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Review

Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group

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SUMMARY

Background & aims: This review aims to clarify the use of indirect calorimetry (IC) in nutritional therapy for critically ill and other patient populations. It features a comprehensive overview of the technical concepts, the practical application and current developments of IC.
Methods: Pubmed-referenced publications were analyzed to generate an overview about the basic knowledge of IC, to describe advantages and disadvantages of the current technology, to clarify technical issues and provide pragmatic solutions for clinical practice and metabolic research. The International Multicentric Study Group for Indirect Calorimetry (ICALIC) has generated this position paper.
Results: IC can be performed in in- and out-patients, including those in the intensive care unit, to measure energy expenditure (EE). Optimal nutritional therapy, defined as energy prescription based on measured EE by IC has been associated with better clinical outcome. Equations based on simple anthropometric measurements to predict EE are inaccurate when applied to individual patients. An ongoing international academic initiative to develop a new indirect calorimeter aims at providing innovative and affordable technical solutions for many of the current limitations of IC.
Conclusion: Indirect calorimetry is a tool of paramount importance, necessary to optimize the nutrition therapy of patients with various pathologies and conditions. Recent technical developments allow broader use of IC for in- and out-patients.

1. Introduction

Indirect calorimetry (IC) measures the oxygen consumption and the carbon dioxide production, which correspond to the cellular respiration and allows to calculate the energy expenditure (EE) of the whole body [1]. The study of the basic principles started more than 100 years ago mainly by physicists and chemists, from the discovery of gas and its components to the establishment of the

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Table 2
Components of the energy expenditure in healthy subjects and diseased individuals [1].

Components of energy expenditure	Definition
Basal energy expenditure (BEE)	Energy expended in fasting state, resting in lying position at neutral ambient temperature, free of physical and psychological stress. Note: Only applicable in healthy subjects.
Diet-induced thermogenesis (DIT)	Oxidation of energy substrates during oral, enteral or intravenous energy intake
Activity energy expenditure (AEE)	Energy expenditure to support physical activity
Resting energy expenditure (REE)	BEE + DIT
Total energy expenditure (TEE)	REE + AEE

inhaled and exhaled gasses separately, to detect the global change in the inhaled and exhaled gas [30]. The expired volume is usually measured by a separate flow meter, or by a dilution technique using a constant flow chamber to calculate the volume [30]. Both systems use the Haldane transformation, i.e. the method to calculate inspired gas volume by the ratio of the inspired and expired nitrogen concentrations, to calculate the inspired gas volume thus simplifying the flow or volume measurements [Table 1] [4,20,28].

Some commercially available simplified devices only measures either VO_2 or the VCO_2 to calculate EE by assuming that the RQ is a fixed value (i.e. 0.8–0.85) [28,31,32]. While this type of assumption may be acceptable in healthy subjects on balanced nutrition [28], it is not recommended for patients because their substrate oxidation may change significantly according to the type of disease and nutrition. Assuming a fixed RQ in patients give inaccurate EE, in turn leading to suboptimal energy prescription. Using the VCO_2 and RQ of prescribed nutrition formulas (food quotient) to calculate EE has been proposed as a way to improve the accuracy of the calculation for ICU patients [32]. The analysis was conducted on stabilized patients who tolerated more than two-thirds of the prescribed nutrition allowing the mean EE bias of 7.7% (=+141 kcal/d) while improving the precision compared to predictive equations. However, the accuracy level of this method for individual patients can only be validated by conducting IC. Thus, this method can be considered as an alternative for predictive equations, but should not be considered as a valid alternative for IC in the general ICU population.

