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Original article

The clinical evaluation of the new indirect calorimeter developed by the ICALIC project

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SUMMARY

Background & aims: The ICALIC project was initiated for developing an accurate, reliable and user friendly indirect calorimeter (IC) and aimed at evaluating its ease of use and the feasibility of the EE measurements in intensive care unit (ICU).

Methods: This was a prospective unblinded, observational, multi-center study. Simultaneous IC measurements in mechanically ventilated ICU patients were performed using the new IC (Q-NRG®) and currently used devices. Time required to obtain EE was recorded to evaluate the ease of use of Q-NRG® versus currently used ICs and EE measurements were compared. Conventional descriptive statistics were used: data as mean ± SD.

Results: Six centers out of nine completed the required number of patients for the primary analysis. Mean differences in the time needed by Q-NRG® against currently used ICs were −32.3 ± 2.5 min in Geneva (vs. Deltatrac®; $p < 0.01$), −32.3 ± 3.1 in Lausanne (vs. Quark RMR®; $p < 0.05$), −33.7 ± 1.4 in Brussels (vs. V-Max Encore®; $p < 0.05$), −26.4 ± 7.8 in Tel Aviv (vs. Deltatrac®; $p < 0.05$), −28.5 ± 3.5 in Vienna (vs. Deltatrac®; $p < 0.05$), and 0.3 ± 1.2 in Chiba (vs. E-COVX®; $p = 0.17$). EE (kcal/day) measurements by the Q-NRG® were similar to the Deltatrac® in Geneva and Vienna (mean differences ± SD: −63.1 ± 157.8 ($p = 0.462$) and −22.9 ± 328.2 (=0.650)), but significantly different in Tel Aviv (307.4 ± 324.5, $p < 0.001$). Significant differences were observed in Lausanne (Quark RMR®: −224.4 ± 514.9, $p = 0.038$) and in Brussels (V-max®: −449.6 ± 667.4, $p < 0.001$), but none was found in Chiba (E-COVX®; 55.0 ± 204.1, $p = 0.165$).

Conclusion: The Q-NRG® required a much shorter time than most other ICs to determine EE in mechanically ventilated ICU patients. The Q-NRG® is the only commercially available IC tested against mass spectrometry to ensure gas accuracy, while being very easy-to use.

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1. Introduction

The use of indirect calorimetry (IC) is the most precise and non-invasive method to measure in- and out-patients' energy expenditure (EE). The need for accurate determination of EE is increasing due to the rising prevalence of patients with clinical conditions characterized by difficulty in estimating EE and variability in energy needs [1]. Especially in ICU patients, EE is highly variable according to the initial injury, severity of disease, nutritional status, lean body mass, frequent changes in clinical condition, and treatment interventions. A number of studies have shown that predictive formulas used to calculate EE are inaccurate and not clinically relevant [2–4]. The hypothesis underlying the development effort of an ergonomic and precise IC is that the prescription of artificial nutrition based on the accurate determination of the patients' EE will allow the optimization of nutrition therapy, and enable monitoring of the metabolic response to the energy prescription, in order to avoid the negative impact of under- or overfeeding on clinical outcomes [5–7]. Energy provision based on the precise measurement of EE by IC is strongly recommended in recent multinational ESPEN 2019 guidelines [8].

Recent studies have shown that a majority of the commercially available IC are poorly accurate, difficult to use and expensive [9,10]. Given the inaccuracy of the estimation by equations and the limits of ICs on the market, the development of an accurate and reliable IC was considered to be a fundamental need for the clinical nutrition community and of utmost importance to personalize nutrition delivery targets [1]. Key factors in the development of a new IC, that were considered critical for wider implementation of IC measurements in critically ill patients, included ease of use and short duration of the measurement [11].

Therefore the multinational ICALIC project was initiated for developing and validating an accurate, reliable and easy-to-use device [1]. Centers with long standing experience in IC were included. This study aimed at evaluating the ease of use of this new IC in ventilated ICU patients by comparing the duration required for preparing the IC to obtain a clinically relevant EE, as well as the feasibility of the EE measurements compared to currently used IC in various clinical settings in different countries.

