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Indirect calorimetry: the 6 main issues

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Abstract

Background and aims: Optimal nutritional therapy, including the individually adapted provision of energy, is associated with better clinical outcomes. Indirect calorimetry is the best tool to measure and monitor energy expenditure and hence optimize the energy prescription. Similarly to other medical techniques, indications and contra-indications must be acknowledged to optimise the use of indirect calorimetry in clinical routine. Measurements should be repeated to enable adaptation to the clinical evolution, as energy expenditure may change substantially. This review aims at providing clinicians with the knowledge to routinely use indirect calorimetry and interpret the results.

Method: We performed a bibliographic research of publications referenced in PubMed using the following terms: “indirect calorimetry”, “energy expenditure”, “resting energy expenditure”, “VCO_2”, “VO_2“, “nutritional therapy”. We included mainly studies published in the last ten years, related to indirect calorimetry principles, innovations, patient’s benefits, clinical use in practice and medico-economic aspects.

Results: We have gathered the knowledge required for routine use of indirect calorimetry in clinical practice and interpretation of the results. A few clinical cases illustrate the decision-making process around its application for prescription, and individual optimisation of nutritional therapy. We also describe the latest technical innovations and the results of tailoring nutrition therapy according to the measured energy expenditure in medico-economic benefits.

Conclusion: The routine use of indirect calorimetry should be encouraged as a strategy to optimize nutrition care.

Key words: Indirect calorimetry, energy expenditure, optimal nutritional therapy, medico-economics

Introduction

Optimal nutritional therapy requires an individually adapted provision of energy as close as possible to patient's real energy expenditure (EE). Indirect calorimetry (IC) is the clinical standard for measuring EE and monitoring the variations over time of healthy or diseased individuals. EE measurements allow to optimize the energy prescription in line with the concept of personalized medicine and goal-oriented therapy, including the adjustment of energy prescription to the dynamic metabolic changes related to the course of the disease or treatments. Both under- and over-nutrition have been shown to negatively influence the clinical outcomes (1, 2). In critical illness, an energy deficit around -6000 kcal has been identified as the cut-off for increased risks of nosocomial infections, prolonged mechanical ventilation and length of stay, as well as lower probability of hospital discharge (3). Therefore, repeated EE measurement has been proposed as Point of Care Testing allowing to identify adequacy, inadequacy or failure of an ongoing nutritional support (4). Until now IC is rarely used in clinical settings because the devices are unavailable, manpower demanding and expensive. A feasibility trial revealed that more than half of critically ill adult patients may benefit a metabolic evaluation to guide nutritional therapy (5) and the benefit in pediatric ICU's is even higher (6). The new generation of indirect calorimeters is characterized by a short duration to obtain a stable measurement, high level of precision and ergonomics, at affordable costs. These technical developments allow a broader use of IC for in- and out-patients. Therefore, the routine use of IC should be encouraged as a strategy to optimize nutrition care.

This review aims at sharing with clinicians the knowledge required for routine use of IC in their practice and interpretation of the results. A few clinical cases illustrate the optimal use of calorimetry as well as its limits, and the decision-making process to use the results for the prescription of optimal nutrition support. We also describe the latest innovations and related benefits, including medico-economics, of tailoring nutritional support according to EE measurement.

Methods

We performed a bibliographic research of publications referenced in PubMed database, using the following terms: "indirect calorimetry", "energy expenditure", "resting energy expenditure", "VCO_2", "VO_2", "nutritional therapy". We included mainly studies published in

83 the last ten years, related to indirect calorimetry principle, innovations, patient-centred
84 benefits, clinical use in practice and medico-economic aspects. Based on authors' clinical
85 experience, we provide few clinical cases.
86

87 **1. Principle of indirect calorimetry**

88 Many methods have been developed to assess EE in humans. (7). Briefly, four techniques are
89 available. The doubly-labelled water is the method of choice for measuring total energy
90 expenditure (TEE) over a period of time (8), but its routine application in clinical settings is
91 limited by the need to use of stable isotopes and mass spectrometer to analyse the samples
92 requiring days to obtain the results. Direct calorimetry and calorimetry room are technically
93 very demanding and costly, and their use is limited to research centers. The Fick method
94 allows to calculate the oxygen extraction across the pulmonary system and to extrapolate
95 the EE. It requires the insertion of a catheter in the pulmonary artery and its invasiveness
96 and relative imprecision limits its use (9).

97 Because of its non-invasiveness, repeatability and affordability, IC is the favourite tool to
98 measure EE in patients with various pathologies, either during spontaneous breathing or
99 mechanical ventilation. Indirect calorimeters measure oxygen consumption (VO_2), carbon
100 dioxide production (VCO_2), air flow and derive EE by the Weir's equation: EE(kcal/day) = 1.44
101 × [3.94 × VO_2(mL/min) + 1.11 × VCO_2(mL/min)+ urinary nitrogen(g/day) x 2,17] **(Figure 1).**
102 Nitrogen balance, that requires a precise quantification of both nitrogen intake and losses,
103 needs time, technical and human resources. The principle that nitrogen is neither utilized
104 nor produced during respiration has enabled the use of formulae deviate minimally from the
105 Weir's equation, neglecting nitrogen (10). J.B. Weir also proposed to derive accurate EE of
106 measurements from the fractional depletion of O_2 concentration alone, not requiring
107 measurement of CO2 emission. This equation is interesting in studies compromised by faulty
108 CO2 measurements (i.e. gas that interferes with CO2 sensing). Recently, Karl Kaiyala
109 reported full derivation of the Weir's equation and a validation in an experimental setup
110 (11).
111

112 The characteristics of the O_2 and CO_2 analysers is critical and has recently gained much in
113 terms of accuracy and linearity (7). Nevertheless, the upper limit for the measurement of O_2

concentration remains around 70%, because above this value of air enrichment a growing inaccuracy is observed due to the impact of small reading error on the overall calculation of EE. The ratio of VCO_2 to VO_2 (VCO_2/VO_2), called the respiratory quotient (RQ), reflects the rate of substrate oxidation in metabolically stable subjects (12). RQ is also a quality indicator of the measurement adequacy (physiological between 0.67 and 1.2).