2.3. The reference device of the 20th century

Numerous indirect calorimeters have been in and out of the market in the past decades. However, the Deltatrac Metabolic Monitor® (Datex, Finland) produced 35 years ago is often viewed as the reference device [9,22–24,33]. This device features both canopy and ventilator measurements [30]. When on ventilator mode, it uses the mixing chamber technique with a unique constant flow chamber to dilute the exhaled gas to enable calculations of VO_2, VCO_2 and EE without directly measuring the expired gas volume [30]. The device has been repeatedly validated, including a comparison against mass spectrometry [30,34,35]. However, existing units are progressively disappearing and the manufacturer no longer offers any support.

2.4. Technology of modern indirect calorimeters

Calorimeters are designed to measure spontaneously breathing patients or mechanically ventilated patients [28]. The different techniques predetermine the limitations of their performances [Table 4].

Devices with breath-by-breath technology can be made smaller as they do not require a bulky mixing chamber. They generate rapid readings by measuring short intervals of gas samples, a valuable feature in case of exercise physiology or rapid shift in substrates oxidation.

Devices with a mixing chamber generate more stable measurements because the gases are physically "averaged" before being analyzed, allowing the gas analyzers to generate very accurate analysis. The mixing chamber typically occupies 3–5 L of space, precluding the making of a small device. The capacity to make reliable measurements in a short duration (e.g. 3–5 min) is also limited, as it takes just as much time for the gas concentrations in the mixing chamber to stabilize.

2.5. Accuracy and reproducibility

Three components of the hardware play a major role: the O_2 and CO_2 analyzers, and the flowmeter. Their accuracy, precision and reproducibility are critical for IC and are influenced by many factors [Table 5]. For breath-by-breath systems, the reaction time of the gas analyzers is important. The reliability of the software to synchronize the signals from the gas analyzers and the expiratory flowmeter to allow continuous calculations is a challenging demand. Small errors in the alignment of the acquired data can lead to great differences in the results. Mixing chamber devices are not as technically demanding. However, the use of the Haldane transformation formula introduces a mathematical limitation, especially in case of O_2 enrichment higher than 60% as the inaccuracy of the analyzers will be enhanced by the calculation [28,30,34].

Outside the calorimeter itself, the collection of inspired and expired gases by an appropriate and airtight system is mandatory [Fig. 2]. Avoiding leaks of inspired and expired gas is crucial, and

Table 3
Required conditions for accurate measurement of energy expenditure in healthy subjects or diseased individuals [1,26,27].

Parameter	Condition	Subject
BEE	At least 10 h after the previous meal Free of drugs Resting in supine position and free of physical stress Awake and free of psychological stress Normal body temperature Ambient temperature in zone of neutrality (27–29 °C)	Only healthy subjects
REE	At least 5 h after the previous meal, or under continuous feeding Minimum 2 h after alcohol and nicotine ingestion, 4 h after caffeine ingestion After 30 min of resting period Resting in supine position and free of physical stress Awake and free of psychological stress Comfortable environmental condition	Healthy subjects or patients
TEE	No specific conditions	Healthy subjects or patients