2. Methods

The primary outcome of this study was to evaluate the ease of use of the new IC (Q-NRG®, Cosmed, Roma, Italy) in ICU patients by measuring the duration needed to obtain a clinically relevant EE in comparison with currently used ICs. Secondary outcome was the comparison of the EE measurements of ICU patients using the Q-NRG® and currently used ICs in nine investigator centers to explore the impact of different clinical settings and practices. All lead investigators in each institution had extensive previous experience with ICs and were familiar with the procedures for measurements using their currently used ICs. Each investigator center was given a one-day training by the manufacturer on the use of Q-NRG®, and were asked to train the local investigators sufficiently before starting the study.

2.1. Study design

This was a prospective, unblinded, observational, multicenter study. Nine academic centers from eight nations were included for the primary analysis. Two centers were later included to collect additional data for secondary analyses.

The initial approval for study was obtained by the Geneva University Hospital from the Swiss authorities: Swissethics for the ethical conduct of the study (N° 15-137), and SwissMEDIC for the use of the newly developed IC (N°2016-MD-0031). The other study centers obtained authorization according to local regulations based on the original approval by the Swiss authorities. The study has been registered on ClinicalTrials.gov (NCT02796430).

2.2. Patients

ICU adult patients (>18 years), who required invasive mechanical ventilation at the investigator centers from September, 2017 until July, 2019 were eligible for the study. Those with extreme ventilation conditions (e.g. $F_iO_2 > 70\%$, PEEP > 10 cm H_2O, Peak ventilator pressure >30 cm H_2O), air leaks from thoracic drain tube, unstable hemodynamics, uncontrolled agitation, unstable body temperature, and premorbid conditions were excluded. Written consent was obtained from the patient or his/her legal representative.

2.3. Study devices

The Q-NRG® is an IC equipped with warm up-free operating technology, and a new intuitive device management software with touch screen operations for a user-friendly interface (see details below). The measurement technology is also upgraded with in-line flow meters and high precision gas analysis, using the dynamic micro-mixing chamber technique with chemical fuel cell O_2 and non-dispersive infrared adsorption digital CO_2 sensors [12]. EE measurement accuracy is further ensured by automatic room air calibration during each measurement, while calibration by means of high precision gas mixture cylinder is required only once a month. The accuracy and precision of gas analysis and RQ measurements by the Q-NRG® have been validated *in-vitro* using gas exchange simulations against mass spectrometry gas analysis and ethanol burning test [13,14].

Each investigator center compared the Q-NRG® with their own IC according to current clinical practice. The indirect calorimeters used in the trial were: Deltatrac® (Datex, Finland) in Geneva, Stockholm, Tel Aviv and Vienna; Quark RMR® (Cosmed, Italy) in Lausanne; Vmax® (Vyaire, California) in Brussels, and E-COVX® (Datex-Ohmeda, Finland) in Chiba. The technical features of the Q-NRG® and the other ICs are summarized in Fig. 1.

2.4. Study intervention

The primary outcome (duration to obtain clinically relevant IC measurements) was defined as the time required to complete the necessary procedures to prepare the device and obtain the first valid reading of measurement after turning on the IC. Time for warm up, patient data input, gas and flowmeter calibrations, and connection to the ventilator circuit were included in the measurement. Time measurements were conducted separately for the Q-NRG® and currently used ICs while preparing the devices according to the procedure stated in the user manual. The detailed procedures can be found in the Supplemental Table 1. Modifications to the basic procedures to adapt to the local risk management rules were allowed as long as they respected the user manual provided by the manufacturer, and included all the steps required for the time measurements. Interruptions of time measurements were recorded as patient care, IC malfunction, and other unexpected reasons.

EE measurements using the Q-NRG® and another IC were conducted simultaneously. The devices were connected to the ventilator circuit as described in the Supplemental Fig. 2. Duration of IC measurement was minimum 20 and up to 30 min, during which a steady-

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Name	Technology**	Spontaneous breath	Mechanical Ventilation	Warm up	Gas Calibration	
Q-NRG® (Cosmed, Italy)	Mixing chamber	Yes	Yes	No	Automatic 1/month	
Deltatrac II® * (Datex, Finland)	Mixing chamber	Yes	Yes	30 min	Manual Each measure	
Quark RMR® (Cosmed, Italy)	Breath by breath	Yes	Yes	30 min	Automatic Each measure	
Vmax Encore® (Vyaire, California)	Breath by breath Mixing chamber	Yes	Yes	30 min	Automatic	
E-COVX® (Datex-Ohmeda, Finland)	Breath by breath	No	Yes	No	No	