Total energy expenditure (TEE) is the sum of basal energy expenditure (BEE), diet-induced thermogenesis (DIT) and activity induced energy expenditure (activity EE) (13) **(Figure 2)**. DIT is defined as the production of heat related to substrate oxidation during energy uptake. DIT varies according to the quantity and type of oxidized substrate (i.e. proteins, carbohydrates, and fat). Activity EE is the most variable component of TEE and depends on the type, intensity and frequency of physical activity. BEE measurements require specific conditions (i.e. free of physical and psychological stress, a thermally neutral environment, fasting state for more than 10 h prior to the measurement), rarely met in the clinical environment. Therefore, BEE is mostly aimed at research purpose. In clinical routine, IC is used to assess REE that reflects vital activities (cardiac, respiratory, secretory, cellular, basal muscle tone). REE contributes from 50% up to 75% of TEE **(Figure 2),** while activity EE has a very limited impact as only active exercise influences EE and nutritional adjustment is not indicated (14).

2. Current innovations in indirect calorimetry

Currently available indirect calorimeters are costly and technically complex, requiring a warm-up time and calibration before each EE measurement (up to 30 min), extensive disinfection after use and a computer to export and analyse the results. Lack of precision of these devices has also been reported compared to the Deltatrac Metabolic Monitor® (Datex, Finland) (15). This 35-year-old device is often considered to be the reference device, although its production was discontinued in the early 90s (16). This calorimeter uses an external mixing chamber which generates stable measurements because the expiratory gas is physically “averaged” before being analyzed. Nevertheless, the need for a large volume mixing chamber (≈ 5 liters) complicated the development of small devices, and the need for stabilization of gas concentrations in the mixing chamber limits the validity of short duration measurements (e.g. <10 min).

145 Recent indirect calorimeters use the “breath-by-breath” technology: O_2 and CO_2
146 concentrations are measured continuously by gas analyzers synchronized with expiratory
147 flow measurements, by the in-line flow meter, to allow gas exchange calculations with every
148 breath. Although this method permits rapid measurements and conception of small devices,
149 it is prone to errors due to the response time of the gas analyzers and software (17).

150 An international group of investigators with a strong interest in metabolic issues, the
151 International Multicentric Study Group for Indirect Calorimetry (ICALIC), has recently
152 developed and validated an IC device that meets clinical needs (Bottom-up strategy) (Table
153 1). This study has been supported by both the European Society for Clinical Nutrition and
154 Metabolism (ESPEN), and the European Society of Intensive Care Medicine (ESICM). The
155 newly developed calorimeter (Q-NRG® calorimeter, Cosmed, Italy) has been tested in vitro
156 (18) and evaluated in a multicentric study (17) **(Figure 3)**. The Q-NRG® is equipped with a
157 newly developed dynamic micro-mixing chamber (2 ml) which reduces time stabilization of
158 gas concentrations and hence the VO_2, and VCO_2 variability. The Q-NRG device samples just
159 a fraction of the expired subject's breath. The sampling flow rate of the device is constant
160 (around 200mL/min, as other calorimeter devices), but the quantity of the gas brought into
161 the Mixing Chamber is proportional to the ventilation of the subject; a patented algorithm
162 developed by the manufacturer, allows the system to sample a quantity of gas that is just a
163 fraction of the expired gas (around 0,015% of minute ventilation). The algorithm takes into
164 account the different levels of ventilation which can be achieved by different subjects at
165 rest, tailoring the sampling flow rate according to the minute ventilation. The ability to
166 obtain data in a short time and with a fast refresh is then reached by minimizing all the
167 pneumatic paths from the micro mixing chamber and the gas analyzers. To put in simple
168 words, the system is "miniaturized" (in a proportion of around 1:100) related to a standard
169 one. Possible variations in terms of water vapor are prevented by equilibrating humidity of
170 the sampled gas by means of a Nafion dryer placed in series with gas analyzers.

171 The device has been validated *in-vitro* and *in vivo* against the gold standard technology for
172 gas composition measurements, mass spectrometer (MAX300-LG, Extrel, Pittsburgh, USA)
173 (19, 20). The REE measurements are obtained in 5 to 7 minutes, on average, without prior
174 calibrations and without disinfection (single-use connectors). The Q-NRG® is a portable

175 device which can be used at the patient's bedside, in spontaneous breathing (canopy or
176 facial mask) or mechanical ventilation (connection to the ventilator).
177
178 **3. Any place for predictive equations?**

179 Many predictive equations have been developed to provide estimated REE using
180 anthropometric data (height, weight, fat mass, fat-free mass...) and clinical conditions
181 (mechanical ventilation, disease severity scores such as SOFA, APACHE, SAPS etc…). The
182 accuracy of these equations is very low when applied to patients with different
183 characteristics than those for whom they have been initially developed. Several studies have
184 assessed the validity of these equations in overweight and obese subjects compared with IC,
185 showing a wide variation in their results (21-23). Likewise, predictive equations are not
186 suitable to estimate REE in patients with anorexia nervosa with body mass index <16 kg/m²
187 (24). In ICU patients, numerous systematic reviews have demonstrated the poor reliability of
188 predictive equations (25). In addition, the body weight (BW) is rarely available and difficult
189 to accurately assess in the ICU as it is generally modified by fluid resuscitation. No equation
190 is sufficiently accurate to be considered clinically acceptable compared to IC, regardless of
191 the BW used for calculations (anamnestic BW, measured BW, adjusted BW, and ideal BW for
192 body mass index at 22.5kg/m^2 and at 25kg/m^2) **(Figure 4)** (26). In mechanically ventilated
193 patients VCO2 measured by the ventilator has been proposed to approximate EE (27).
194 However, Oshima et al. reported that EE from CO_2 ($EEVCO_2$) was not sufficiently accurate to
195 consider it as an alternative to measured EE, since the variability of RQ is likely to influence
196 the accuracy of the results (28). Despite limitations, and if IC is not available, ESPEN
197 guidelines (29) recommend the use of VCO_2 obtained from the ventilators of mechanically
198 ventilated patients, as previously described (27). In the absence of VCO_2 measurement, the
199 use of simple weight-based equation (20-25kcal/kg/day) should be preferred.
200
201 **4. Evidence supporting patient-centred benefits of using IC**
202 There is a lack of recognition of the impact on clinical outcome of feeding patients according
203 to their real EE. Optimal nutrition, i.e. avoiding under- and over-feeding, has been associated
204 with better clinical outcomes in ICU patients (1, 2). There is a relative risk of overfeeding
205 during the early phase of critical illness (0 to 5 days post ICU admission) when 50 to 75% of