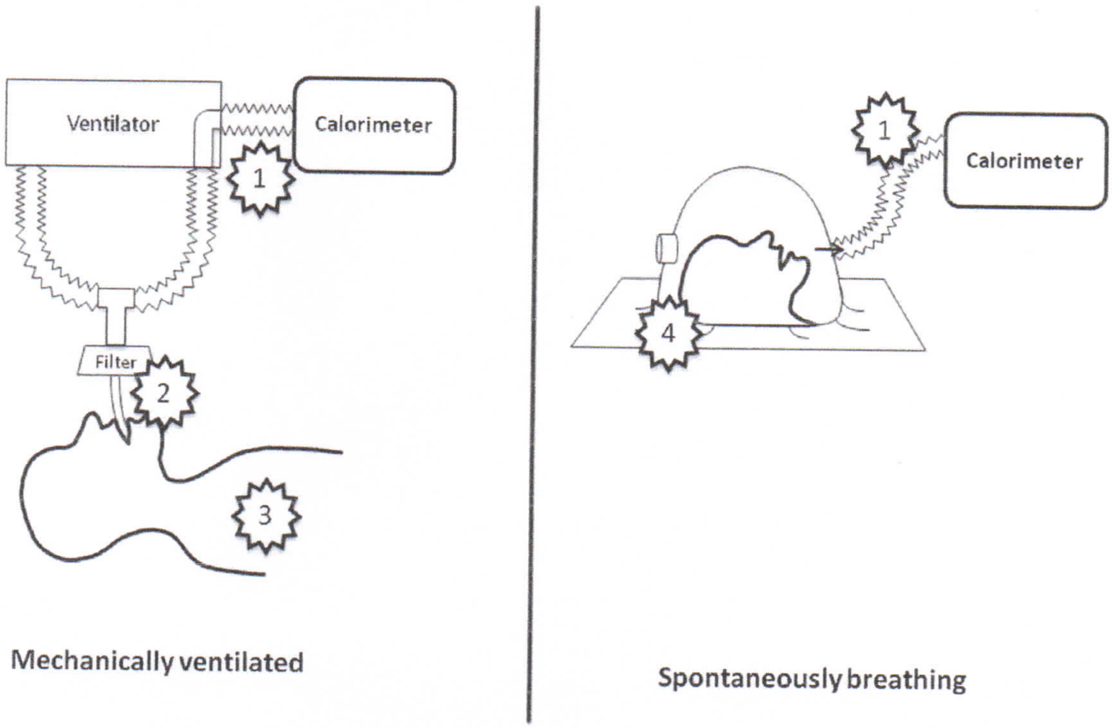

Fig. 2. Sources of air leaks during indirect calorimetry in spontaneously breathing patients and on those on mechanical ventilation. The avoidance of respiratory gas leaks is crucial to the accuracy of the energy expenditure measurement. 1: Tube connections with gas collection devices and calorimeters must be "air-tight". 2: For patients on mechanical ventilation, leaks from the cuff of the endotracheal tube must be detected, as they can be significant in cases of high airway pressure. 3: Pathologies (e.g. bronchial fistula) and treatments (e.g. chest drain) causing air leaks from the lung must be detected. 4: Canopy and drape must be inspected for cracks and tears, and fitting tightly to each other. The drape should fully cover the surroundings of the canopy to avoid leaks.

Table 6
The Fick method (thermodilution) and related equations.

Calculation of O_2 content in blood
$CaO_2 = (Hb) \times 1.38^{\#} \times SaO_2 + (0.003 \times PaO_2)$
$CvO_2 = (Hb) \times 1.38^{\#} \times SvO2 + (0.003 \times PvO_2)$
#: O_2 carrying capacity of Hb (1.34–1.39/gram, depending on literature)
Fick equation
$VO_2 = (CaO_2 - CvO2) \times CO \times 10$ or
$VO_2 = 1.38 \times (Hb) \times (CO) \times (SaO_2 - SvO_2)/10$

$Ca(v)O_2$: content of O_2 in arterial (venous) blood, $Sa(v)O_2$: O_2 saturation of arterial (venous) blood, $Pa(v)O_2$: partial pressure of O_2 in arterial (venous) blood, CO: cardiac output (L/min).

3.2. Practical recommendations of clinical use

IC is successful when an appropriate device is used in optimal conditions, and the results are analyzed by experienced professionals in order to individualize the nutrition care. Although, these conditions are not easily met, practical recommendations are proposed below according to patient characteristics. Table 8 summarizes the important checkpoints for a successful routine use of IC. It can easily be adapted to create protocols after adjustment for the local medical practices.

Table 7
Clinical situations requiring careful interpretation of energy expenditure measured by indirect calorimetry [26,27].