Fig. 1. Technical features of the Q-NRG® and comparator indirect calorimeters. The listed features are according to the instruction manuals. All systems are open-circuit devices (*: No longer commercially available).

state condition, defined as coefficient of variation (CV) of VO_2 and $VCO_2 \leq 5\%$ for 5 min measurement or CV $\leq$ 10% for 25 min measurement [15], was reached. Data obtained by the entire time frame were used to calculate the agreement between devices, in order to minimize the effect of short-term variations in unstable ICU patients. The details of the patient management during the IC measurements included the types of ventilators and ventilation modes, the various ranges of oxygen and airway pressure support, modes of sedation and patient's level of consciousness and severity of illness.

2.5. Sample size calculation and statistical analyses

The primary outcome was the duration required to obtain clinically relevant EE measurements with the Q-NRG®, in comparison to the duration needed with currently used ICs. Considering the difference of the currently used ICs, the staff expertise, and other practical issues between the study centers, we aimed to obtain the required number of outcome analysis data from each center. The estimated duration for setting up the currently used IC for EE measurements was 20 ± 5 min. We expected to reduce the time by 20% (effect size of 4 min) from the currently used IC at each study center. In order to achieve the level of statistical significance of 0.05 with the power of the analysis at 90%, 34 patient data were needed from each study center. Since the required data is only the time recording, the drop-out rate was expected to be 30%. Thus, 49 patient enrollments were needed to allow for analysis based on 34 valid outcome data for each institution.

Data are expressed as mean ± SD. The data analysis was *per* protocol using Student t-test for the primary analysis for the duration needed to start EE measurements in minutes by calculating for the means, at statistical significance of $p < 0.05$. Secondary analyses were carried out by comparing EEs measured by Q-NRG® and currently used ICs. EE from Q-NRG® and currently used ICs were analyzed by linear regression, repeated measures ANOVA, and Bland Altman plots. CV of EE was analyzed by ANOVA. Number of patients below 34 in four centers did not allow to apply a statistical analysis (see § power analysis above). All statistical analyses and calculations were carried out by SPSS version 26 (SPSS Inc, USA).

3. Results

Six centers completed the planned number of valid measurements during the study period to be included in the primary analysis for a total inclusion of 277 patients. The remaining centers included a smaller number of patients (Supplemental Table 2). Patients characteristics and demographic data varied among the institutions reflecting the different population of the countries and the different roles of the ICUs at each institution, as shown in Table 1. Treatments at the time of EE measurements including mechanical ventilation (devices and modes), vasoactive agents, and nutrition therapy, also varied among the institutions (Supplemental Table 3).

3.1. Primary outcome

The time required to obtain clinically relevant EE measurements with the Q-NRG® (minutes, mean ± SD) was 7.5 ± 1.8 in Geneva, 9.0 ± 2.7 in Lausanne, 5.3 ± 0.8 in Brussels, 10.9 ± 7.2 in Tel Aviv, 8.1 ± 2.1 in Vienna, and 5.1 ± 0.7 in Chiba. The differences between the institutions were largely attributable to local conduct rules (e.g. medical safety regulations, division of roles among medical professions, etc.) at each institution.

The time required to obtain clinically relevant EE measurements was significantly shorter ($p < 0.001$) with the Q-NRG® compared to most of the currently used ICs, namely the Deltatrac® in the centers in Geneva, Tel Aviv, and Vienna, Quark RMR® in Lausanne, and V-max® in Brussels (Fig. 2, Table 2). Mean differences (minutes, mean ± SD) were −32.3 ± 2.5 in Geneva, −32.3 ± 3.1 in Lausanne, −33.7 ± 1.4 in Brussels, −26.4 ± 7.8 in Tel Aviv, −28.5 ± 3.5 in Vienna. No difference was observed in comparison with the E-COVX® in Chiba ($p = 0.31$) with a mean difference of 0.2 ± 1.2 min. Of note, the E-COVX® does not require calibration during the preparation procedure.