206 energy is covered by glucose endogenous production through the mobilization of muscle
207 proteins, glycogen, and lipid stores during illness. We still have no clinical available measure
208 of the amount of glucose produced during illness over time. Throughout this early phase,
209 endogenous energy production covers nearly two thirds of the energy needs and careful
210 interpretation of REE measured by IC is necessary for the adequate prescription of energy in
211 order to avoid overfeeding (30) **(Figure 5)**. The optimal energy provision to the ICU patients
212 remains an ongoing debate (31). Randomized controlled trials (RCTs) reported positive
213 outcome in patients receiving calories closer to the measured REE. The TICACOS study
214 showed trend toward lower mortality in the patients who received higher calorie guided by
215 IC performed day-to-day (cumulative energy balance of 2008 +/- 2177 kcal vs -3550+/- 4591
216 kcal) (hospital mortality of 32.3 versus 47.7%, respectively, P=0.058) (32). Heidegger et al.
217 found a significant reduction in nosocomial infection in patients receiving supplemental
218 parenteral nutrition (SPN) to cover with calorie target (cumulative energy balance of 124+/-
219 1589 kcal vs -2317+/-2657 kcal) (hazard ratio 0.65, 95% CI 0.43–0.97; P=0.0338) (33). REE
220 was measured only once to tailor the nutrition support for 5 days. Ideally, the REE should be
221 measured every day or at least if the clinical condition changes. Furthermore, how much of
222 the measured EE should be administered daily is not known yet and probably depends on
223 the phase of disease. The EAT-ICU study reached on day 1 the 100% calorie target according
224 to measured EE and did not find any significant advantage compared to standard therapy
225 regarding physical quality of life at 6 months nor improvement of any studied outcomes
226 (25kcal/kg/day) (34). However, to our knowledge, few RCTs documenting the effect of
227 different energy level provision and using IC to determine the goal, controlled the amount of
228 proteins delivered between groups. The main method currently available to determine
229 protein needs is to measure nitrogen balance, which requires a precise quantification of
230 both nitrogen intake and losses. Ideally, total urinary nitrogen should be measured and not
231 estimated from the urinary urea content that is highly variable in clinical conditions
232 associated with renal failure and water retention, e.g. in critically ill patients or those with
233 cardiac failure (35). Few clinical studies have measured nitrogen balance because of the
234 resources needed. Further RCTs evaluating the effect of different calorie provision using IC,
235 as well as different protein amount between groups, are required.
236

237 Monitoring REE is also a useful strategy for weight -losing or gaining- patients by achieving a
238 negative or positive energy balance, respectively. Combining IC with the measurement of
239 body weight and composition may be useful to further optimize the nutrition prescription by
240 observing the effect of energy intake on these parameters, and also for the interpretation of
241 feeding energy requirement over time. Fat-free mass (FFM), including muscles, organs,
242 bone, total water, is the primary determinant of REE (36) due to its mass, while its O_2
243 consumption per gram of tissue is small. FFM will impact the REE depending on factors such
244 as its quantity, assessed by body composition measurements, and metabolic activity, which
245 could be influenced by race, gender, physical activity, and diseases. Clinical conditions
246 associated with muscle wasting, hypercatabolism and/or immobilization, lead to REE
247 variations.

248 **5. Use of indirect calorimetry in clinical practice**

249 Measurements may be repeated at a frequency varying according to the dynamic of the
250 clinical evolution. Similarly to other medical techniques, indications and contra-indications
251 must be considered to properly use IC in clinical practice and are described below. In the
252 future, COntinuous Metabolic MOnitoring (COMMO) could be possible, providing real-time
253 values, as other monitor equipments in ICU do (37).

254 **5.1. Indications for indirect calorimetry**

255 IC allows the customization of energy prescription in spite of important REE variations, due
256 e.g. to sepsis, paralysis, etc. Kreymann et al. previously suggested that IC could be used to
257 monitor the development of sepsis syndrome and septic shock (38). More recently, in a
258 retrospective cohort study, Zusman et al. showed reduced REE in ICU patients who died,
259 probably resulting from multi-organ dysfunction in sepsis leading to metabolic shutdown (2).
260 Inversely, Frankenfield et al. reported that the diagnosis is not a useful factor in predicting
261 REE (39). This highlights the importance of IC-based REE measurements as metabolic needs
262 may shift through the course of the disease.

263 REE is influenced by the natural course of disease (inflammation, immune system activation,
264 etc.), physical immobilization which leads to muscle wasting reaching up to 300 - 600g of
265 lean mass per day, and medical interventions (treatments, surgery, ventilation, etc.). IC
266 should be repeated as the clinical condition varies to better define the changing energy

267 target. **Figure 6** illustrates the dynamic evolution of measured REE during refeeding of
268 anorexia nervosa patients (40).