- Physical agitation or unstable sedation and/or analgesia
- Air leaks (>10% of minute volume)
- Unstable body temperature (>±1 °C change over last 1 h)
- Unstable pH (>±0.1 change over last 1 h)
- Oxygen enrichment (FiO_2 >60%)
- Organ support therapies: renal replacement or liver support therapy (pH alterations when conducted intermittently), ECMO (direct O_2 supply to the blood and CO_2 removal from the blood)

FiO_2: fraction of inspired oxygen, ECMO: extracorporeal membrane oxygenation.

3.3. Calorimetry: important considerations

IC is the only easy-to-use, non-invasive method to measure the EE of healthy active or inactive subjects, or of patients with various levels of metabolic stress in order to obtain immediate results [3,38]. Nevertheless, the lack of sufficient knowledge to interpret the results generated by IC may lead to erroneous prescription. The conditions of IC measurement are of paramount importance. The general statement is: the more stable the clinical situation, the more reliable the IC results. Whenever a situation is changing, IC should be repeated. For instance, IC obtained during the early phase of a critical illness should be repeated within the next 24–48 h to obtain a result reflecting the dynamic evolution of the disease [Fig. 3].

4. Developments of indirect calorimetry

4.1. The global initiative to promote calorimetry

Commercially available calorimeters are usually of large size and heavy weight, need time-consuming warm-up and calibration before measurement, require PCs to record and analyze results, require cumbersome disinfection of the device and repeated-use components after measurements, and are sold at relatively high costs [27,28]. The best way to promote IC is to make

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conventional mixing chamber method, using the mass spectrometer as the gas analyzer. The practical characteristics will be evaluated in a multicenter study which will start during the 1st semester of 2016, to ensure that the device is easy to use and fits the conditions found in various clinical settings.

Market release of the device is anticipated for 2017. Training courses are organized by ESPEN as part of the Life Long Learning (LLL) Courses and will be multiplied to allow optimal use of IC.

5. Why you should use indirect calorimetry

5.1. Rationale for measuring energy expenditure by indirect calorimetry

Energy expenditure of a patient is massively influenced by a number of intrinsic and extrinsic factors [Table 10] [19]. These factors have synergic or antagonist impact on the EE level and the estimation of the EE using a predictive equation based on anthropometric characteristics (i.e. body weight, height, gender, and age) is frequently inaccurate [3,20,39]. The use of multiplicative factor usually called "stress factor" has been proven to further deteriorate the estimation of EE based on equations. For example, obese patients present significant EE variations due to their underlying illnesses, variable body composition and degree of malnutrition [40]. Patients with chronic obstructive pulmonary disease or those with cancer have an elevated EE, which can be easily underestimated by predictive formula [41–43]. Critically ill patients with trauma or sepsis have dynamic changes of their EE during the successive phases of their critical illness [3,44–47]. Although much effort has been made to create predictive equations adapted to the clinical evolution of acute illness [48], IC remains the gold standard to measure EE [3,19]. The full benefits of nutrition support may be expected only if the patient specific EE is reflected in the nutrition prescription, according to the changes that occur during the course of the illness.

Table 9
Characteristics of the new indirect calorimeter defined by a bottom-up process of development.

Characteristics	Description
Accuracy	
Gas analyzers	±0.02% for O_2 and CO_2 (after calibration)
Flow analyzer	±2% (after calibration)
Ease-of-use	
Portable	<2 kg, maximum foot print:15–30 cm
Interface	Intuitive software, user manual not required
Calibration	• Gas analyzer: Automatic periodic calibration against room air (no calibration gas required) • Flow analyzer: Automatic
Measurement	
Duration	<10 min for standard measurement
Recording	• Local memory buffer • Various exportation formats (Excel, CSV, etc)
Connectivity	Wireless or USB
Battery operated	Up to 10 measurements (duration 20 min), 4hrs (continuous measurement)
Safety	
Approval	EC certification
Disinfection	• Device covered by easy to clean material • Single use components for patient contact (sampling tube, flow meter)
Compatible	Hospital devices
Availability	
Cost	<10'000 US $
Market	Worldwide

