adjust the O₂ or CO₂ concentration of the resulting gas mixture to predefined values. The gases are thoroughly homogenized in a mixing cylinder (100 ml) before the measurement by the new indirect calorimeter. Measurements of O₂ and CO₂ concentrations by the indirect calorimeter analyzers are validated against predefined concentrations.

2.1.2. Data analysis

Gas composition in respiratory gases were studied [9,10], to determine the ranges of O₂ and CO₂ concentrations to validate the accuracy of the gas composition analyzers for indirect calorimetry measurements. The goal for the clinical application of the new calorimeter to perform calorimetry measurements in patients with elevated fraction of inhaled oxygen (FiO₂) was also considered to determine the upper limit of O₂ concentration to be tested for the validation.

2.2. Gas exchange simulation

2.2.1. Procedures

Gas exchange simulator analysis aims at validating VO₂ and VCO₂ measurements in the mechanically ventilated setting. Gas exchange simulation system was developed by modifying the CO₂ injection method described by Weissman et al. [8] (Fig. 2). CO₂ gas is injected at a fixed rate into the simulated breath gas provided by the mechanical ventilator (Evia Infinity 500® Drager®, Germany) to simulate VCO₂. The rate of CO₂ injection can be adjusted by the precision mass flow controller (EL-FLOW® F-201CV-500, Bronkhorst®, Germany) to directly simulate predefined VCO₂ levels. Flow rates of the CO₂ gases with different CO₂ concentrations were adjusted using the web-based gas conversion factor calculator (Fluidat® on the Net, https://www.fluidat.com/default.asp). By injecting CO₂ at the end of the inspiratory circuit and before a small mixing chamber (500 ml) and the test lung, the O₂ concentration in the artificial breath gas provided by the mechanical ventilator is diluted by the injected CO₂ gas by the time the gas mixture reaches the expiratory circuit. Decreased O₂ concentration in the expiratory circuit air was detected by the calorimeter as VO₂, thus completing the gas exchange simulation. The use of CO₂ gas with identical concentration to the O₂ provided by the mechanical ventilator enables the simulation of VO₂ and VCO₂ of the identical values. Environmental temperature, humidity, and atmospheric pressure is recorded and used for converting volume measurements (ATPS; ambient temperature and pressure, saturated gas condition) to reporting units (STPD; standard temperature and pressure, dry gas...
of O2 simulates VO2 of the same level as the VCO2. (VO2: oxygen consumption (ml/min); VCO2: carbon-dioxide production (ml/min); FiO2: fraction of inhaled oxygen).

Gas exchange is measured by the indirect calorimeter as decrease in O2 and increase in CO2 concentrations from inhaled to exhaled breath. The system simulates gas exchange by injecting CO2 gas using a precision mass flow controller into the circulating O2 gas provided by the mechanical ventilator. CO2 injection rate can be adjusted to directly simulate various levels of VCO2. By injecting CO2 gas of the same concentration as the FiO2, the resulting dilution of O2 simulates VO2 of the same level as the VCO2. (VO2: oxygen consumption (ml/min); VCO2: carbon-dioxide production (ml/min); FiO2: fraction of inhaled oxygen).

Condition) for VO2 and VCO2. Results of the measurements of the simulated gas exchange by the new indirect calorimeter are validated against predefined VO2 and VCO2 values.

2.2.2. Data analysis

VO2 and VCO2 data from indirect calorimetry on adult mechanically ventilated patients conducted for clinical studies published within the last 5 years were analyzed to determine the gas exchange simulation values to be tested. Only studies conducted in the mixed ICU setting were selected to avoid bias on the patient population. Selection by the type of indirect calorimeter was also considered an important factor, as recent studies using different calorimeters have presented considerable variability in the measurements among the devices. The Deltatrac® Metabolic Monitor (Datex, Finland) was found to be the most widely used device, and the only device that has been validated for accuracy in the in-vitro settings. For these reasons, the VO2 and VCO2 values measured by the Deltatrac® were selected for the analysis [2,5,11,12]. VO2 and VCO2 results were analyzed as weighted averages according to the number of enrolled patients in each study. Since VO2 and VCO2 in the simulation are identical, the main target value of the validation was determined as approximately the mean of the weighted averages of VO2 and VCO2. The upper and lower limits of the ranges for the simulation were defined according to the analyses of VO2 values, which has a greater impact on the calorimetry results [1,2].