269 Day-to-day variations of REE may provide an insight about clinical improvement or
270 deterioration of clinical condition. While REE is generally reduced during shock phases, REE
271 frequently increases with inflammatory conditions, although in an unpredictable way.
272 Hypermetabolism is the result of an elevated pro-inflammatory cytokine production, which
273 is associated to increased production and release of counter-regulatory hormones, such as
274 cortisol, glucagon, and catecholamines. The prognostic value of IC has been reported
275 recently to reflect skeletal muscle mass and predict mortality in 126 patients with cirrhosis
276 (41). However, the results are still controversial and should still not be applied in clinical
277 practice. Likewise, Maxwell et al. reported that the nutritional support in patients with RQ <
278 0.83 on day 3 is associated with a reduced protein utilization and optimizes the achievement
279 of positive nitrogen balance by day 7, in 27 patients with severe traumatic brain injury (42).
280 Wu et al. reported that in severe sepsis, the higher the REE in the first 5 days after
281 admission, the higher the mortality (OR 1.018, 95% CI, 1.010–2.544, p = 0.031) (43), whereas
282 Kreymann et al. previously reported that the hypermetabolism might reflect the patient
283 skeletal muscle mass reserve to respond to infection (38). Further studies are needed to
284 better understand the metabolic evolution during sepsis and possible prognostic value of
285 REE.

286 **5.2. Methodology: standard operating procedures (SOP)**

287 The IC standard operating procedures concretely depend on the device used. However, in
288 accordance with the user manual, the following steps are generally required:

289 - a warm up time (5 to 30 min) before starting the measurement
290 - automatic or manual gas analyzers calibration using gases (N_2-O_2-CO_2) of known
291 concentration as reference
292 - an antibacterial filter placed between the IC and the canopy or the sampling line in
293 the ventilator circuit
294 - disinfection of all disposables in contact with the patient (skin, secretions, exhaled
295 air), unless they are for single use only. Particular attention and extensive
296 disinfection procedures are required after measuring patients with serious infection
297 (e.g. pseudomonas, tuberculosis, etc…).

298 **5.3. How to optimize REE measurement by indirect calorimetry?**

299 Conditions required to achieve reliable REE measurement and are summarized in **Table 2**.
300 The quality of any IC measurements is influenced by the stability of the metabolic
301 conditions, detectable by the steady state period, at the time of the measurement. The
302 steady-state period (STS) is defined as a period of low VO_2 and VCO_2 variations, usually
303 <10%. STS achievement is required to validate REE measurements (44). Recent guidelines in
304 healthy subjects and non-critically ill patients suggested that measurements of only 4
305 minutes need to be averaged to determine the EE, once steady-state is achieved (12).

306 In order to ensure a stable and accurate result, IC must be conducted with strict adherence
307 to resting conditions, not always possible in critical care. To attain these, the patient has to
308 be informed and reassured about the safety of the measurement, either in fasted state or on
309 continuous artificial nutrition, and be in a quiet environment without loud noises, music or
310 any sources of distraction. Routine nursing care or activities involving other health care
311 professionals, such as physical mobilization and painful or anxiety-provoking procedures,
312 should be avoided. In ICU patients, change of sedation level, vasoactive agents' dose or
313 mechanical ventilation parameters during IC lead to hardly interpretable results.

314 **5.4. How long should a measurement last?**

315 With most calorimeters, the achievement of reliable results requires a 15 to 30 minutes
316 measurement. If a steady state is obtained after 15 minutes, there is no interest in
317 prolonging the test.

318 **5.5. How to interpret the indirect calorimetry results?**

319 Raw variables generated by IC are: VO_2, VCO_2, REE, coefficient of variation for VO_2 and VCO_2.
320 Normative values are summarized in **Table 3** and their interpretation is illustrated by 5
321 clinical cases.
322 The possible causes of altered IC results are summarized in **Table 4.**

323 **5.6. How to tailor nutrition support according to IC results?**

324 The mean indirect calorimetry EE value reflects patient's REE at the time of measurement
325 and it should be used to tailor the prescription of the nutritional therapy. However, if the
326 measurement shows significant variability (> 10%), the result cannot be considered as

327 reliable and should not be used to determine the energy target. This variability may be due
328 to gas leaks and / or changes in treatments and a new measurement under better conditions
329 should be performed. In order to determine total patient's caloric needs, measured REE has
330 to be extrapolated to TEE. Multiplication factors accounting for nutrition related
331 thermogenesis and level of physical activity should be applied with clinical judgment, and is
332 not required during continuous feeding in the ICU. Measurement during the acute phase
333 (<72 hours) should be interpreted with caution. During this acute phase, the body produces
334 and uses endogenous substrates resulting from proteolysis, lipolysis and gluconeogenesis.
335 This is the reason why the current guidelines recommend the introduction of a progressive
336 nutrition, aimed at the total coverage of the patient's needs (REE) only from the 4th day
337 after admission to intensive care. A new IC measure is required in order to adjust the energy
338 target when the clinical situation changes significantly (30).

339 **5.7. Examples of clinical cases**

340 Clinical condition deeply influences REE measurements. We report below 5 clinical cases to
341 discuss the interpretation of IC results, as well as a few frequent and relevant question.

342

343 **6. Medico-economic aspects**

344 To date and to our knowledge, there is no full economic analyses of IC. This medico-
345 economic analysis should include the costs related to the measurement of EE by IC and the
346 potential benefits to tailor nutrition support according to the measured EE. Its use is limited
347 by the current high cost of the devices, manpower, calibration gas, and technical
348 maintenance. However, the newly developed device minimizes these limitations, allowing
349 clinicians to perform fast and accurate measurements.

350 Promoting a large use of IC to measure EE of in- and out patients should optimize nutrition
351 care, clinical outcomes and costs. This hypothesis is based on two recurrent observations : -
352 malnutrition increases morbidity, length of stay and costs in a large spectrum of diseases
353 and treatments (45), and avoiding over- and underfeeding, in ICU patients attenuates the
354 catabolic response to the injury, improves gastrointestinal function, and improves clinical
355 outcomes reflected by a decrease in complication rates, duration of mechanical ventilation
356 and length of stay, likely leading to cost savings. Therefore, tailoring the prescription of

357 feeding according to a target defined by IC is still debated for ICU patients. Recently, Berger
358 et al. reported that feeding patients to meet an individualized measured energy target using
359 SPN in case of failure of exclusive enteral nutrition from day 4 was associated with improved
360 immunity, less systemic inflammation and a trend of less muscle mass loss (46). Pradelli et
361 al. also reported that optimisation of energy provision using SPN is a cost-saving strategy in
362 critically ill adults for whom EN is insufficient to meet energy requirements (47). Further
363 studies are needed to better understand the medico-economic impact of targeting IC
364 measured needs in ICU patients.