3.2. Secondary outcome

EE measurements by the Q-NRG® were comparable to the measurements using the Deltatrac® in Geneva and Vienna (mean

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Table 1
Patients demographics.

	Geneva, CH (n = 49)		Lausanne, CH (N = 49)		Brussels, BE (N = 49)		Tel Aviv, IL (n = 48)		Vienna, AT (n = 48)		Chiba, JP (n = 34)	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age, years	61	17	58	17	65	12	59	19	67	13	62	16
Male, n (%)	28	(57)	34	(69)	33	(67)	34	(70)	36	(75)	16	(52)
Height, cm	170	9	169	9	172	10	167	8	173	8	160	13
Body Weight, kg	77	23	79	21	78	19	83	26	65	36	62	16
BMI	27	8	28	7	26	5	29	8	22	12	24	6
Harris-Benedict (kcal/d)	1536	396	1585	328	1605	372	1613	344	1412	528	1310	303
ESPEN Formula (kcal/d)	2040	669	2218	654	2072	765	2346	768	1698	962	1550	645
APACHE II	19	7	26	8	21	7	25	5	NA	NA	29	11
SAPS II	40	14	54	16	46	15	NA	NA	39	11	58	19
SOFA	7	2	7	3	7	3	8	3	8	3	9	5
Admission category, n (%)												
Medical	32	(65)	18	(36)	40	(82)	23	(48)	0	(0)	19	(56)
Emergency Surgery	12	(25)	27	(55)	5	(10)	21	(44)	14	(29)	4	(12)
Elective Surgery	3	(6)	2	(4)	3	(6)	4	(8)	34	(71)	11	(32)
Trauma	2	(4)	2	(4)	1	(2)	0	(0)	0	(0)	0	(0)
Sepsis n (%)	26	(36)	20	(32)	15	(31)	18	(37)	2	(4)	9	(27)
Comorbidities, n (%)												
Metabolic	17	(34)	10	(20)	4	(8)	20	(42)	5	(10)	4	(12)
Endocrine	5	(10)	1	(2)	3	(6)	20	(42)	2	(4)	2	(6)
Neurological	6	(12)	2	(4)	12	(24)	1	(2)	1	(2)	4	(12)
Chronic Liver	3	(6)	2	(4)	3	(6)	2	(4)	0	(0)	2	(6)
Chronic Lung	2	(4)	3	(6)	13	(27)	19	(40)	3	(6)	2	(6)
Chronic Heart	9	(18)	15	(30)	10	(20)	11	(23)	36	(75)	4	(12)
Dialysis	0	(0)	6	(12)	2	(4)	0	(0)	0	(0)	3	(9)
Immunocompromised	3	(6)	5	(10)	10	(20)	13	(27)	3	(6)	6	(18)

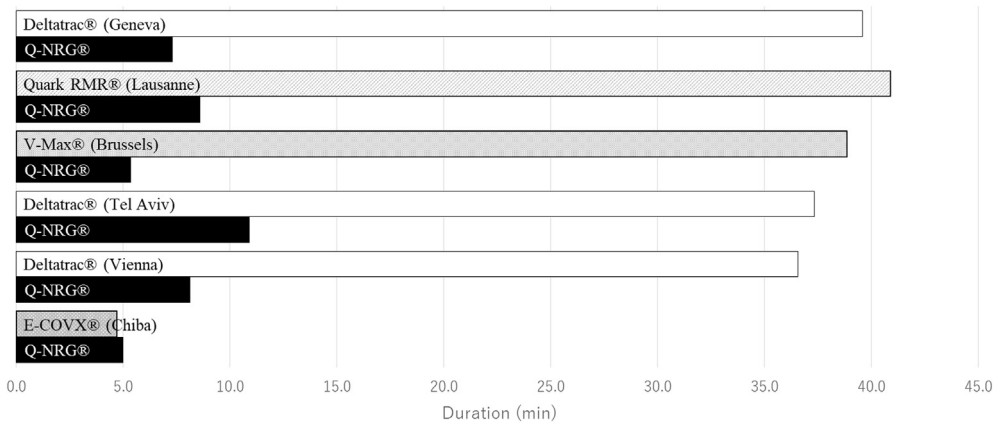

Fig. 2. Primary Outcome: Duration required to obtain clinically relevant EE measurements using the Q-NRG® vs. currently used indirect calorimeters. Comparison of duration required to obtain clinically relevant EE measurements against different currently used indirect calorimeters at each study center. The type of indirect calorimeter as comparator is indicated within the bar graph. $^{*}p < 0.05$.