5.2. Is measured EE always reflecting the energy needs?

This critical question has been asked many times and is frequently investigated, but the answer remains controversial. In general, the measured EE defines the energy target for the prescription of nutrition. However, during the early phase of an acute illness, endogenous energy supply covers most of the energy needs, a condition that is marginally affected by exogenous energy supplementation [Fig. 4] [49,50]. The energy administered may then massively exceed the requirements and generate relative overfeeding [3], a condition associated with deleterious consequences [Table 11] and poor outcome. This transitory period generally ends as soon the patient's overall condition improves. However, the value of IC measurements to evaluate the evolution of endogenous energy production needs further investigation. Therefore, careful interpretation of EE by IC in this phase is necessary for the adequate prescription of energy to avoid overfeeding. However, excessive restriction of energy will result in underfeeding, which has been associated with progressive loss of lean body mass [51], leading to poor outcomes. It should also be noted that predictive equations will not be able to take into account this type of metabolic alteration, and the degree of error in the estimation of EE will be unpredictable.

5.3. Respiratory quotient: another advantage of indirect calorimetry

IC allows for non-invasive measurement of EE in spontaneously breathing patients or those on mechanical ventilation, with or without O_2 enrichment [9,22,25,28]. An advantage of IC over other methods to measure EE is the capacity to derive the respiratory quotient (RQ) from direct measurements. The RQ corresponds to the quotient of VCO_2 and VO_2 ($RQ = VCO_2/VO_2$) [25,28], which enables the calculations of the substrate oxidation rates for glucose and lipids. This would especially allow detecting net lipogenesis. For patients with chronic illnesses, EE reflects the energy needs while the RQ reflects the composition of oxidized substrates [5]. This information is helpful to tailor the prescription of the nutrition regimen [28] by observing the match between the energy intake and the food quotient, i.e. the RQ of the energy substrates according to their food composition.

For critically ill patients, it allows to visualize the metabolic alterations, especially during the early phase. IC measurements should be repeated to monitor the dynamic changes, and to optimize the prescription of energy [3].

5.4. Routine use of indirect calorimetry

IC is rarely routinely used in medical institutions across the world [7,25] in spite of its value for a wide range of patients. Such a limited use of IC is mainly due to the unavailability of calorimeters, the insufficient awareness about the impact of optimal nutrition support on the patients outcome [20], the lack of expertise for interpretation of results, costs of device and related-manpower. This section aims at clarifying these issues.

5.5. Critical illness

Patients in the ICU for >4 days or those after major surgery are good candidates for IC as they undergo severe stress related to variable metabolic needs [52]. Indeed, these patients are at high nutritional risk, as they are unable to resume sufficient oral intake instantly and often require enteral or parenteral nutrition [7,53,54]. Studies in critically ill patients have repeatedly reported gross underfeeding during the ICU stay [55]. Various factors such as gut

Table 10
Factors influencing energy expenditure.

- Age, sex, body height, body mass, body temperature Brain activity, endocrine profile, systemic inflammation
- Muscle contractions or paralysis, physical activity
- Fasting or post-absorptive state
- Environmental temperature
- Drugs (e.g. alpha adrenergic stimulant, beta-blockers, sedatives, muscle relaxants)

intolerance and treatment interventions delay full enteral feeding, resulting in insufficient energy provision. Underfeeding is closely associated with higher complication rates and poor outcomes [13,17,56–59]. Overfeeding has also been repeatedly associated with poor outcome and results often from the use of predictive equations [60]. Recent evidence points out the importance of optimal nutrition starting within 3–4 days after ICU admission [16,18,20,61–63], at a time when predictive equations are exceedingly unreliable due to the variable responses of individual patients to the critical illness [8]. In other words, optimal nutrition promotes better clinical outcome and IC is necessary to tailor the prescription to the real needs of the patient [62–64].