365

366 **Strengths and limitations**

367 In this review, the principle of indirect calorimetry was deliberately not developed as the aim
368 was to provide an educational tool for the routine use of indirect calorimetry and the
369 interpretation of the results. In this regard, the five clinical cases represent the main
370 strength of this review, based on clinicians' experiences.

371

372 **Conclusion**

373 Indirect calorimetry is the gold standard to measure energy expenditure to optimize the
374 energy prescription in line with the concept of personalized and goal oriented medicine: the
375 latter requires an adjustment of the energy prescription to the dynamic metabolic changes
376 related to the course of the disease or treatments. Using indirect calorimetry goes along
377 with a feeding protocol, and with the monitoring of the achievement of the prescribed goals.
378 The routine use of IC should be encouraged as a strategy to optimize nutrition care.
379 Education for use of IC must be disseminated worldwide.

380

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383

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Conflicts of interest

All the coauthors have contributed to the development and validation of the new indirect calorimeter (Q-NRG) in collaboration with the manufacturer, but independently in terms of financial support (see above). All coauthors have a major motivation to promote calorimetry for clinical and research activities as they consider IC has a corner stone for optimal nutrition, but they do not have commercial interest or receive personal benefits for this action.

Statement of authorship

Najate Achamrah and Claude Pichard have outlined this manuscript. Marta Delsoglio, Elisabeth De Waele, and Mette M. Berger adapted the pedagogic content and critically reviewed the manuscript.

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Figure 1: Principle of indirect calorimetry. Schematically the oxidation of substrates (fat, carbohydrates and proteins) results in the production of energy (ATP), water and nitrogen. Indirect calorimetry measures the differences of concentrations of O_2 and CO_2 between the inspired and expired gases, and the flow of gas. Energy expenditure is then calculated using the Weir equation. F: fat; CHO: carbohydrates; P: proteins; N_2: Nitrogen; H_2O: water; ATP: adenosine triphosphate.

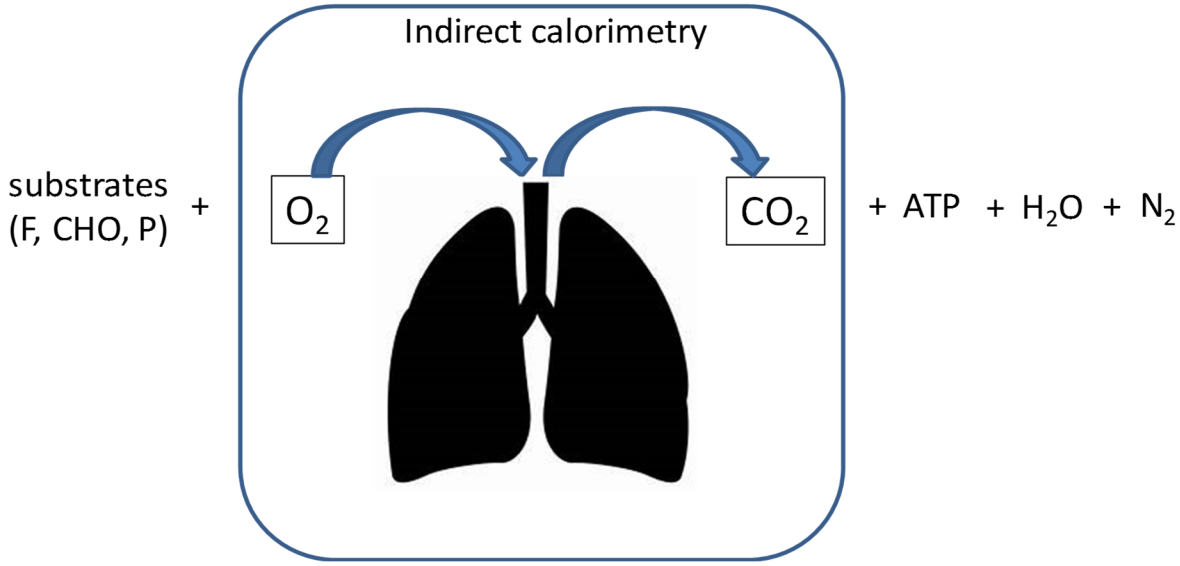

Figure 2: Components of total energy expenditure. Total energy expenditure is the sum of basal energy expenditure, diet-induced thermogenesis and activity induced energy expenditure. REE represents 50% to up to 75% of TEE. DIT varies according to the quantity and type of oxidized substrate. The contribution of AEE is limited when patient is bed rested. AEE: activity induced energy expenditure; DIT: diet-induced thermogenesis; REE: resting energy expenditure; TEE: total energy expenditure.

