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Original article

In vitro validation of indirect calorimetry device developed for the ICALIC project against mass spectrometry

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SUMMARY

Rationale: Accurate evaluation of the energy needs is required to optimize nutrition support of critically ill patients. Recent evaluations of indirect calorimeters revealed significant differences among the devices available on the market. A new indirect calorimeter (Q-NRG®, Cosmed, Roma, Italy) has been developed by a group of investigators supporting the international calorimetry study initiative (ICALIC) to achieve ultimate accuracy for measuring energy expenditure while being easy to use, and affordable. This study aims to validate the precision and the accuracy of the Q-NRG® in the *in-vitro* setting, within the clinically relevant range for adults on mechanical ventilation in the ICU. Mass spectrometry is the reference method for the gas composition analysis to evaluate the analytic performances of the Q-NRG®.
Methods: The accuracy and precision of the O_2 and CO_2 measurements by the Q-NRG were evaluated by comparing the measurements of known O_2 and CO_2 gas mixtures with the measurements by the mass spectrometer (Extrel, USA). The accuracy and precision of the Q-NRG® for measurements of VO_2 (oxygen consumption) and VCO_2 (CO_2 production) at clinically relevant ranges (150, 250 and 400 ml/min STPD) were evaluated by measuring simulated gas exchange under mechanically ventilated setting at different FiO_2 settings (21–80%), in comparison to the reference measurements by the mass spectrometer-based mixing chamber system.
Results: The measurements of gas mixtures of predefined O_2 and CO_2 concentrations by the Q-NRG® were within 2% accuracy versus the mass spectrometer measurements in Passing Bablok regression analysis. In a mechanically ventilated setting of FiO_2 from 21 up to 70%, the Q-NRG® measurements of simulated VO_2 and VCO_2 were within 5% difference of the reference mass spectrometer measurements.
Conclusion: In vitro evaluation confirms that the accuracy of the Q-NRG® indirect calorimeter is within 5% at oxygen enrichment to 70%; i.e. maximum expected for clinical use. Further recommendations for the clinical use of the Q-NRG® by will be released once the ongoing multi-center study is completed.

1. Introduction

Accurate evaluation of the energy needs is required for adequately feeding critically ill patients [1,2]. For this reason, guidelines issued by both the European and American clinical nutrition societies recommend measuring energy expenditure by indirect calorimetry [3–5]. However, recent evaluations of indirect calorimeters revealed significant differences among the devices used for the measurements [6,7], raising questions regarding the accuracy of the devices available on the market. A new indirect calorimeter (Q-NRG®) has been developed by a group of investigators supporting the international calorimetry

Abbreviations: FiO_2, fraction of inhaled oxygen; FeO_2, fraction of exhaled oxygen; $FeCO_2$, fraction of exhaled CO_2; $FedCO_2$, fraction of exhaled CO_2 after dilution; VO_2, volume of consumed oxygen; VCO_2, volume of produced CO_2; RQ, respiratory quotient.

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study initiative (ICALIC) in collaboration with a manufacturer (Cosmed, Italy) to achieve ultimate accuracy for measuring energy expenditure while being easy to use, and affordable [8]. In order to evaluate the accuracy and precision of the Q-NRG®, *in-vitro* test methods have been proposed with predefined goals [9].

The aim of the current study was to validate *in-vitro* the precision and the accuracy of the newly developed indirect calorimeter in the clinically relevant measurement ranges for adults on mechanical ventilation in the ICU. Mass spectrometry was selected as the reference method for the gas composition analyses to evaluate the analytic performances of the Q-NRG®. None of the calorimeters available on the market have passed this level of critical tests.

2. Materials and methods

2.1. Study device

The Q-NRG® has been developed according to the technical and practical requirements defined by the ICALIC investigators (ref [8]). The requested features include; rapid startup and warm-up free operation, lightweight and compact body, quick calibration, rapid measurements, easy operation, and documented accuracy of FiO_2 level up to 70% [Supplemental Fig. 1].