Table 2
Primary outcome: Time required to obtain energy expenditure measurements using the Q-NRG® versus other indirect calorimeters marketed to date.

	Comparator	Mean Difference (min)	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper	T	df	p value (2-tailed)
Geneva	Deltatrac®	−32.3	2.5	0.4	−33.0	−31.5	−90.0	48	<0.001
Lausanne	QuarkRMR®	−32.3	3.1	0.4	−33.2	−31.4	−73.5	48	<0.001
Brussels	V-max®	−33.7	1.4	0.2	−34.1	−33.3	−172.3	48	<0.001
Tel Aviv	Deltatrac®	−26.4	7.8	1.2	−28.9	−24.0	−21.8	40	<0.001
Vienna	Deltatrac®	−28.5	3.5	0.5	−29.5	−27.5	−57.1	47	<0.001
Chiba	E-COVX®	0.2	1.2	0.2	−0.2	0.6	1.0	33	0.31

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Table 3
Secondary outcome: Energy expenditure measurements with the Q-NRG® compared to other indirect calorimeters marketed to date.

	Comparator	Mean Difference (kcal/d)	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper	t	df	p value (2-tailed)
Geneva	Deltatrac®	−63.1	157.8	22.5	17.8	108.5	2.8	48.0	0.462
Lausanne	QuarkRMR®	−224.4	514.9	73.6	76.5	372.3	3.1	48.0	0.038
Brussels	V-max®	−449.6	667.4	95.3	257.9	641.2	4.7	48.0	<0.001
Tel Aviv	Deltatrac®	−307.4	324.5	50.7	205.0	409.9	6.1	40	<0.001
Vienna	Deltatrac®	22.9	328.2	50.0	−123.9	78.1	−0.5	42	0.650
Chiba	E-COVX®	49.8	204.1	35.9	−0.21	0.64	0.65	33	0.312

differences ± SD of −63.1 ± 157.8 kcal and −22.9 ± 328.2 kcal, p values of 0.462 and 0.650, respectively), but significantly different in Tel Aviv center (307.4 ± 324.5 kcal, p < 0.001). A significant difference was found compared to the Quark RMR® in Lausanne (−224.4 ± 514.9 kcal, p = 0.038) and to the V-max® in Brussels (−449.6 ± 667.4 kcal, p < 0.001) but not when compared to E-

