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Mit Nachrichten der

AKE
Arbeitsgemeinschaft
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THE HYPOTHESIS BECOMES REALITY

Optimizing energy prescription improves intensive care (ICU) outcome

Malnutrition remains very frequent in hospital[1] and particularly in intensive care settings[2]. The problem of this persistence is partly explained by the absence of immediately visible consequences of acute underfeeding: they are not easily measurable and become obvious only after 7-14 days, i.e. frequently after discharge from the ICU, prolonging the hospital stay. By contrast the consequences of insufficient oxygen delivery are immediate, requiring the ICU team attention. This is an important reason why nutrition support is so frequently forgotten early on, resulting in large energy deficits. Contradictory studies have been published over the last years regarding the respective merits of hypo- and hypercaloric feeding, increasing the confusion for clinicians. The principal problem appears now to be the prescription of a reasonable energy and protein target, and to monitor its achievement.

Mette M Berger

The optimal level of energy target is difficult to predict in critically ill patients due the high variability of resting energy expenditure during illness (alteration by shock, sedation, fever, etc). Further a reasonable prediction requires at least knowing the accurate pre-illness weight (knowing that actual body weight). This information is frequently missing in ICU patients: when an actual body weight is available, it is flawed by fluid accumulation during resuscitation. The guidelines recommended that expenditure be measured on an individual basis by indirect calorimetry. This technique is relatively expensive[3], and there are several obstacles to its measurement in clinical settings thus affecting the accuracy of any such measurements[4], but this tool may prove to be very important in the near future. Coming studies are suggesting that indirect calorimeters might prove essential as well.

PHYSIOLOGICAL AND PRACTICAL CONSIDERATIONS

The mean healthy adult's resting energy expenditure (REE) is about 40 kcal/m^2/hour. It is modulated by age, sex, lean body mass, total body surface, temperature, feeding and activity. Energy metabolism of aerobic organisms is based on electron transfer in redox systems, and ATP production . It is accepted that the human body produces daily its own mass of ATP, and requires extrinsic energy provision under the form of glucose, fat and proteins for the maintenance of a living body. The rationale for indirect calorimetry, is that the energy requirements can be extrapolated from O_2 consumption and CO_2 production using the Weir equation[7] (Table 1). Double labelled water, the other gold standard, further enables determination of total energy expenditure (TEE), but is not applicable in clinical settings. TEE includes resting energy expenditure (REE), energy expenditure for physical activity, dietary thermogenesis and growth/tissue repair. Whatever the condition, the basal amount of energy required for maintaining lean functional body mass – that is, the REE – is incompressible. Providing a little more energy to enable movement constitutes isocaloric feeding[8]. Indirect calorimetry, despite being the gold standard for REE determination, remains unavailable in the vast majority of ICUs[9]. Further, this technique cannot always be performed for technical reasons (e.g. leaks in ventilator system, leaky chest drains, inspired O_2 fraction > 60%, use of NO, etc). Finally in critically ill patients REE and TEE can be very different though as shown by clinical studies[10-12]. TEE measured by doubly-labelled water is 1.4 times the measured REE as shown by a metabolic study in critically ill in septic and trauma patients[10]: the energy requirements were in the upper range of the 25-30 kcal/kg recommendations. Negative protein balances occurred already after 5 days, the protein changes being independent of the balances of both fat and glucose[10]. These problems have lead to the development of predictive equations as surrogates, most of which have been shown to be inaccurate[13]. The Harris & Benedict (adjusted or not for ideal body weight in particular in obesity), the Owen, the Mifflin, the American College of Chest Physicians (ACCP), the Ireton-Jones 1992 and 1997, the Penn State 1998 and 2003, and the Swinamer 1990 are the most commonly used. They all have repeatedly been shown to be poorly correlated with the results of indirect calorimetry in ICU patients . Further the equations are open to misinterpretation, as they often include a subjective "stress factor". Recently, Faisy et al developed an equation calculating REE on the basis of body weight, height, minute ventilation, and body temperature which is clinically more accurate than the other predictive equations for metabolically stable, mechanically ventilated patients[15]. The growing number of obese patients further complicates the picture, as the estimation of the requirements is even more difficult in these patients . A study comparing "eucaloric feeding" with hypocaloric enteral nutrition support (i.e. > 20kcal versus < 20 kcal/kg adjusted body weight (= current body weight - IBW) * 0.25 + IBW) showed that the hypocaloric version was as effective as eucaloric feeding in critically ill, obese patients (BMI 38) with shorter ventilation times and ICU stays[18]: importantly indirect calorimetry was not used to determine the exact energy requirements. As no equation is correct, the hypocaloric version may indeed well correspond to accurate feeding in obesity.