The Q-NRG® is equipped with a dynamic micro-mixing chamber (2 ml) to enable rapid adaptation to the changes of metabolic rate while maintaining the stability of the conventional mixing chamber technique. A conventional mixing chamber device consisted of a large (5–8 L) mixing chamber to collect the entire amount of expired air, which required up to 15 min to reach the equilibrium concentration of the gas mixture. The dynamic sampling technology of the Q-NRG® allows for collection of minimal amount of expired air into the micro-mixing chamber by rapidly adapting to the expiratory air flow rate, enabling prompt response to the metabolic change of the measured subject.

2.2. Study design

In-vitro tests were planned to evaluate the accuracy of the O_2 and CO_2 analyzers and the VO_2 (volume of consumed oxygen; ml/min STPD) and VCO_2 (volume of produced CO_2; ml/min STPD) measurements of the Q-NRG®. Experimental models to generate gas mixtures of predefined O_2/CO_2 concentrations (i.e. Gas mixture analysis) and to simulate VO_2 and VCO_2 conditions under mechanical ventilation (i.e. Gas exchange simulation analysis) were combined to validate the measurements by the Q-NRG® against the reference measurements by the mass spectrometer [9]. These methods are described below.

2.3. Gas mixture analysis model

Gas mixture analysis allows for the evaluation of the performances of O_2 and CO_2 analyzers. O_2 and CO_2 gases were diluted in nitrogen (N_2) gas using precision mass flow controllers (F-201CV-20k, F-201CV-500; Bronkhorst, Germany) to create gas mixtures with various O_2 and CO_2 concentrations. High purity O_2 gas (99.9995%, Carbagas, Switzerland) and N_2 gas (99.999%, Carbagas, Switzerland), and high precision CO_2 gas (1% and 5%, ±0.02% accuracy, Airliquid, USA) were used to create the predefined gas mixtures. O_2 and CO_2 concentrations were adjusted within the ranges that are observed during calorimetry in the clinical setting [10]. The flow controllers were allowed to warm up for 30 min prior to the start of the experiments to obtain stable flow control. After setting the flow rates of the gases to the amounts needed for the desired concentration, the measured flow rates were monitored on the control screen to confirm adequate and stable flow rate. The gas mixture was allowed to run for at least 1 min after confirming stable flow rates to ensure sufficient homogenization of the mixed gases. The created gas mixture was sampled and measured directly by the mass spectrometer. The limit of accuracy was predefined as 2% of the targeted concentration for both O_2 and CO_2.

2.4. Gas exchange simulation analysis model

Gas exchange simulation analysis allows for the evaluation of VO_2 and VCO_2 measurements of the Q-NRG®. Gas exchange of a mechanically ventilated subject was simulated using the gas dilution principle [9]. Briefly, a mechanical ventilator (Evita Infinity 500®, Dräger, Germany) was used to generate simulated breath cycles in volume controlled mode (tidal volume 500 ml, respiratory rate 15/min), in different levels of fraction of inhaled oxygen (FiO_2). CO_2 gas of identical concentration to FiO_2 was injected into an artificial lung using a precision mass flow controller. The injected CO_2 simulated the VCO_2 while the resulting dilution of the O_2 concentration simulated the VO_2, at a theoretical respiratory quotient (RQ; $=VCO_2/VO_2$) of 1.0. CO_2 gas flow was adjusted to simulate clinically relevant VO_2 and VCO_2 values of 150, 250, and 400 (ml/min, STPD). High-precision mixtures of 21, 40, 60, 70, and 80% O_2 or CO_2 (Balance = N_2) were used to simulate clinically relevant FiO_2; measurements at 70 and 80% FiO_2 were conducted to test the measurement limit of the Q-NRG®.