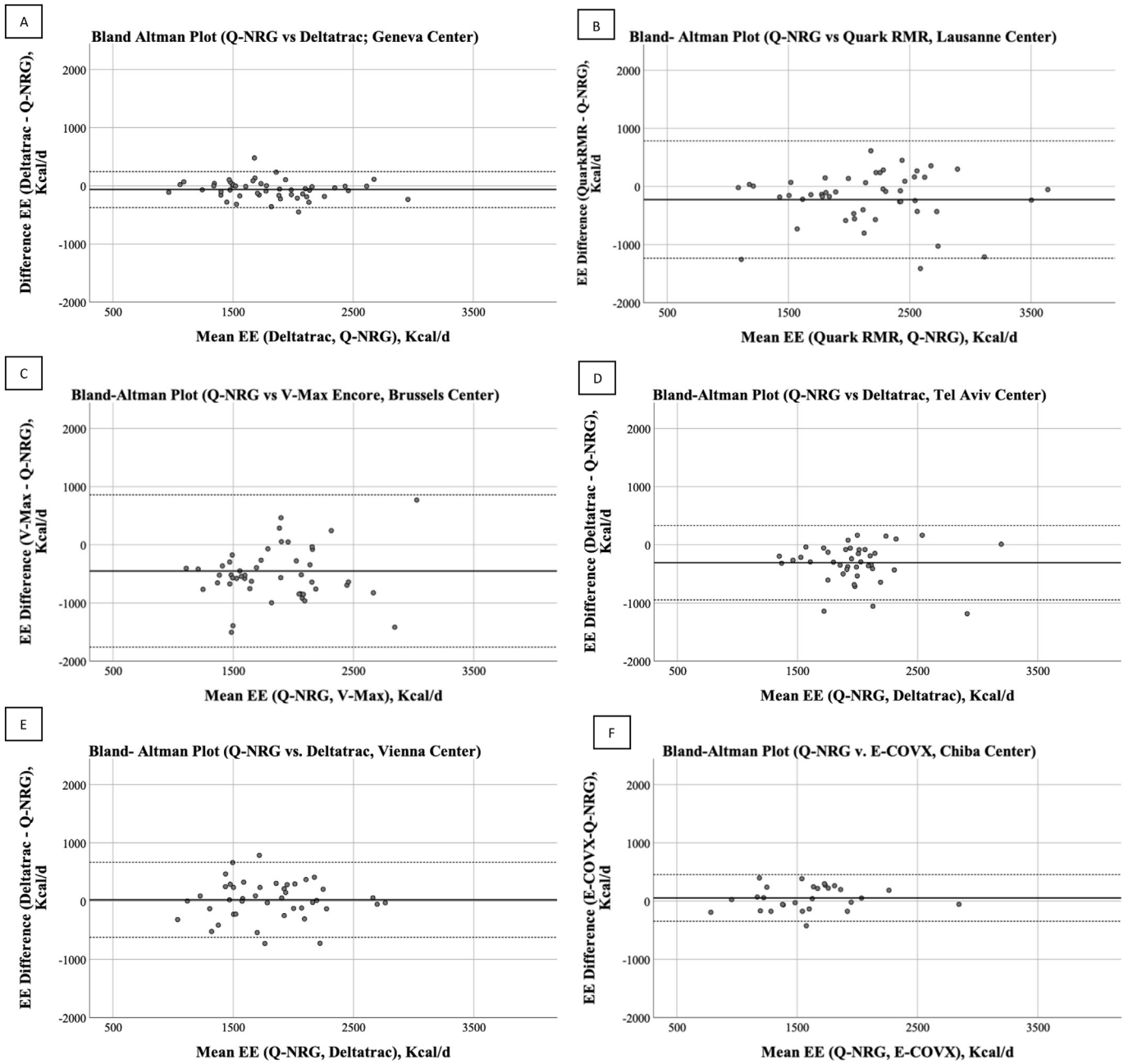

Fig. 3. Secondary outcome: Comparison of EE measured by the Q-NRG® and currently used indirect calorimeters. Bland-Altman plots of measured EE values using the Q-NRG® and currently used indirect calorimeters at each study center. The solid line indicates the mean difference and the dotted line indicates the standard limits of agreement (±1.96SD). (EE: energy expenditure). A. Geneva, vs Deltatrac., B. Lausanne, vs Quark RMR C. Brussels, vs Vmax D. Tel Aviv, vs Deltatrac E. Vienna, vs Deltatrac F. Chiba, vs E-COVX.

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COVX® in Chiba (49.8 ± 204.1 kcal, p = 0.165) (Table 3). The Bland-Altman plots depict measurements within the variance of 2SDs for the mean differences (Fig. 3). The difference in the limits of agreement was greatest against the V-max® in Brussels (±1308.1) followed by Quark RMR® in Lausanne (±512.9), and varied between centers using the Deltatrac®(±309.3~±643.3).

4. Discussion

The results of the ICALIC trial clearly demonstrate that in different clinical settings, in different countries and across a range of institutions, the Q-NRG® requires significantly less time for EE determination than most currently existing IC devices used at each investigator center.

The definition of the ICU patient's nutritional targets is the first task of a clinician before prescribing nutrition support. However, it is difficult to estimate the caloric needs of such patients due to the complex and dynamic metabolic alterations observed during critical illness [16,17]. The most recent international guidelines recommend the use of IC to measure the EE in ICU patients for the accurate determination of caloric needs [8,18,19]. Unfortunately, recent studies have shown that the commercially available ICs are inaccurate [9,10] and the inconvenience of the measurements (large device size, long warm up duration and calibration, complex maintenance, etc.) have led to a very limited use of IC in clinical practice [11].