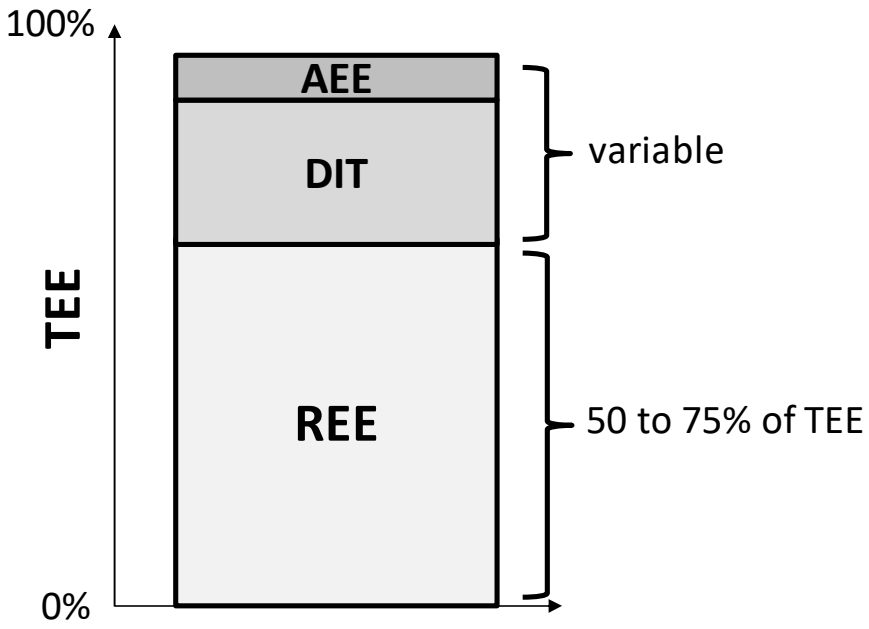

Figure 3: Q-NRG® calorimeter (Cosmed, Italy). The Q-NRG® calorimeter has new characteristics: high level of accuracy and reproducibility for clinical and research use, no warm-up time delay, flexible site for sampling, fast sampling rate, micro-mixing chamber , compatibility with most ventilators, working with a FiO2 up to 70%, reduced in weight and size instrument, less sensitive to transport, easy disinfection, affordability.

Figure 4: Bland & Altman plots comparing energy expenditure measured by indirect calorimetry and calculated according to 20 kcal/kg ESPEN first week predictive equation (adapted with permission from Graf et al. Clinical Nutrition, 2017 [26]). The ESPEN equation shows large variability (>700 kcal/d) when compared with indirect calorimetry, and therefore cannot replace IC measurements. ESPENmes= YYY

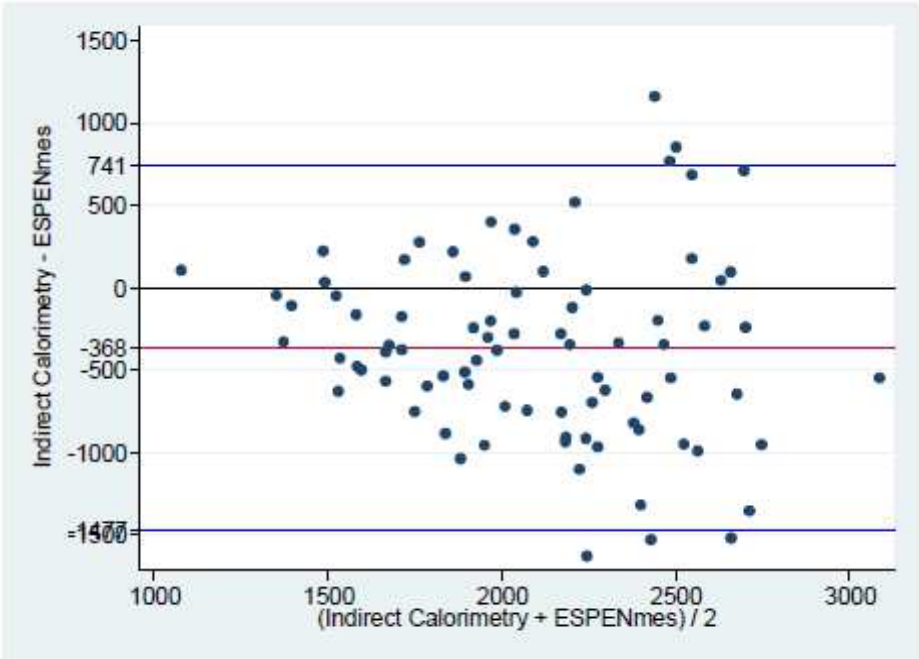

Figure 5: Relative overfeeding during the early phase of critical illness (reproduced with permission from Oshima et al. Clinical Nutrition, 2017 [17]). During the early phase of critical illness, endogenous energy production covers up to 2/3 of the energy needs and careful interpretation of REE measured by IC is necessary for the adequate prescription of energy to avoid overfeeding. Solid bold line: total energy expenditure; grey bold line: adapted endogenous energy production; dotted bold line: early energy administration; thin line: combined endogenous and exogenous energy administration.

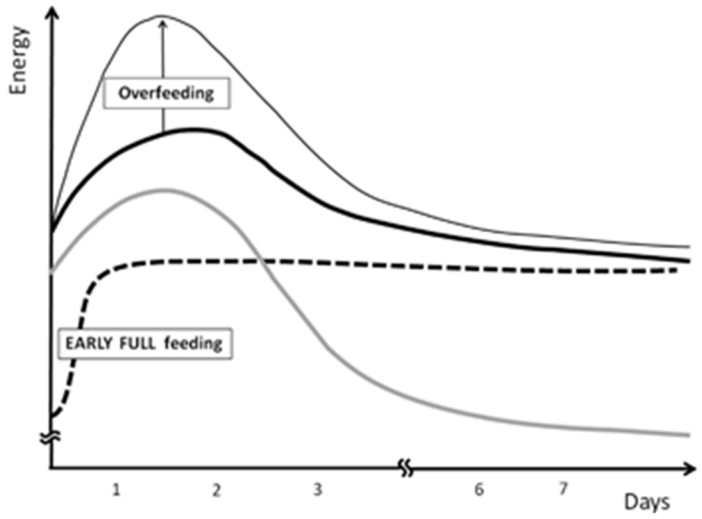

Figure 6: Repeated REE measurement in 9 anorexia nervosa patients during refeeding for a time period of 10 weeks. REE progressively increases during refeeding.
Average (solid line) of all values for week 0, 2, 4, 6, 8 and 10. Values of the filled horizontal area are the mean ± SEM of age-, sex- and height-matched controls. * $p < 0.0001$, † $p < 0.001$, ‡ $p < 0.05$, anorexia nervosa patients versus controls (unpaired t test). Reproduced with permission from [40].