NUTRITIONAL AND METABOLIC INDICATORS IN CRITICAL ILLNESS

In clinical settings we are confronted with the failure of all classical nutrition indicators such as plasma proteins[19] and bioimpedance[20] in the early phase of critical illness. Energy balance, calculated on indirect calorimetry basis or guideline recommended equations, appears as the only practical tool to assess the patients' nutritional status. It has been shown that the ongoing cumulated energy balances can predict which patient is reaching a critical edge of deficit. At the cellular level, it has recently been shown that mitochondrial alterations appear already after 12 hours of fasting in healthy subjects: short-term fasting (up to 24h) affects mononuclear cell mitochondrial function adversely and increases calf intramyocellular lipid (IMCL) content[22]. These cellular data are convincing, but it is challenging to detect the clinical macroscopic effects of fasting before the visible deleterious effects of underfeeding become visible.

CONSEQUENCES OF UNDER AND OVER FEEDING

Both underfeeding and overfeeding have well defined adverse effects and should be avoided[23]. In the 80ies, the concept of hyperalimentation prevailed, with the introduction of high glucose content parenteral nutrition due mainly to the absence of lipid emulsions in the U.S. This new therapy indeed saved several lives, but at the same time caused serious complications. Further the concept of counting separately non-protein calories while not including the calories from proteins contributed to overfeeding. Since the Biolo et al studies investigating the impact of calorie restriction and bed rest on lean body mass, this way of reasoning should definitively be banned, and all substrates included in the total energy counts . After the study by Fong et al in volunteers[26] parenteral nutrition (PN) became considered a poison, as its delivery before an endotoxin challenged primed a stronger inflammatory response compared with enteral nutrition. The next two decades were charac-

> „Both underfeeding and overfeeding have well defined adverse effects and should be avoided."

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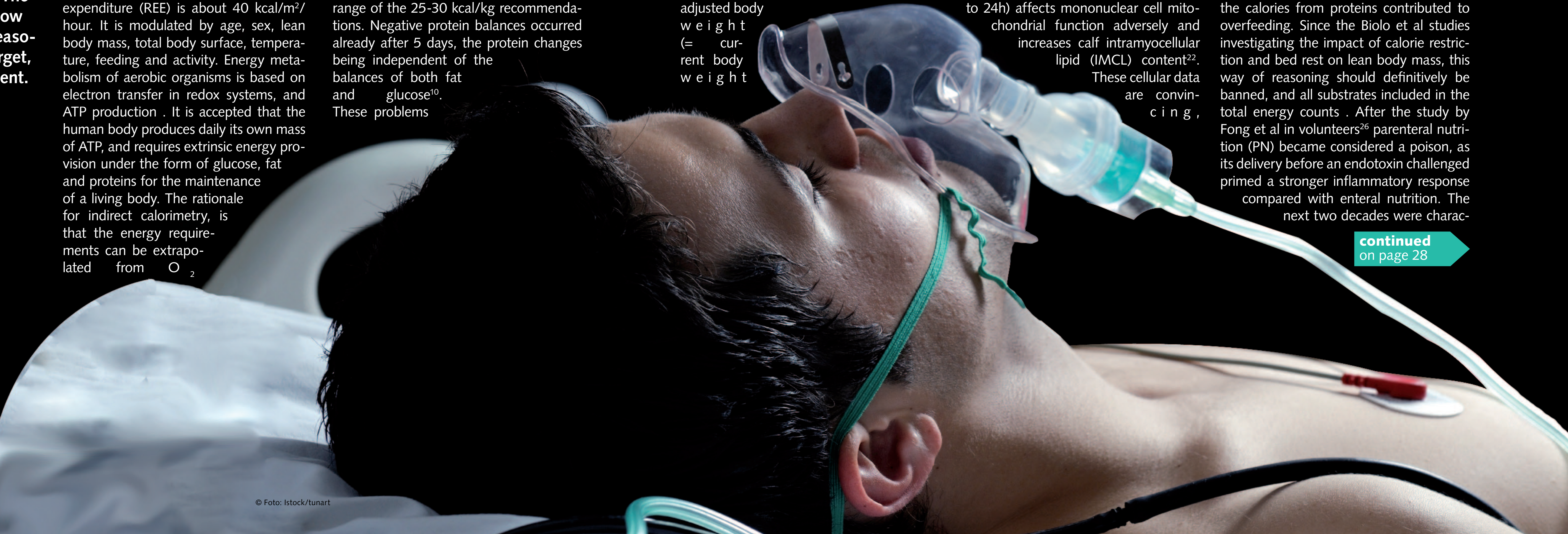