The Q-NRG® was developed on behalf of the ICALIC study group of experts, with the goals of achieving the accuracy and precision of EE measurements required for clinical and research use, and at the same time to be simple to use and be available at an affordable cost [1]. The Q-NRG® features the new micro-dynamic mixing chamber technology with high precision gas analysers for the accuracy and stability of EE measurements, while enabling warm-up free operation with limited maintenance requirement of monthly gas calibration [1]. Once the technical requirements were incorporated into the new device, great efforts were made to optimize functional aspects and usability of the device. Functional requirements included the interactive software designed to be as intuitive as possible for clinicians at all levels (physician, registered dietician, respiratory therapist, nursing, advanced practice providers), while providing essential information for daily clinical care and when desired, more extensive data for research use. All features were tested in clinical and experimental settings during the device development. The primary outcome of this study demonstrates the unique ease-of-use of the Q-NRG® for routine clinical practice, as our results show a marked and significant reduction in the time required to obtain EE measurement when using the Q-NRG® in comparison with most of the other existing ICs.

Accuracy and precision of the EE measurements by the Q-NRG® has also been demonstrated in a strict experimental setting both for mechanically ventilated and spontaneously breathing subjects [12,14]. In the current study, due to the difficulty of evaluating the accuracy of EE measurements in the actual ICU patients, the EE measurements by the Q-NRG® were directly compared with the currently used IC at each investigator center. The EE measurements by the Q-NRG® compared well with the Deltatrac® in Geneva and Vienna, the Quark RMR® in Lausanne, and E-COVX® in Chiba. The difference in the limits of agreement observed with the Deltatrac® in Tel Aviv and V-Max Encore® in Brussels in the secondary analysis can be attributed to the difference in the patient conditions, mechanical ventilators and ventilator settings. The difference in the limits of agreement among centers using the Deltatrac® as comparator may be due to the variable performance of the Deltatrac® units at each center. The production and service by the manufacturer of the Deltatrac® have been discontinued, making it difficult to ensure optimal performance for all existing units.

Of note, the Q-NRG® is equipped with a micro-dynamic mixing chamber to enable highly responsive measurements with the stability of mixing chambers similar to existing ICs on the market. The device also features a second mixing chamber to stabilize FiO_2 readings in mechanical ventilation mode, as the instability of FiO_2 readings can have considerable effects on EE measurements [20]. Another feature of the Q-NRG® which favours its accuracy is the expired air sampling and flow measurement in the immediate proximity of the patient's mouth. This limits the effects of potential air leakage in the system and explains the discrepancy sometimes observed with other existing IC devices.

The global data collection in this study was aimed at evaluating the practical use of the device and not for detailed evaluation of the effects of confounding factors on IC measurements. A secondary analysis is warranted to investigate the influence of factors that potentially affect calorimetry measurements such as types and settings of ventilators and various patient conditions, using raw VO_2 and VCO_2 measurements by the Q-NRG® compared to other ICs.

4.1. Study limitations

Due to the impossibility of blinding the ICs, the comparisons were made in an open-label manner. To limit this bias, the protocol defined the necessary procedures to start EE measurements and required the procedures to be conducted in accordance with the user manual of each tested IC. In addition, the new device was compared to those routinely used in each center, which the investigators were more accustomed to the handle at study initiation. Another limitation is the lack of a standard outcome to measure the ease-of-use of a medical device. As time consuming procedure was considered to be one of the reasons for the limited IC application in critically ill patients, the primary outcome was defined as the duration needed to start EE measurements with the IC in the current study.

Finally, this study does not address the optimal timing of applying measured EE values during the ICU stay, as well as their repetition during the evolution of the treatments. Future studies should clarify these issues as well as the cost-effectiveness of IC.

5. Conclusion

The Q-NRG® indirect calorimeter required a much shorter duration to determine EE in mechanically ventilated ICU measurements than most of the other ICs on the market. This was true across multiple countries, institutions, and ICU settings. The Q-NRG® is the only commercially available device extensively tested against mass spectrometry to ensure accurate gas value results, while being very easy-to use by a range of medical providers. This combination of features should allow for a much broader use of IC and enable optimization, or personalization, of the nutritional support prescription and thereby limit the risk of under- or over-feeding known to promote increased morbidity. Future studies should focus on the optimal timing of EE measurements, as well as their repetition during the evolution of ICU care.

