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Original article

Methods to validate the accuracy of an indirect calorimeter in the *in-vitro* setting

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SUMMARY

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 O_2 and CO_2 analyzers. Reference gas of known O_2 (or CO_2) concentration is diluted by pure nitrogen gas to achieve predefined O_2 (or CO_2) concentration, to be measured by the indirect calorimeter. O_2 and CO_2 concentrations to be tested were determined according to their expected ranges of concentrations during calorimetry measurements.

2) Gas exchange simulator analysis validates O_2 consumption (VO_2) and CO_2 production (VCO_2) measurements. CO_2 gas injection into artificial breath gas provided by the mechanical ventilator simulates VCO_2. Resulting dilution of O_2 concentration in the expiratory air is analyzed by the calorimeter as VO_2. CO_2 gas of identical concentration to the fraction of inspired O_2 (FiO_2) is used to simulate identical VO_2 and VCO_2. Indirect calorimetry results from publications were analyzed to determine the VO_2 and VCO_2 values to be tested for the validation.

Results: O_2 concentration in respiratory air is highest at inspiration, and can decrease to 15% during expiration. CO_2 concentration can be as high as 5% in expired air. To validate analyzers for measurements of FiO_2 up to 70%, ranges of O_2 and CO_2 concentrations to be tested were defined as 15–70% and 0.5–5.0%, respectively.

The mean VO_2 in 426 adult mechanically ventilated patients was 270 ml/min, with 2 standard deviation (SD) ranges of 150–391 ml/min. Thus, VO_2 and VCO_2 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.

Abbreviations: VO_2, volume of oxygen consumption; VCO_2, volume of carbon-dioxide production.

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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 (VO_2) and carbon dioxide production (VCO_2) correspond to energy expenditure [1]. The accuracy of the calorimeters depends on accuracy of the analyzers to measure O_2 and CO_2 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 VO_2 and VCO_2 [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 VO_2 and VCO_2 measurements of the new calorimeter: − Gas composition analysis aims to validate the O_2 and CO_2 analyzers; − Gas exchange simulation analysis aims to validate the measurements of VO_2 and VCO_2 using the CO_2 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 O_2 and CO_2 analyzers. A very simple and widely used method was adopted to build a precision gas mixing system to provide gas mixtures of predefined O_2 or CO_2 concentrations by diluting O_2 (99.9%) gas (or CO_2 gas; 1% or 5%) with nitrogen (N_2; 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 O_2 or CO_2 gas and N_2 gas simultaneously, to precisely adjust the O_2 or CO_2 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 O_2 and CO_2 concentrations by the indirect calorimeter analyzers are validated against predefined concentrations.

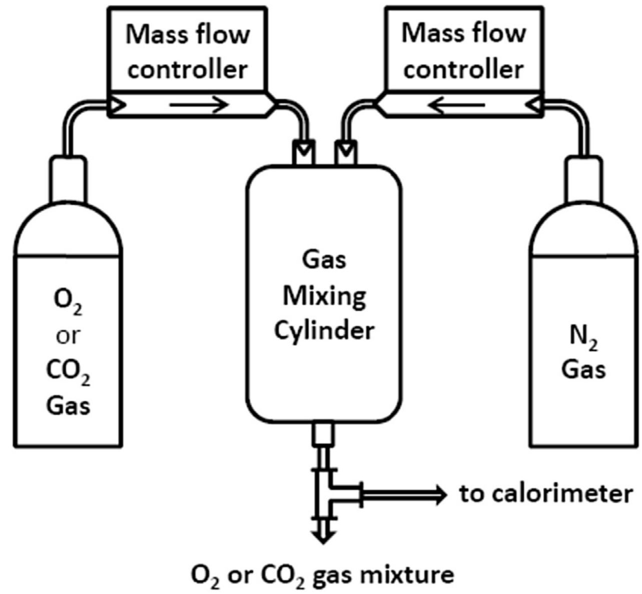

Fig. 1. Precision gas mixing system. O_2 or CO_2 gases are mixed with nitrogen gas to create flowing gas mixtures of predefined O_2 or CO_2 concentrations. The flow rates of the gases are regulated simultaneously by using two precision mass flow controllers. The gases are homogenized in the mixing cylinder before measurement by the indirect calorimeter. The flow rates can be adjusted to obtain gas mixtures of various O_2 or CO_2 concentrations.

2.1.2. Data analysis

Gas composition in respiratory gases were studied [9,10], to determine the ranges of O_2 and CO_2 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 (FiO_2) was also considered to determine the upper limit of O_2 concentration to be tested for the validation.

2.2. Gas exchange simulation

2.2.1. Procedures

Gas exchange simulator analysis aims at validating VO_2 and VCO_2 measurements in the mechanically ventilated setting. Gas exchange simulation system was developed by modifying the CO_2 injection method described by Weissman et al. [8] (Fig. 2). CO_2 gas is injected at a fixed rate into the simulated breath gas provided by the mechanical ventilator (Evita Infinity 500®, Drager®, Germany) to simulate VCO_2. The rate of CO_2 injection can be adjusted by the precision mass flow controller (EL-FLOW® F-201CV-500, Bronkhorst®, Germany) to directly simulate predefined VCO_2 levels. Flow rates of the CO_2 gases with different CO_2 concentrations were adjusted using the web-based gas conversion factor calculator (Fluidat® on the Net, https://www.fluidat.com/default.asp). By injecting CO_2 at the end of the inspiratory circuit and before a small mixing chamber (500 ml) and the test lung, the O_2 concentration in the artificial breath gas provided by the mechanical ventilator is diluted by the injected CO_2 gas by the time the gas mixture reaches the expiratory circuit. Decreased O_2 concentration in the expiratory circuit air was detected by the calorimeter as VO_2, thus completing the gas exchange simulation. The use of CO_2 gas with identical concentration to the O_2 provided by the mechanical ventilator enables the simulation of VO_2 and VCO_2 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

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