2.5. Mass spectrometer

Quadruple mass spectrometer (MAX 300-LG®, Extrel®, Pittsburgh, USA) designed for gas analysis was specially tuned for breath air composition measurements. Questor 5® Process Control Software (Extrel®, Pittsburgh, USA) was used to monitor and control device functions during gas analysis, as well as collecting and exporting the measured results. Gas compositions were measured by relative analyses of the ambient gas ions; N_2, O_2, argon, and CO_2. Ultra high purity N_2 gas (99.9997%, Carbagas, Switzerland) was used for the background calibration, and reference gas (16% O_2, 5% CO_2, balance N_2, Airliquid, USA) with accuracy certification of ±0.02% was used to calibrate the O_2 and CO_2 concentration readings.

2.6. Mass spectrometry system for validating gas exchange simulations

The mass spectrometer was used to analyze gas compositions of the inspiratory and expiratory air samples [Fig. 1]. Inspiratory gas was sampled directly from the ventilator circuit to measure inspiratory O_2 and CO_2 (FiO_2, $FiCO_2$). Expiratory gas was first collected in the mixing chamber, where it was measured for the exhaled O_2 (FeO_2) and CO_2 ($FeCO_2$) concentrations. The collected gas was then exhausted into a constant flow of air, generated by a flow generator (Cosmed, Rome, Italy) and monitored by a mass flow meter (Sensirion, Zurich, Switzerland). The constant flow of gas was collected in a second mixing chamber, where it was measured for CO_2 ($FedCO_2$) for the second time. The concentrations of CO_2 before ($FeCO_2$) and after ($FedCO_2$) the dilution were compared, together with the constant flow rate (Q, L/min) to calculate the volume of exhaled air (Ve, L/min). The results of gas composition measurements and exhaled gas volume were used to