Authors' contribution

All authors contributed to the study conception, investigation and design. Material preparation, data collection and analysis were performed by TO and MD. The first draft of the manuscript was written by TO and all authors commented on previous versions of the manuscript. CP was responsible for funding acquisition and supervision. All authors read and approved the final manuscript.

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Conflict of interest

T Oshima received research grant from the public Foundation Nutrition 2000.

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Appendix A. Supplementary data

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References

[1] Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, et al. Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr 2017;36(3):651–62. https://doi.org/10.1016/j.clnu.2016.06.010.

[2] Fraipont V, Preiser JC. Energy estimation and measurement in critically ill patients. JPEN J Parenter Enteral Nutr 2013;37(6):705–13.

[3] Guttormsen AB, Pichard C. Determining energy requirements in the ICU. Curr Opin Clin Nutr Metab Care 2014;17(2):171–6.

[4] Zusman O, Kagan I, Bendavid I, Theilla M, Cohen J, Singer P. Predictive equations versus measured energy expenditure by indirect calorimetry: a retrospective validation. Clin Nutr 2018. https://doi.org/10.1016/j.clnu.2018.04.020.

[5] Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381(9864):385–93.

[6] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35(10):1728–37. https://doi.org/10.1007/s00134-009-1567-4.

[7] Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365(6):506–17.

[8] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38(1):48–79. https://doi.org/10.1016/j.clnu.2018.08.037.

[9] Sundstrom M, Tjader I, Rooyackers O, Wernerman J. Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr 2013;32(1):118–21.

[10] Graf S, Karsegard VL, Viatte V, Heidegger CP, Fleury Y, Pichard C, et al. 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(1):60–5.

[11] De Waele E, Spapen H, Honore PM, Mattens S, Van Gorp V, Diltoer M, et al. Introducing a new generation indirect calorimeter for estimating energy requirements in adult intensive care unit patients: feasibility, practical considerations, and comparison with a mathematical equation. J Crit Care 2013;28(5):884 e1–6.

[12] Oshima T, Dupertuis YM, Delsoglio M, Graf S, Heidegger CP, Pichard C. In vitro validation of indirect calorimetry device developed for the ICALIC project against mass spectrometry. Clin Nutr ESPEN 2019;32:50–5. https://doi.org/10.1016/j.clnesp.2019.05.004.

[13] Oshima TDYM, Delsoglio M, Graf S, Heidegger CP, Pichard P. In vitro validation of indirect calorimetry device developed for the ICALIC project against mass spectrometry clinical nutrition ESPEN. 2019.

[14] Delsoglio M, Dupertuis YM, Oshima T, van der Plas M, Pichard C. Evaluation of the accuracy and precision of a new generation indirect calorimeter in canopy dilution mode. Clin Nutr 2019. https://doi.org/10.1016/j.clnu.2019.08.017.

[15] Compher C, Frankenfield D, Keim N, Roth-Yousey L. Evidence analysis working G. Best practice methods to apply to measurement of resting metabolic rate in adults: a systematic review. J Am Diet Assoc 2006;106(6):881–903. https://doi.org/10.1016/j.jada.2006.02.009.

[16] Oshima T, Graf S, Heidegger CP, Genton L, Pugin J, Pichard C. Can calculation of energy expenditure based on CO2 measurements replace indirect calorimetry? Crit Care 2017;21(1):13.

[17] Graf S, Pichard C, Genton L, Oshima T, Heidegger CP. Energy expenditure in mechanically ventilated patients: the weight of body weight! Clin Nutr 2015. https://doi.org/10.1016/j.clnu.2015.11.007 (article in press).

[18] Gonzalez-Granda A, Schollenberger A, Haap M, Riessen R, Bischoff SC. Optimization of nutrition therapy with the use of calorimetry to determine and control energy needs in mechanically ventilated critically ill patients: the ONCA study, a randomized, prospective pilot study. JPEN J Parenter Enteral Nutr 2018. https://doi.org/10.1002/jpen.1450 (1941-2444 (Electronic)).

[19] McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2016;40(2):159–211.

[20] Oshima T, Heidegger CP, Makhlouf AM, Graf S, Dupertuis YM, Pichard C. Mon-LB310: can mechanical ventilators affect indirect calorimetry measurements? Clin Nutr 2017;36(Supplement 1):S293. https://doi.org/10.1016/S0261-5614(17)31116-0.