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terized by predominance of enteral feeding with the appearance complications of underfeeding, and even severe malnutrition. The earliest study to show worsening of outcome related to growing negative energy balances came from the UK and was conducted in 57 critically ill patients[27]: the authors showed that a cumulated energy deficits around –10'000 kcal was associated with an increase of mortality, in a study where the energy targets had been set by indirect calorimetry.

CLINICAL DATA AND CONTROVERSIES

Several studies have been published over the last years with apparent opposite conclusions regarding the optimal level of energy intake in critical illness. Such a situation is tragic as it aggravates the lack of interest of clinicians who already tend to have limited knowledge in this area[28]: confusion may lead the clinician to decide "leave this issue until the experts agree". Indeed some studies suggest that feeding the critically ill patient according to current recommendations is deleterious in terms of glycemic control and outcome[29-31], while others confirm that malnutrition causes complications and increases mortality at levels of energy deficit that are current in clinical practice[32] after only a few days. Negative energy balances and low feeding supply have been shown to be a major issue cross diagnostic categories.

Two prospective studies conducted in ICUs with feeding protocols and using the same computerized information system customized for nutritional supervision (Metavision, iMDsoft, Tel Aviv) showed that an increasing energy deficit was associated with clinical complications, particularly increase of infection rates. In both studies a large proportion of the patients benefited from energy targets set by indirect calorimetry: energy deficit developed in respectively 55 % and 60 % of their patients. The cut off for increasing complication rates in both studies was between –4'000 and –10'000 kcal of cumulated energy balance corresponding to –50 to –130 kcal/kg. The same type of impact on infectious complications was observed in a neuro-ICU after subarachnoid haemorrhage where the mean cumulative energy balance over the first 7 days was –117 kcal/kg[36]. In a prospective study in patients with major burns, the intake cut off separating patients with and without nutrition related complications was shown to be about 30 kcal/day[37]: the lower delivery was associated with 32.6 % death rate versus 5.3 % ($p < 0.01$) in those receiving an adequate feeding. Pneumonia rate doubled, and sepsis rate increased 1.8 fold ($p < 0.05$), and the length of stay was prolonged by 12.6 days ($p = 0.01$). In a French study including 38 medical ICU consecutive adult patients intubated at least 7 days on exclusive enteral nutrition (EN) started within 24 h of admission patients with mean energy deficit >5021 kJ/d (1200 kcal/d) had a higher ICU mortality rate than patients with lower mean energy deficit after the 14th ICU day ($p = 0.01$)[38]. The study suggests that large negative energy balance is an independent determinant of ICU mortality in a very sick medical population on prolonged mechanical ventilation.

Rubinson et al showed in 138 patients, that the incidence of bacteraemia was directly related to energy delivery with a steep increase in those patients receiving less than 25 % of the American College of Chest Physicians (ACCP) recommendations[33]: the data show a significant difference appearing already by day 7 after admission. A multicentric Canadian cluster intervention study showed that evidence based feeding algorithm indeed improved nutritional support, resulting in increased days on enteral nutrition in the intervention, with shortening of hospital stay[39]. But in both groups of hospitals, mean daily energy delivery was insufficient with 1014 or 1284 kcal/day, which complicated the interpretation of the results, as underfeeding was occurring in both groups. Using the same recommendations of the ACCP a study from Johns Hopkins Hospital including 187 medical ICU patients showed that unintentional hypocaloric feeding occurred in 51 % of ICU days[30]. As the first week corresponds to the initiation of feeding, the energy delivery is of course lowest during the first days, to increases thereafter.

„Several studies have been published with opposite conclusions regarding the optimal level of energy intake."

A randomized British ICU study including 277 patients and testing enteral immunonutrition ended up delivering a median intake of 14 kcal/kg/day (underfeeding) in both groups of their study[40], which compromised the interpretation of their results.

In 2009, Alberda et al reported the results of an international multicenter study and showed that the level of energy intake was very low cross countries averaging 14 kcal/kg/d[2]: 2,772 mechanically ventilated patients received an average of 1,034 kcal/day and 47 g protein/day. Of note, an increase of 1,000 kcal per day was associated with progressive mortality reduction. At the opposite, hypercaloric feeding has well known deleterious consequences on glycemic control, liver function, infections, and outcome[8].