3. Results

3.1. Gas composition analysis

O2 concentration is known to decrease about 5% between inhaled and exhaled breaths, while the CO2 concentration increases about 5%. The new indirect calorimeter is designed to measure patients treated with elevated FiO2 up to 70% under mechanical ventilation, as well as patients without O2 enrichment (FiO2 21%). To validate the analyzers for all the variable situations possibly encountered in clinical indirect calorimetry measurements, ranges for the validation of O2 and CO2 analyses were defined as 15–70% and 0.5–5.0%, respectively.

3.2. Gas exchange simulation

VO2 values from 4 clinical studies enrolling a total of 426 adult mechanically ventilated patients were analyzed (Table 1). The weighted mean of VO2 and VCO2 according to the number of patients enrolled for each study was 270 and 226 ml/min, respectively. The weighted means of the 95% limits of the normal distribution (2 SD) ranges of VO2 were 150 and 391 ml/min, respectively (Table 1). Thus, gas exchange simulation values to be tested in the validation were defined as 150, 250, and 400 ml/min (Table 2). Gas exchange simulations are conducted in FiO2 levels of 21, 40, 60, and 80%, to validate the accuracy of the measurements in its intended range of use (FiO2 21–70%).

4. Discussion

The procedures for the two in-vitro tests to validate the accuracy of the new indirect calorimeter developed for the ICALIC project have been defined. The ranges for the parameters to be evaluated in each test have been defined to establish the accuracy of the new indirect calorimeter for clinical and research use.

4.1. Previous validations of indirect calorimeters

Accuracy of indirect calorimeters has been a matter of debate [3,5]. The Deltatrac Metabolic Monitor® is probably the most rigorously tested commercial indirect calorimeter during its 35 years of clinical use. The Deltatrac Metabolic Monitor® was found to be the most widely used device, and the only device that has been validated for accuracy in the in-vitro and in-vivo settings. For these reasons, the VO2 and VCO2 values measured by the Deltatrac® were selected for the analysis [2,5,11,12]. VO2 and VCO2 results were analyzed as weighted averages according to the number of enrolled patients in each study. Since VO2 and VCO2 in the simulation are identical, the main target value of the validation was determined as approximately the mean of the weighted averages of VO2 and VCO2. The upper and lower limits of the ranges for the simulation were defined according to the analyses of VO2 values, which has a greater impact on the calorimetry results [1,2].
year history since market release, but its production has been discontinued more than ten years ago [8,13]. *In-vitro* tests had been conducted during its development phase [13], followed by validations against other methods to measure energy expenditure, such as the Fick method and doubly labeled water [13]. Many comparisons studies were conducted against commercial and non-commercial experimental calorimeters [5,12], including a mass spectrometer based calorimetry device [14]. These tests have helped to demonstrate the accuracy and stability of the Deltatrac®, as well as its limitations [15]. The results of the validation studies have encouraged the use of device in the optimal conditions [16], contributing to the reliability of the measurements.

Many indirect calorimeters have been developed using new techniques, precision analyzers and modern data processors [1]. However, recent studies to investigate the accuracy of indirect calorimeters have been conducted mainly as comparisons of measurements using different devices in human subjects [4,5], precluding the discussion on the accuracy of the measurements. The absence of a gold standard and the large variability of measured results among indirect calorimeters have raised doubts about their accuracy, and discouraged clinicians from implementing indirect calorimetry in their daily practice [17].