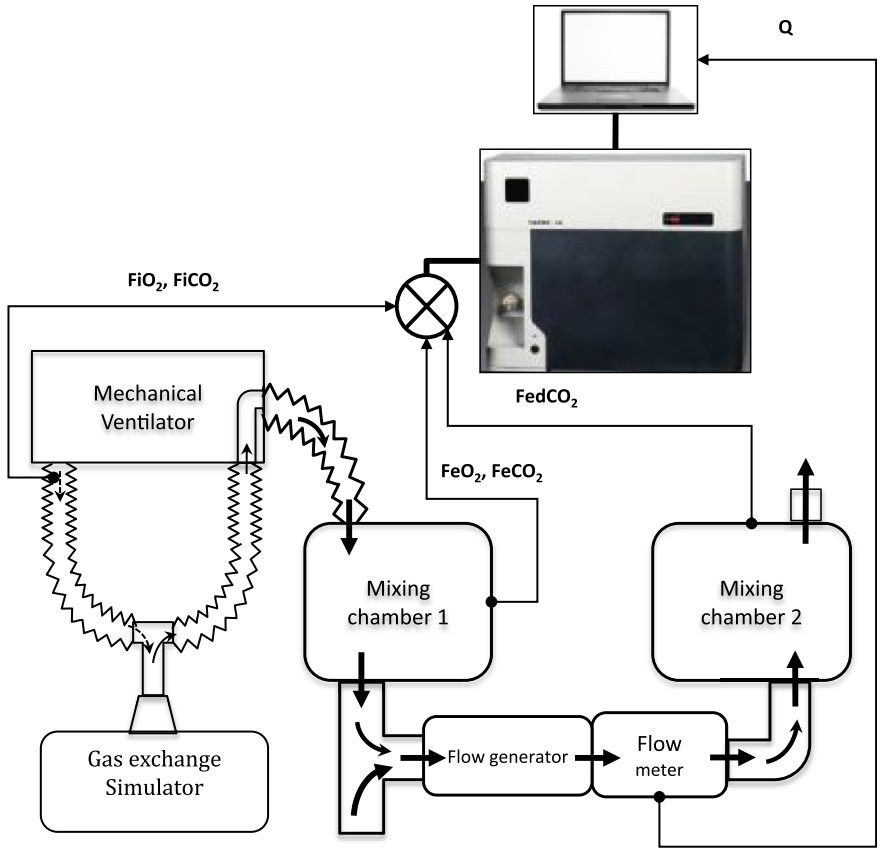

Fig. 1. Mass spectrometer based mixing chamber indirect calorimetry system: Mass spectrometer has an air system consisting of 2 mixing chambers and a constant flow generator. The mass spectrometer serves as the gas composition analyzer. FiO_2 is measured by sampling the inspiratory arm of the ventilator circuit. Simulated exhaled air will be collected inside mixing chamber 1, where FeO_2 and $FeCO_2$ will be measured. The exhaled air will be mixed in a constant flow generated by an independent flow generator, which is monitored by a flow meter. Mixed gas will be collected inside mixing chamber 2, where diluted CO_2 content ($FedCO_2$) will be measured. Exhaled air volume can be calculated as the result of the CO_2 dilution by a known constant flow of ambient air. O_2 reduction and CO_2 elevation in a known amount of exhaled air volume enables the calculation of VO_2 and VCO_2. (FiO_2: fraction of inhaled oxygen, FeO_2: fraction of exhaled oxygen, $FeCO_2$: fraction of exhaled CO_2, $FedCO_2$: fraction of exhaled CO_2 after dilution, VO_2: volume of consumed oxygen, VCO_2: volume of produced CO_2).

calculate the VO_2 and VCO_2. Simulations were considered valid if the measured RQ was within 5% of the targeted value of 1.0 (0.95–1.05), and measured VO_2 values within 10% of the targeted values. Differences up to 15% were allowed for high FiO_2 settings (70 and 80%).

2.7. Data acquisition and statistical analyses

i) Gas mixture analysis

Ten measurements of each simulated concentration for a total of 120 measurements for O_2 test and 130 measurements for CO_2 test were obtained using the Q-NRG® under control panel mode, each measurement after 5-second sampling of gas to flush the analyzer and the pneumatic circuit. Mass spectrometer measurements were obtained simultaneously as continuous recordings, and averaged for the 5-second acquisition period corresponding to the sampling period by the Q-NRG® to generate 10 separate measurements of each simulated concentration for the comparison.

The systematic difference (constant and proportional) between O_2 and CO_2 gas mixture measurements by the Q-NRG® were analyzed as comparison with the reference measurements by the mass spectrometer using, the Passing Bablock regression analysis (Analyze-it software, UK).

ii) Gas exchange simulation analysis

Simultaneous measurements were conducted with the Q-NRG® and the reference mass spectrometer based mixing chamber system. The two devices were connected to the simulation circuit simultaneously. The results were obtained as consecutive averages of 5-minute durations. Measurements were repeated at least 20 times to obtain 10 valid measurements for the comparison.

The VO_2 and VCO_2 measurements of the simulated gas exchange by the Q-NRG® were compared to the reference mass spectrometer system; less than 5% differences from the MS values were considered acceptable. Accuracy and precision of the VO_2 and VCO_2 measurements by the Q-NRG® were evaluated as % differences of the mean values against the measurements by the mass spectrometer system, and also as ratios to the measurements by the reference mass spectrometer based mixing chamber indirect calorimetry system. The mean values of VO_2 and VCO_2 were compared according to the simulated conditions in the different FiO2 settings, and also as the overall difference for all simulated conditions within each FiO2 setting. The ratios were presented as box-plots of the median and inter-quartile ranges; ratios within the range of 0.95–1.05 were considered acceptable. All graphs were created using SPSS Statistics Software (IBM, USA).