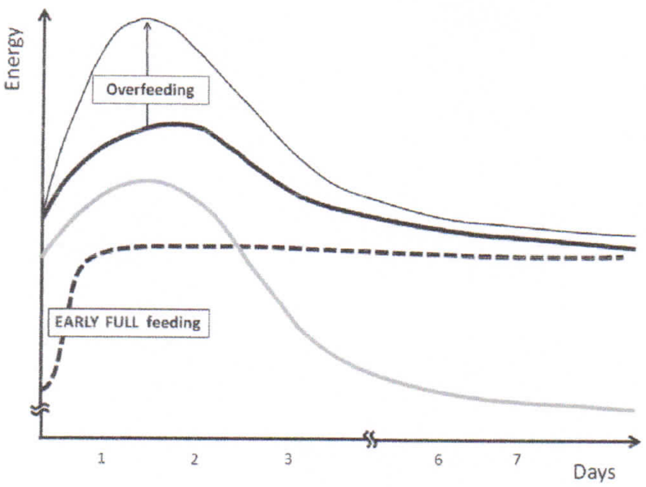

Fig. 4. Conceptual presentation of the relative overfeeding frequently related to parenteral nutrition during the early phase of critical illness. During the acute phase of the critical illness, the release of endogenous energy substrates is increased and meets total energy expenditure (TEE), and administering energy does not immediately terminate this response. Introducing full feeding in this early phase usually results in overfeeding, as the endogenous energy production is not attenuated by energy administration thus creates an excessive energy source above TEE. (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).

Table 11
Effects of overfeeding and underfeeding.

	Insufficient energy intake	Excessive energy intake
Early signs	Hypoglycemia Hypothermia	Hyperglycemia Hyperlipidemia (triglycerides) Hypercapnea
Delayed signs	Infectious complications Impaired immunity Impaired healing Loss of lean and fat body mass Impaired muscle function	Infectious complications Impaired immunity Liver steatosis Increased fat mass

The course of EE of severely ill patients features dynamic changes as a consequence of stress, prolonged bed rest, atrophy of the metabolically active lean tissue mass (i.e. 300–600 g of tissue/day), medications (catecholamine, sedatives, neuromuscular blocking agents, etc) [44,65–68], and modified by mechanical organ support therapies such as mechanical ventilation, renal replacement and liver support therapies. Thus, IC should be repeated as the clinical condition changes to accurately define the energy target [16,63].

The obese patients constitute an increasing proportion of the ICU patient population. Their energy requirements are particularly poorly addressed by predictive equations [19]. IC is the only way to determine their metabolic requirements accurately.

In summary, it is recommended to perform IC on days 3 or 4 after ICU admission, major surgery or trauma in order to set the energy target [Fig. 5].

5.6. *In patients and outpatients with chronic conditions*

Patients with chronic conditions are good candidates for IC, although their changes of EE are not as dynamic as in ICU or surgical patients. Indeed, chronic diseases or treatments modify the metabolically active lean body mass and the level of daily physical activity, which in turn significantly alter the energy needs and challenge the estimation of EE by predictive equations. Typically, important modifications of the body composition or of the physical activity deeply influence EE. Table 12 shows the most common pathologies with important EE alterations.

IC is necessary to confirm the energy expenditure and optimize the recommendation for food intake or the prescription of nutrition support. Repetition of IC should be considered according to the appearance of substantial modification of the patient status. Conducting IC together with the measurement of the body weight and the body composition is useful to further optimize the nutrition prescription by observing the effect of energy intake on these parameters [25,74].