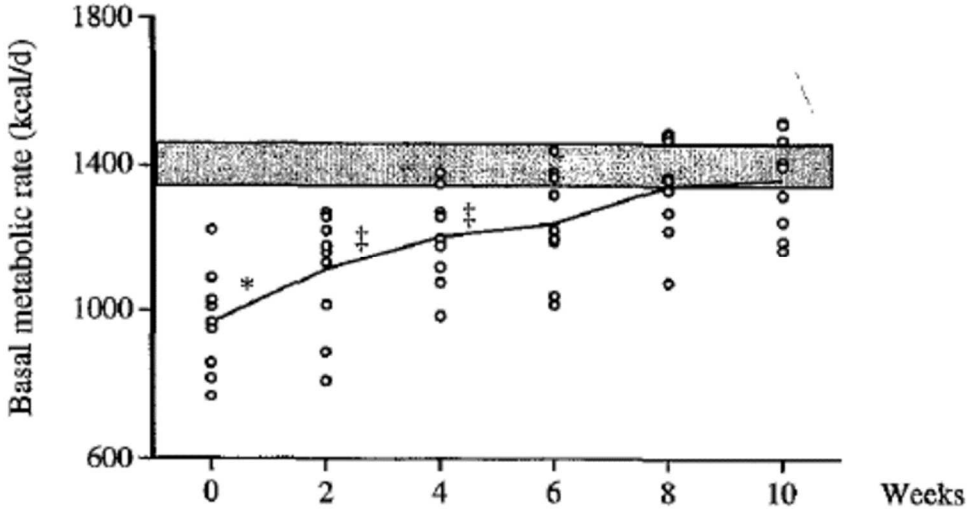

Table 1: Ideal characteristics of a new indirect calorimeter in clinical settings

High accuracy (error < 3%)
Rapid measurements (< 15’)
Ease of use (hardware and software)
Easy disinfection and maintenance
Reduced size, portable and battery power
Affordable (acquisition and maintenance)

Table 2: Considerations for reliable REE measurement with indirect calorimetry

	Conditions	Reliability limiting factors
Patient	Resting	Agitation, involuntary muscle movements
	Body temperature	Changes >0°C <1 hr before and/or during IC
	Ventilation	Changes in ventilatory parameters (FiO_2, PEEP, Peak ventilatory pressure) <1 hr before and/or during IC
	Air leaks	Loss of O_2 and/or CO_2
	$FiO_2 \leq 70\%$	Technical limit of IC (cf § 1)
	PEEP ≤ 10cmH_2O	Air leaks
	Medications	Changes in vasoactive agent, sedative/analgesic dose (20%) <1 hr before and/or during IC
	NO, heliox, haemodialysis	Currently unclear, likely no effects
Indirect calorimeter	+/- Warm-up time +/- Calibration	According to manufacturer recommendations
	Steady-state period	VO_2 and VCO_2 variability ≥ 10%
	RQ between 0,67 and 1	See Table 3 for possible causes of RQ<0,67 or >1.2
	Disinfection after measurements	In all case of infection particularly with multi resistant micro-organisms (pseudomonas, tuberculosis, etc…)

Table 3: Normative values of row parameters from indirect calorimetry. These values are valid for Body Mass Index (BMI) between 18,5 and 30kg/m², but do not apply to ICU patients who have much higher VO_2 and VCO_2 values

VO_2	90-120 ml/min/m²
VCO_2	50-90 ml/min/m²
RQ	Physiological between 0,67 and 1.2, dependent on substrate oxidation (0,7 for fat; 0,8 for proteins; 1 for carbohydrates)
EE	20 – 45 kcal/kg/day
Coefficient of variation (VO_2, VCO_2)	≤ 10% of variation for 30 min of measurement

Table 4: Possible causes altering IC results

IC results	Clinical conditions	Metabolic conditions
Increased VCO_2 and RQ>1.2	Overfeeding Hyperventilation	Hypermetabolism
Increased VO_2	Overfeeding Sepsis, hyperthermia Agitation Hyperthyroidism Pheochromocytoma	Hypermetabolism
Decreased VCO_2 and RQ<0,67	Underfeeding Air leaks β blockers	Hypometabolism
Decreased VO_2	Underfeeding Hypothermia Sleeping Hypothyroidism Myorelaxant treatment, paralysis, coma Sedative agents	Hypometabolism

Table 5: Examples of clinical cases

Type	History	IC values	Q1: Is the result of this indirect calorimetry reliable?	Q2: Was the indirect calorimetry performed at an appropriate time?	Q3: Which energy target to prescribe? Can the measure value be applied?
1-ICU	A 26-yr old male weighing 90 kg is admitted in ICU after a traumatic brain injury. He is mechanically ventilated (FiO2=60%, PEEP=8cmH_2O), with no vasoactive agents, sedation with propofol, and pain controlled with morphine. Ventricular drain for intracranial pressure monitoring and cerebrospinal fluid drainage is inserted. The patient is continuously fed with enteral nutrition with total caloric intake of 1,500 Kcal/day.	IC is performed on day 2 after ICU admission. During the measurement, the patient is normothermic and agitated. The measurement is made over a period of 30min. IC results are: VO_2 =490 ml/min, VCO_2 = 350 ml/min, RQ = 0.75, REE = 3560 Kcal/day, the coefficient variation in the first 5min was 14% for VO_2 and VCO_2.	No, the coefficient variation is out of acceptable limits for VO_2 and VCO_2 (>10%), probably due to the physical agitation during the measurement.	The measurement was performed two days after ICU admission, i.e. still during the early phase of the acute illness, when the endogenous energy production covers most of the energy needs (see Figure 5). Careful interpretation of REE by IC in this phase is necessary for an adequate prescription of energy in order to avoid overfeeding.	During this transitory period (0 to 5 days post ICU admission), a safe strategy is to use the weight-based equation, 20-25 kcal/kg/day, with a caloric target of 2250 kcal/day. The IC measurement should be repeated on day 3-4 after ICU admission to adjust caloric intakes. This clinical case highlights the time wasting of IC measure during the first days of ICU admission.
			Q1: What is the energy target to be prescribed on day 4?	**Q2: What is the energy target to be prescribed on day 10?**	**Q3: How do you interpret IC results?**
2-ICU	A 68-year-old man admitted to the ICU for respiratory failure due to nosocomial pneumonia, pulmonary adenocarcinoma diagnosed 3 years earlier: 60.5 kg, BMI 19.7 kg/m2. He was intubated upon admission. Enteral feeding was started after 36 hours. On day 4, while clinicians had prescribed 1200 kcal (20 kcal/kg), the patient's	The first IC was performed on day 4 in a calm patient: normocard (hr 75/min) with a minimal dose of noradrenalin, tachypneic (resp.rate 27 with a P/F ratio of 130), RQ= 0.75, VO2= 240 ml/min, VCO2= 181 ml/min = 1635 kcal (26.8 kcal/kg) – coefficient of variation 5%. On day 10, IC is repeated in a still intubated, calm and non-sedated patient: he is moderately tachypneic (rr	Enteral nutrition prescription is increased to 1600 kcal based on IC results.	Energy target is adapted to second IC result (1850 kcal), using high protein enteral nutrition with fiber.	The measured values reflect change over time in a more mobile patient and were used for prescription, The change in RQ from 0.75 to 0.86 correspond to a better fed state. A single IC on day 4 was not able to pick the evolution which might have been towards a lower value: but was higher in this case.