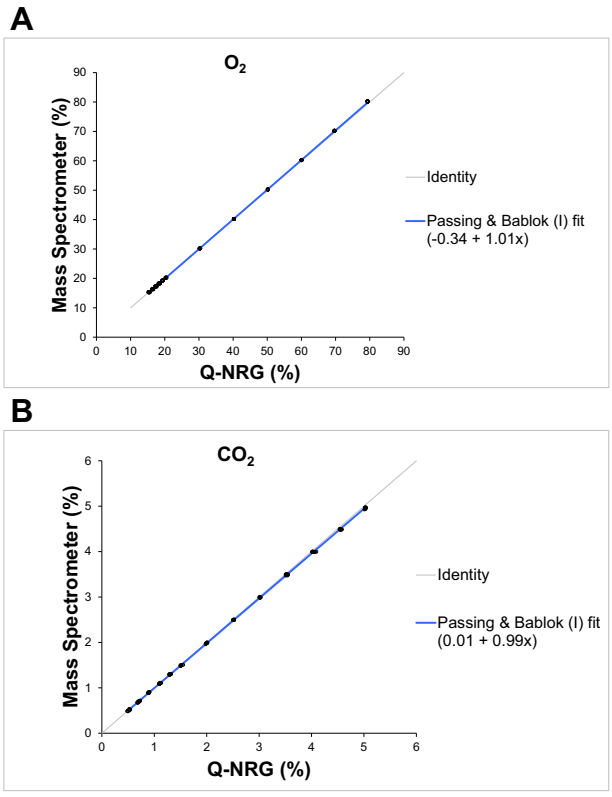

Fig. 2. Linearity of gas composition measurements by the mass spectrometer versus the new indirect calorimeter (Q-NRG®): According to the Passing-Bablok regression analysis, the constant and proportional biases (95% confidence intervals) were −0.34 (−0.39 ~ −0.29) and 1.01 (1.01–1.01), respectively for O_2 concentration (A), 0.01 (0.00–0.01) and 0.99 (0.99–0.99), respectively for CO_2 concentration (B). Black dots depict the individual measurements, and blue lines depict the regression line. A. O_2 concentration in gas mixture. B. CO_2 concentration in gas mixture.

3. Results

3.1. Gas mixture analysis

The O_2 gas mixture measurements by the Q-NRG® presented a constant bias of −0.1 while the proportional bias was 1.01, according to the Passing Bablock analysis against the O_2 concentration measured by the mass spectrometer [Fig. 2A]. The CO_2 gas measurements presented a constant bias of −0.02, and a proportional bias of 1.00 [Fig. 2B].

3.2. Gas exchange simulation analysis

Measurements of simulated gas exchange at different FiO_2 levels using the Q-NRG® were compared with the measurements by the mass spectrometer based mixing chamber system. Percent difference of the Q-NRG® measurements against the reference mass spectrometer measurements were within the predefined limits of 5% accuracy in all simulated gas exchange levels (150, 250, and 400 ml/min STPD) at FiO_2 of 21, 40, 60, and 70% [Table 1]. VO_2 and VCO_2 measurements exceeded the limits at FiO_2 80%, suggesting the limit of the accuracy of the system at this range of FiO_2.

VO_2 and VCO_2 measurements by the Q-NRG® were also analyzed as the ratio against the mass spectrometer based mixing chamber system measurements [Fig. 3]. The median results were within the 5% acceptable range for all measurements conducted at FiO_2 21, 40, and 60%, in all simulated range of VO_2 and VCO_2. Both VO_2 and VCO_2 measurements presented less precision at FiO2 70%, and exceeded the limits at FiO_2 80% [Supplemental Tables 1 and 2].

4. Discussion

The present study demonstrates the precision and the accuracy of the newly developed indirect calorimeter (Q-NRG®), when compared against the gold standard mass spectrometer. VO_2 and VCO_2 measurements in the gas exchange simulation analyses are within 5% of accuracy for values within the clinically relevant range of FiO_2 up to 70%. The results support the technical specification of the Q-NRG®, designed for measuring patients mechanically ventilated at FiO_2 up to 70%. None of the calorimeters available on the market passed this level of critical tests.