When analyzing in detail several papers supporting negative effects of feeding, there is a high proportion of studies that actually do "overfeed", with the expected deleterious clinical consequences: it flaws the interpretation of the results. An important characteristic of ICU patients is that they do not tolerate overfeeding, not even that delivered with the intention to catch up on energy deficit. In a large multicentric study conducted in 40 Spanish ICUs and including 725 patients on either enteral or parenteral nutrition, Grau et al showed that overfeeding (>27 kcal/kg) was one of the determinants of altered hepatic function[23]. The consequence is that the accumulated energy deficit cannot be recovered by feeding 120-130 % of patients requirements. The problem with the development of early deficits is that «gavage», i.e. feeding above the patient's requirements (as is done to produce «foie gras» in geese), very rapidly causes liver dysfunction. The problem starts as early as 110-120 % of true requirements, with early increases of the liver enzymes ASAT and ALAT, followed by increased markers of cholestasis or a combination of both[23]. In case of early insufficient energy delivery, the patients get a "double hit": first by the complications of underfeeding followed by those of overfeeding. The only way to go is therefore to prevent the constitution of a relevant energy deficit. McCowen et al attempted to determine in 40 patients whether the frequency of hyperglycemia and infectious complications might be reduced by an "underfeeding strategy" in patients requiring more than 5 days of PN[31]. Parenteral nutrition providing 25 kcal/kg was not associated with more hyperglycemia or infections than a deliberate underfeeding strategy: but this was in 2000, before the glucose control strategies – there were indeed more hyperglycemia in the 25 kcal/kg group. A few years later, Ahrens et al again tested the hypothesis in 40 surgical patients[41]. Patients were randomized to receive either a "low-calorie" PN (20 "NON"-protein kcal/kg/day) or a standard PN (30 non-protein kcal/kg/day): to this, the investigators added lipid emulsions 3 times weekly resulting in additional 3*1000 = 3000 kcal for all patients. The authors concluded that the administration of a "low-calorie" PN resulted in fewer (0 % versus 33 %) and less-severe hyperglycemic events and lower insulin requirements. The problem of this study is that indeed, all patients were overfed, the pseudo-low-calorie group being less overfed than the other, doing of course better! We now know that energy from all substrates must be included in the calculations[25]! The praxis consisting in counting only the "non-proteins calories" should be banned definitively.

In a study including 200 ICU patients on parenteral nutrition Dissanaike et al showed that increased parenteral caloric intake is an independent risk factor for blood stream infections in patients receiving PN[29]: 3 of their patient groups received more than 26 kcal/kg per day, the mean energy intake in the group with blood stream infection being 35 kcal/kg! This study should have been called "effects of overfeeding".

CAUSES OF INSUFFICIENT ENERGY DELIVERY

Our group showed some years back that the promotion of enteral nutrition was associated with insufficient energy delivery and energy deficit[42]. This has been confirmed by several studies since[43]. The energy gap builds up during the first week , i.e. during the period of maximal GI intolerance: the alterations of the gut function are worst in the severest patients[44] . Elevated gastric residual volumes (GRV), which reflect the pyloric and intestinal dysfunction and the severity of disease, remain a major deterrent to adequately feeding patients with gastric delivered enteral nutrition[45]. Enhancing the delivery of EN early on by the aggressive use of prokinetics seems possible[46].

A further nutritional problem comes from the use of non invasive ventilation (NIV) during several hours per day. The COPD and pneumonia patients frequently benefit form NIV: this category is at high risk of malnutrition as they have an increased breathing workload, and increased energy requirements. A study including 49 patients under NIV shows that energy balances become increasingly negative with increasing time under the time, with patients having more than 4 hours per pay having systematic negative energy balances exceeding –1000 kcal/day. In absence of feeding tube, this cannot be compensated by oral feeding[47].

TOOLS TO SOLVE THE PROBLEM

Teaching basic nutritional knowledge in the medical schools is a high priority, and its absence is a worldwide problem[48]. The "FAST HUG" strategy[49], "F" standing for feeding, has not yet penetrated optimally the critical care milieu. ICU nurses and doctors are too busy with lifesaving tasks, and do not feel confident enough in their knowledge to introduce early feeding. Möwe et al recently showed in a large survey of 4512 ICU professionals that nutritional knowledge remains low[28].