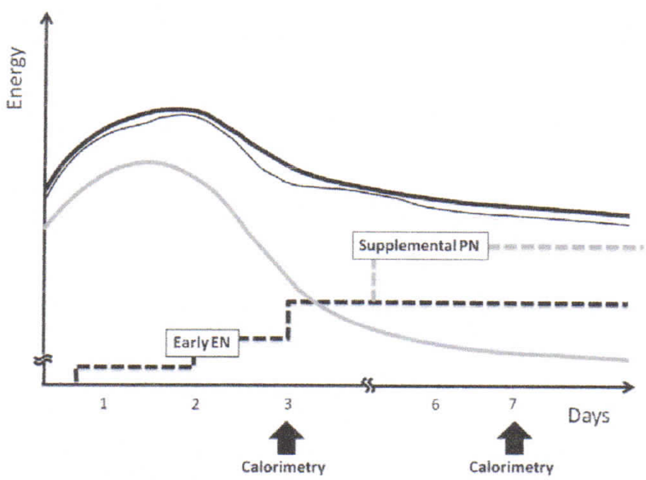

Fig. 5. Conceptual presentation of optimal feeding strategy to avoid both overfeeding and underfeeding in critical illness: Introducing the adequate amount of feeding in proportion to the body's capacity to down-regulate endogenous substrate production avoids both early overfeeding and late underfeeding. Repeated calorimetry is needed to monitor the dynamic changes of energy expenditure, however, providing the optimal amount of energy still requires special attention to avoid both underfeeding and overfeeding. (Solid bold line: Total energy expenditure; grey bold line: adapted endogenous energy production; dotted bold line: energy administration by EN; grey dotted bold line: energy administration by PN; thin line: combined endogenous and exogenous energy administration).

Table 12
Common chronic pathologies and treatments with important alterations of energy expenditure.

Conditions	Effects on energy expenditure	
Respiratory diseases		
COPD	↑	Increased respiratory efforts [69]
Cystic fibrosis	↑	[70]
Metabolic diseases		
Adrenal gland disease	↑ or ↑↓	Increased release of catecholamine [71] Unpredictable change after surgical treatment
Thyroid diseases	↑ or ↓	Altered release of thyroxine [72]
Muscle tone alteration		
Neuromuscular degenerative diseases	↓	Degeneration and disuse of muscle tissue
Paralysis	↓	Disuse and atrophy of paralyzed body area
Seizure, involuntary movements	↑	Increased muscle activity [73]
Cachexic conditions		
Cancer	↑ or ↓	Cancer growth and inflammation Progressive reduction of lean body mass
AIDS	↑ or ↓	Chronic infection and inflammation Progressive cachexia
Cardiomyopathy	↓	Progressive reduction of lean body mass
Malnutrition		
Obesity	↑ or ↓	Increased lean body mass, unless obesity is associated with sarcopenia
Anorexia	↓	Low energy intake and reduced lean body mass
Organ support therapies		
Hemodialysis/peritoneal dialysis	↑ or ↓	Chronic inflammation Progressive reduction of lean body mass
Continuous positive airway pressure (CPAP)	↑ or ↓	Increased respiratory efforts, modified by mechanical support

5.7. *Impact of IC on patient care and hospital economy*

Malnutrition is associated with increased morbidity, length of stay and costs [75]. Oral nutritive supplements, and enteral and parenteral nutrition are related with improved outcome, but both underfeeding and overfeeding have been shown to mitigate the impact of nutrition support [63,76,77]. The prescription of nutrition therapy aims at matching the energy target as defined by predictive formulas. Unfortunately, these formulas are often inaccurate. Therefore, we hypothesize that promoting a large-scale use of IC to measure EE of in- and outpatients should optimize nutrition care, clinical outcome and costs.

6. Conclusion

Calorimetry is needed to optimize nutrition care for patients with various clinical conditions. The use of calorimetry is currently limited by various setbacks, mainly related to the lack of an adequate device. An ongoing initiative to develop a new calorimeter is expected to provide practical solutions for the current limitations, and make available a calorimeter corresponding to the requirements by clinicians for in- and outpatients, featuring accuracy, ease-of-use and affordable cost. Online and live educational courses will further mount the optimal use of calorimetry.

Conflict of interest statement

All authors have declared that they have no conflict of interest related to this project.

Statement of authorship

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

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