4.1. Mass spectrometry as gold standard

Mass spectrometry is the gold standard method of gas composition analysis [11,12]. The technology is used in situations where the accuracy, precision, and the resolution of the measurements are of great priority, such as atmospheric gas analyses for environmental monitoring and researches. It can be applied to breaths gas analyses and metabolic measurements of various populations, owing to the rapid response, limited sampling amount, and the ultimate accuracy and precision [12].

In this study, mass spectrometry was selected as the reference method for the gas composition analysis to evaluate the analytic performances of the Q-NRG®. Such an approach has never been used to validate commercially available calorimeters, except for the Deltatrac Metabolic Monitor® [11,13]. The Deltatrac® was long regarded as the gold standard of indirect calorimetry and was used as the reference device in many of the recent studies to evaluate or validate the measurements by the commercially available indirect calorimeters [14,15]. Although a well maintained Deltatrac® is an accurate and reliable device, it has come off production more than a decade ago and is no longer supported by the manufacturer. In addition, these validation studies have been conducted in the clinical setting, precluding the possibility to determine the absolute accuracy of the tested devices [14,15]. The *in vitro* nature of the current study enables the evaluation of the accuracy and precision of the measured values against the predefined values that were carefully planned for the clinical relevance of the results [9]. Moreover, the use of the mass spectrometer, the gold standard for gas composition measurements, strengthens the validity of the results.

4.2. Measurement of gas composition

Gas composition analysis was conducted on a system mixing two gases to create a new gas mixture with predefined concentrations of O_2 or CO_2. The results obtained by the mass spectrometer in the current study clearly demonstrate that the system was able to generate accurate and precise flowing gas mixtures to be used for validating the new indirect calorimeter. The Q-NRG® generated measurements within sufficient accuracy and precision in comparison to the mass spectrometer measurements. Gas flow rates were determined by calculating the conversion factors according to the concentration and flows of the original gases using specialized website (Fluidat® on the web, Bronkhorst®, The Netherlands) [9]. Measures were taken to optimize the technical evaluation, including warm-up time of

Table 1
Accuracy and precision of the gas exchange simulation analyses. Means of 10 simultaneous measurements by the Q-NRG® indirect calorimeter and the mass spectrometer based mixing chamber system are compared. Duration of each measurement was 5 min. Results are listed according to the FiO_2 and simulated VO_2 and VCO_2 levels. Measured values are presented as mean (standard deviation). Mass spectrometer measurements are presented in italics. Percent differences were calculated using the mass spectrometer measurements as the reference. Results that exceed the predefined 5% limits presented in bold type. (FiO_2: fraction of inhaled oxygen, VO_2: volume of consumed oxygen, VCO_2: volume of produced CO_2).