- Energy requirement and target: Determining the correct energy target is the first issue. We need indirect calorimetry! Following the ESPEN guidelines (20-25 kcal/kg/day) in non-obese patients probably remains the safest in absence of calorimetry[50].
- Early EN: Artinian et al[51] showed that early EN was able to reduce mortality, despite and increased risk of VAP, and particularly in the sickest patients.
- Prevention the development of energy deficits > 4000 kcal: early EN and the use of combined feeding[52]. Supplemental PN, i.e. combined EN and PN feeding, is a way to overcome the digestive problems[53].
- Protocols: Lack of standardized practice and of protocols has been shown to be a primary cause of insufficient feeding.
- Optimizing the use of the gut with prokinetics and possibly acupuncture[54], which does probably not mean "force feeding" [46]: the sick gut is telling us something important, that we should listen too.

Optimizing the energy delivery, by individualizing and adapting it to the patients daily conditions is a new concept[3]. Recently, a prospective controlled rando-

Conclusio

Nobody knows yet exactly how long acutely ill patients can tolerate fasting without deleterious biochemical consequences: data in healthy subjects show that the time is probably shorter than previously believed. Clearly, the tolerable length of limited intake will depend on the severity of the disease. Hemodynamic instability and persistent shock may compromise the partial or total use of the gut for feeding. Although the evidence is strongly against prolonged hypocaloric feeding >96 h, the demonstration that limiting isocaloric feeding improves outcomes in the critically ill still awaits a high quality prospective trial. Which hospital director would today imagine an ICU without medical ventilators, while mechanical ventilation has never proven to be life saving in a prospective randomized trial? This lake of evidence is also true for the use of a parachute[59] while undergoing gravitational challenge! Possibly the increasing evidence of the necessity of individualizing energy delivery will push us thinking similarly about the acquisition of indirect calorimeters.

Method	Principle	Prerequisite
Indirect calori-metry	Estimates the metabolic rate from measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2). The essential assumption is that under steady state conditions respiratory gas exchange is in equilibrium with gas exchange within the mitochondria, thus measuring indirectly oxidative phosphorylation. Energy requirements are extrapolated from O_2 consumption and CO_2 production using the Weir equation 7: total kcal = 3,9 x L 0_2 used + 1,1 L $C0^2$ Medium duration (30-40 minutes) measurement determines resting energy expenditure (REE) 24h measures ➔ TEE	Stable conditions: not change in vasoactive drugs or inspired oxygen fraction < 60 %, stable temperature, absence of movement, no leaks in the system, no use of NO.
Double-labelled water method	Method based on the assumption that ingested double-labelled water ($2H_2O$ and H_218O) is distributed rapidly and homogeneously within the body water pool and more importantly that oxygen atoms in exhaled carbon dioxide and water are in isotopic equilibrium. By giving a dose of H_218O, both the water and carbon dioxide pool will be labelled, whereas when $2H_2O$ is given only the water pool will be labelled.	High technical skills and research setting.

Table 1: Principles of the principal energy expenditure determination methods.

mized trial including 112 critically ill patients, tested the clinical impact on outcome of two different strategies in 2 groups of patients[55]: indirect calorimetry was realized every 48 hours In the study group, energy target was adapted daily to these results (tight calorie control study = TICACOS) while the target was fixed in the control group, set at 25 kcal/kg/d. The authors observed a significant difference in energy delivery (+600 kcal/day) and in protein delivery (+13 g/day) between the groups, in favour of the calorimetry group. As a consequence daily and cumulated energy balances were positive in the intervention group, versus negative in the control group. This tighter energy management was associated with a significant reduction of post-ICU mortality. The study has weaknesses, but it is the first to show that individualized nutritional support brings clinical benefit. Combined nutrition, with PN to top up on insufficient EN is a tool to prevent growing energy deficit while using the gut. Several international trials are ongoing. The first results of the Swiss SPN bi-centric, randomized trial, enrolling 305 patients, show that this strategy results in a significant lesser incidence of infections: the authors were applying a glucose control strategy, and there were no more hyperglycemia in the supplemented group[56]. Visualization of the real ongoing energy delivery appears as an important tool. Computer assisted nutrition support has been show to be more efficient in achieving energy targets . The computerized information systems (CIS) also called Patient Data Management Systems (PDMS) are expensive though, much more than the calorimeters. As an alternative it is easy to constitute an Excel file (available worldwide), and to customize tables enabling rapid check of protein, glucose, lipid and calorie delivery in 24 hours, reporting the true deliveries of feed and drug solutions on the sheet, while including the sedative propofol (lipid), and other glucose containing solutions.

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