### 4.2. Validation of the new indirect calorimeter

The ICALIC project was initiated to develop and validate a new indirect calorimeter, with the support of two international academic societies (European Society for Clinical Nutrition and Metabolism, ESPEN; European Society of Intensive Care Medicine, ESICM). The study group consists of 7 centers from 6 countries across Europe. The new calorimeter has been designed to be accurate, easy to use, and compact for easy to handling while being affordable [11]. The current study defines first step of the validation process, to evaluate the accuracy of the measurements by the new indirect calorimeter in the *in-vitro* setting. Additional validations can be planned for evaluating the effects of different conditions (Supplementary Table 2), such ventilation modes and different types of ventilators. Clinical validations will follow to evaluate the practical use in the multicenter setting (Clinicaltrials.gov: NCT02796430).

### 4.3. Strength and weakness

The strength of this study is the strict *in-vitro* setting, enabling the evaluation of accuracy and precision against a predefined target. Simulations are based on a very simple principle using high precision equipment to allow for repeated measurements in stable conditions. CO₂ injection technique allows for the ventilator settings (pressure, volume, respiratory rate) to be adjusted according to the aim of the test. These methods should become the standard of test for any new indirect calorimeter to be qualified for use in clinical practice and research.

The study limitations are mostly related to the gas exchange simulation. The FiO₂ levels that can be used for the simulation test depend on the availability of specially formulated CO₂ gases that matches the FiO₂. The current plan is to conduct the tests in FiO₂ levels of 21, 40, 60, and 80% to cover the range for the clinical application (up to 70%), as shown in Table 2. VO₂ and VCO₂ to be simulated for the validation were determined based on the data from mechanically ventilated adult patients. Thus, the recommendation is valid only for validating the device for this patient cohort, and not for non-ventilated or pediatric cohort. Further validations for different patient groups should be tested using VO₂ and VCO₂ values relevant for such cohort. Simulated values are identical for VO₂ and VCO₂, while it is generally lower for VCO₂ in clinical measurements. However, attempting to simulate VO₂ and VCO₂ at ratios closer to clinical measurements would complicate the analyses, as the accuracy of the simulations depend on the accuracy of the CO₂ concentrations and FiO₂ in the gases used for the simulations. Another limitation would be the absence of the temperature and humidity in the artificial breath gas, which can also affect the measurements in the clinical setting. However, the new indirect calorimeter is recommended for use with heat and moisture exchange filter instead of a humidifier, to eliminate humidity and avoid water droplet accumulation within the ventilator circuit. We believe the current *in-vitro* simulation test can generate results enabling the analyses of unforeseen effects in the *in-vivo* measurements that follow, in the later phase of the study.

### 5. Conclusion

The procedures for the *in-vitro* tests to validate the accuracy of the new indirect calorimeter developed for the ICALIC project have been defined. The ranges for the parameters to be evaluated in each test have been defined to establish the accuracy of the device for clinical and research indirect calorimetry measurements. The combined methods should be considered as the standard method for the comprehensive validation of accuracy of an indirect calorimeter, for the device to be qualified for clinical and research use.

### Conflict of interest

To received financial support as an unrestricted academic research grant from public institutions (Geneva University Hospital) and the Foundation Nutrition 2000 Plus, and travel expenses for congress and research meetings from Cosmed. CP received financial support as research grants and an unrestricted academic research grant, as well as an unrestricted research grant and consulting fees, from Abbott, Baxter, B. Braun, Cosmed, Fresenius-Kabi, Nestle Health Sciences, Novartis, Nutricia-Numico, Pfizer, and Solvay, outside the submitted work. MR is an engineer working in the research and development division of Cosmed, Italy. The other authors declare that they have no competing interests related to the current work.

### Acknowledgement

**Funding**

Financial support came from the European Society for Clinical Nutrition and Metabolism (ESPIN) and the European Society of Intensive Care Medicine (ESICM), APSI-ICU quality funds of the Geneva University Hospital, Public Foundation Nutrition 2000Plus.

**Statement of authorship**

Taku Oshima and Claude Pichard have outlined this manuscript, which was developed, enriched, reviewed and approved by each of the co-authors.

### Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnesp.2017.08.009.

### References