FiO_2 (%)	21			40			60			70			80		
Simulated VO_2 (ml/min)	150	250	400	150	250	400	150	250	400	150	250	400	150	250	400
A. VO_2 simulation measurements															
Q-NRG® (ml/min)	145 (4.6)	236 (1.3)	380 (1.5)	141 (3.8)	246 (3.2)	379 (1.6)	137 (3.1)	222 (2.8)	359 (5.3)	147 (1.5)	236 (13.3)	397 (12.6)	129 (13.9)	216 (18.0)	343 (5.2)
Mass Spectrometer (ml/min)	*149 (2.9)*	*243 (1.9)*	*387 (2.2)*	*146 (1.9)*	*250 (2.9)*	*386 (1.6)*	*142 (3.2)*	*228 (2.2)*	*374 (4.2)*	*140 (3.2)*	*226 (7.8)*	*400 (23.3)*	*141 (6.9)*	*223 (3.9)*	*346 (8.2)*
% difference	−3.2	−3.0	−1.7	−3.5	−1.7	−1.8	−3.7	−2.8	−4.1	4.9	4.1	−0.8	**−8.6**	−2.8	−0.9
Overall % difference	−2.6			−2.3			−3.6			2.7			−4.1		
B. VCO_2 simulation measurements															
FiO_2 (%)	21			40			60			70			80		
Simulated VCO_2 (ml/min)	150	250	400	150	250	400	150	250	400	150	250	400	150	250	400
Q-NRG® (ml/min)	143 (4.9)	239 (1.7)	382 (2.0)	140 (1.1)	246 (6.2)	397 (1.7)	140 (0.6)	233 (1.0)	403 (3.0)	140 (8.2)	233 (9.9)	420 (18.6)	142 (5.6)	227 (7.3)	380 (13.1)
Mass Spectrometer (ml/min)	*147 (2.9)*	*240 (2.1)*	*383 (2.3)*	*141 (1.4)*	*246 (3.4)*	*384 (1.3)*	*141 (1.0)*	*233 (2.1)*	*390 (3.6)*	*140 (4.7)*	*232 (9.0)*	*420 (27.9)*	*142 (3.4)*	*241 (2.7)*	*381 (2.3)*
% difference	−2.5	−0.5	−0.2	−0.8	0.1	3.3	−1.0	0.1	3.4	0.5	0.4	0.2	−0.6	**−5.7**	−0.2
Overall % difference	−1.1			0.9			0.8			0.4			−2.2		

the flow controllers and visual confirmation of the flow rate. Calibrated gases with the highest possible precision were used, and the tests were conducted in a temperature-controlled environment [9].

Yet, the accuracy of the resulting gas mixture concentration can still be affected by factors such as the calculations for the gas control settings, the accuracy of the flow controllers, and the concentrations of the original gases. Mass spectrometer is the only method reliable enough to be considered as the reference for gas composition analysis in such a setting.

4.3. Measurement of gas exchange

Gas exchange analysis is based on the principle of gas dilution. This method has been documented in previous publications to validate the measurements of indirect calorimeters [16]. However, the method is prone to systematic errors, depending on the precision of injected CO_2 gas concentration and gas injection rates, as well as FiO_2 stability provided by the ventilator. These errors can significantly affect the simulated gas exchange and generate misleading results. Sufficient measures were taken to avoid such errors, namely the use of precision CO_2 gas mixtures and mass flow controllers for the gas injection, as well as the use of pre-mixed O_2 gas instead of O_2 mixture from the ventilator to provide stable FiO_2.

The only way to verify the precision of the model is to conduct the same measurement using a reference device, in our case the mass spectrometer. The mass spectrometer made it possible to correct possible slight imprecisions in O_2 and CO_2 concentrations used for the simulation. Gas exchanges were then simulated using a set-up made of dilution chambers connected to a flow generator and the mass spectrometer, in order to obtain VO_2 and VCO_2 analysis similar to an indirect calorimeter. Then, the simulated gas exchange was verified using the mixing chamber system that was adapted for using the mass spectrometer as the gas composition analyzer. The mixing chamber method has been repeatedly validated for indirect calorimetry measurements to be used for clinical and research purposes [13]. The verification of the simulated VO_2 and VCO_2 conditions using this system has confirmed the validity of the gas exchange by the simulator. Thus, the gas exchange simulation method has been proven to be sufficiently accurate for the validation of the indirect calorimetry measurements by the new indirect calorimeter. Q-NRG® was able to generate results within the predefined limits for VO_2 and VCO_2 simulations at FiO_2 settings of 21, 40 and 60%, and 70%. At FiO_2 80%, the measurements by the Q-NRG® exceeded the 5% limits suggesting the limit of the device at this level of O_2 concentration. These results are in agreement with the technical specifications of the Q-NRG®, designed for measuring energy expenditure in adult ICU patients who are mechanically ventilated at FiO_2 up to 70%.