	intake had been progressed to 940 kcal/24h. He needed 1 u/hr of insulin to goal blood glucose 6-8 mmol/l.	22 /min), P/F 160, afebrile (36,7°C). He has received 1490 kcal last 24 hrs. RQ= 0.86, VO2= 268 ml/min, VCO2= 230 ml/min, EE = 1870 kcal (30.1 kcal/kg).			
			Q1: Can this indirect calorimetry be considered reliable?	**Q2: How do you interpret an RQ of 0.85?**	**Q3: What is the energy target to be prescribed?**
3 - ANOREXIA	A 21-yr old woman with a diagnostic of anorexia nervosa is followed-up at the Nutrition Outpatients Clinic with a body mass index of 13.4kg/m². Body composition assessment with DEXA reports: fat-mass = 1.3kg (4.4%) and fat-free mass = 31.7kg (95.6%).	REE measurement is performed with IC using canopy mode, in a quiet room, with stable temperature and humidity, in the morning, with empty stomach. Results obtained are: VO2=119ml/min, VCO2=95ml/min, RQ=0.85, REE = 809 Kcal/day, the coefficient variation in the first 5min was 5% for VO2 and VCO2.	Yes, the measurement is performed in stable conditions and the coefficient variation is within acceptable limits for VO2 and VCO2 (<10%).	The RQ is within the normal range (0.67 to 1.2). It suggests the predominant use of protein as a fuel source and indicates that the patient is likely to require an increase caloric intake in the form of carbohydrates and lipids to reduce protein oxidation. Protein turnover and needs can be assessed by measuring 24 hours urinary nitrogen excretion. If this measurement is unavailable, it can be estimated by measuring urinary urea excretion which represents 85% of total nitrogen in human.	REE reflects the energy needs to maintain vital activities (e.g. heat production, cardiac, respiratory, secretory, cellular, etc). The patient is severely malnourished with a very low body mass index (<18,5kg/m²). More than 809 kcal/day should be prescribed to achieve a positive energy balance and weight gain (see Figure 6). In this condition, the risk of refeeding syndrome is real and should be reduced by lower calorie intake to prevent a refeeding syndrome, starting at 10kcal/kg/day.
			Q1: How do you interpret the IC results?	**Q2: What is the energy target to be prescribed?**	
4 - OBE	A 38-yr woman with body mass index of 32kg/m² (82kg) is admitted for body weight loss (5kg during one month). Her total caloric intake is 1900 kcal/day. She has no regular physical activity. Body composition assessment with Dual	REE measurement is performed by IC using the canopy mode, in a quiet room, with stable temperature and humidity, in the morning, after an overnight fast. Results are as follows: VO2=245ml/min, VCO2=198ml/min, RQ=0.81, REE = 1677 Kcal/day, the	Body weight loss results from a negative energy balance, i.e. for this patient either by decreased energy intakes or increased TEE (see Figure 6).	We suggest to target 1700kcal/day and encourage physical activity to increase TEE and protect fat-free mass from catabolism.	

S I T Y	energy X-ray (DEXA) features 47.5% of fat-mass and 52.5% of fat-free mass.	coefficient of variation during the first 5min was 6% for VO2 and VCO2.			
			Q1: How do you interpret the IC results?	**Q2: What is the energy target to be prescribed?**	
5 - E L D E R L Y	A 72-yr old man with BMI of 22,5kg/m² is hospitalized in orthopaedics for fracture of the femoral neck. Body composition assessment with DEXA reports 46% of fat-mass and 53% of fat-free mass.	IC is performed and reported: VO2=130ml/min, VCO2=105ml/min, RQ=0.80, REE = 1300 Kcal/day, the coefficient variation in the first 5min was 5% for VO2 and VCO2.	Age-related decrease of VO2 has been demonstrated in healthy individuals, as well as in injured and critically ill patients. This decrease is associated with a decline in cardiac output related which is defined as a decrease of muscle mass and function.	At least 1300kcal/day and 1.2 to 1.5g protein /kg/day should be prescribed in association with physiotherapy to avoid/limit muscle wasting.	
			Q1: How do you interpret the IC results?		
6 - S U R	A 32-yr old man with Crohn disease and BMI of 20kg/m² (body weight=59kg) is admitted for ulcerative ileitis with stenosis. He received parenteral nutrition before surgery. The surgeon performed an ileum and	IC measurement at day 2 shows REE=2200kcal (with RQ=0,89 and coefficient of variation for VO2 and VCO2=6%). The patient was febrile (38°), hemodynamically stable, and has abdominal pain controlled with morphine.	The indirect calorimetry was performed 2 days after surgery, the patient was febrile (38°). Infectious complication of surgery could occur and lead to increased REE (hypermetabolism). Thus, careful interpretation of REE is necessary to avoid overfeeding. We suggest to repeat IC measurements on day 3-4		

G E R Y	short right colonic resection (5cm), with immediate restoration of continuity. At day 1 after surgery, parenteral nutrition provided 1500kcal/day and enteral nutrition was started with 250kcal/day.	after surgery, and adjust the energy prescription as the clinical condition changes to accurately define the energy target.	