4.4. Study limitations

The limitation of the current validation is the *in vitro* nature of the investigation, which is also the greatest strength of the study. The gas exchange simulation model does not account for the humidity or the temperature encountered in human subject measurements. These effects can be corrected using predefined equations and has been validated in basic gas physiology studies. Moreover, the device is recommended for use with heat and moisture exchange filter to avoid random effects of condensation droplets that affect gas sampling and flow monitoring during calorimetry measurements. Mode and setting of the ventilator was fixed throughout the investigation, while it will vary according to patient condition in the ICU. The variable

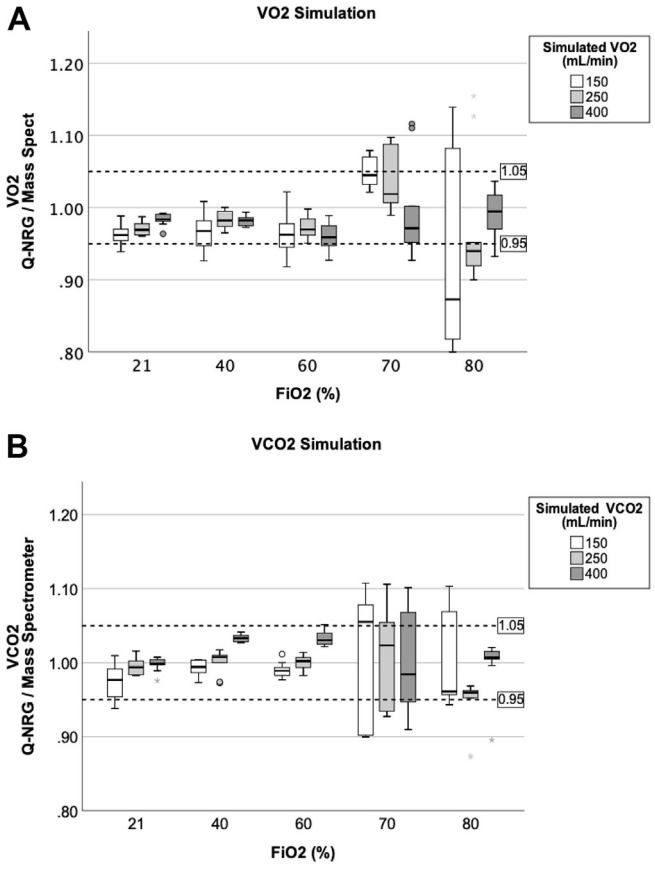

Fig. 3. VO_2 and VCO_2 measurements by the Q-NRG® compared to the reference mass spectrometer system: Results are presented as ratios Q-NRG® measurements against the mass spectrometer measurements of simulated VO_2 and VCO_2. Boxplots depict the median and inter-quartile ranges of 10 measurements for each target simulation in 4 different FiO_2 settings (21, 40, 60, 70, and 80%). Dotted lines depict the 5% limits of accuracy. (VO_2: volume of consumed oxygen, VCO_2: volume of produced CO_2, FiO_2: fraction of inhaled oxygen), A. VO_2 measurements, B. VCO_2 measurements.

conditions including the type of ventilator can introduce random errors in gas exchange measurements. As random errors are difficult to simulate comprehensively in the *in vitro* setting, these effects will be investigated as a part of the secondary outcomes in the clinical study, currently underway in 9 centers from 8 different countries to investigate the ease of use of the Q-NRG® calorimeter.

5. Conclusion

In vitro evaluation confirms that the accuracy of the Q-NRG® indirect calorimeter is within the 5% at oxygen enrichment up to 70% expected for clinical use. Further recommendations for the clinical use of the Q-NRG® by will be released once the ongoing multi-center study is completed.

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Statement of authorship

Taku Oshima and Claude Pichard have designed and conducted the study, analyzed the results, and outlined this manuscript. Yves Marc Dupertuis, Marta Delsoglio, Severine Graf, and Claudia-Paula Heiddegger contributed to the study design, conducted the study, and critically reviewed the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.05.004.

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