Hypermetabolism in Critical Care: The Role of Metabolism Measurement and Its Nutritional Implications

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In recent years a key role has been assumed in all areas of critical care medicine by the accurate assessment of the patient's energy state. A definition of needs is crucial in responding adequately to the state of acute imbalance that almost all illnesses bring about. Nutrition in relation to the metabolism plays a key role in influencing prognosis and patient outcome. Criticality goes hand in hand with complex responses from the biochemical point of view. Knowing these and how exactly to define them is the topic of this brief chapter.

12.1 The Definition of "Hypermetabolism"

"Hypermetabolism" is a state of enhanced metabolic activity, characterised by an increase of the basal metabolic rate. Catabolic reaction rate is higher than anabolic one. These changes are the result of a systemic response to a damage or a trauma suffered by the organism under stress. As for the autonomic nervous system, the sympathetic component is intensely active, while the parasympathetic activity is reduced.

Some of the main clinical and biochemical features of hypermetabolic patients are:

1. Increase of energy expenditure and oxygen consumption
2. Stress-induced hyperglycaemia
3. Hyperlactatemia
4. Loss of muscle mass due to hypercatabolism of proteins
5. Negative nitrogen balance

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12.2 Biochemistry of Hypermetabolism [3, 9, 14]

Gluconeogenesis (Focus On)
Gluconeogenesis is a metabolic pathway that leads to generation of glucose using non-glucidic substrates, such as pyruvate, lactate, glycerol, ethanol and glucogenic amino acids. This process occurs when blood glucose level is low, and in humans it happens mainly in the liver. Most steps of gluconeogenesis are the reverse of those we find in glycolysis (except for three exergonic reactions). Gluconeogenesis begins in the mitochondria, where pyruvate is converted to oxaloacetate and then to malate. Malate is then transported to cytoplasm, where it is oxidised to oxaloacetate and converted to phosphoenolpyruvate. Other reactions take place in the cytoplasm and they are the same as in reversed glycolysis.

Fructose1,6-bisphosphatase is the key enzyme in this process. This is controlled by allosteric regulation (by binding an effector molecule to allosteric site, the enzyme's active site will be able to catalyse reactions). Fructose1,6-bisphosphatase can bind positive allosteric modulators such as citrate, enhancing its attraction to substrates, or negative effectors such as AMP (adenosine monophosphate) and fructose2,6-bisphosphate, reducing its affinity to reagents. The reaction catalysed by fructose1,6-bisphosphatase is the rate-limiting step of gluconeogenesis.

Stress response is characterised by a raise of energy expenditure: proteins are used as an energy source by the liver, where gluconeogenesis is highly active. Hepatocytes are able to produce glucose, using pyruvate as a substrate. The energy needed for this metabolic pathway is provided by beta oxidation and later by the citric acid cycle.

Acute-phase proteins: they are serum proteins whose levels rise (positive acute-phase proteins) or decrease (negative acute-phase proteins) when inflammation occurs. They are a useful marker to detect inflammation, and together with fever, leucocytosis and other symptoms such as tachycardia, hypertension, shivering, anorexia and malaise, they constitute the so-called acute-phase reaction.

Positive proteins: they are part of the innate immune system, but they serve several different functions. Some of them destroy or inhibit microbes (i.e. C-reactive protein, mannose-binding protein, complement factors, ferritin, ceruloplasmin, serum amyloid A and haptoglobin); others give negative feedback to the inflammatory response, such as serpins (serine protease inhibitor). Coagulation factors and alpha-2-macroglobulin mainly stimulate coagulation, probably in order to trap pathogens and to limit the infection. Other products of the coagulation system can increase vascular permeability, acting as chemotactic agents for phagocytic cells.

Negative proteins: they include albumin, transferrin, transthyretin, retinol-binding protein, antithrombin and transcortin. When inflammation occurs, these proteins' synthesis decreases with the purpose of sparing amino acids to produce positive acute-phase proteins. Transferrin reduction is also due to an upregulation of its receptors, but this mechanism does not seem to change in relation with inflammation.

When a patient undergoes stress response, protein synthesis is reduced, and hepatocytes begin producing *acute-phase proteins*. There is an enhancement of plasma concentration of positive acute-phase proteins (e.g. C-reactive protein, ferritin, ceruloplasmin) and a decrease of negative acute-phase protein concentration, for example, serum albumin levels. *Protein hypercatabolism* attempts to respond to the increased energy needs. This leads to one of the main features of stress response: the loss of patient's lean body mass. An important difference between starvation and *stress reaction* is the *inflammatory response* (first local and then systemic) activated by the injury. Inflammation causes the release of cytokines, hormones and neuronal signalling molecules to the hypothalamus. These changes in the hormonal profile determine a strong *fight-or-flight*-like response. The so-called stress hormone (e.g. catecholamines, cortisol, glucagon) levels are increased, inducing various consequences on the organism. This response is a maladaptive process.

The systemic response to stress causes several biochemical changes, for example, the increase of oxygen consumption and body temperature and the alteration of metabolic profile to keep up with the high oxygen demand. Gluconeogenesis, which takes place in the liver and uses lactate, glycerol and amino acids to produce glucose, plays a key role in this process. Furthermore, cells fail to respond to the hormone insulin, a process called *insulin resistance*. This occurs especially in insulin-dependent tissues such as muscle and adipose tissue, which need insulin to regulate glucose intake and therefore glycaemia. Insulin resistance seems to be a consequence of insulin receptor downregulation and reduced transcription of GLUT-4, caused by inflammatory mediators, and is one of the mechanisms responsible for *stress-induced hyperglycaemia* (SIH), and in critical patients it is associated with a worse outcome. In addition, it shows up an imbalance in plasma levels of metabolic hormones. The hormonal response includes augmented levels of catecholamines, cortisol and glucagon and a strengthening of gluconeogenesis and glycolysis in the liver, hence the further higher levels of glycaemia. This condition is particularly emphasised in critical patient as part of an adaptive response whose final aim is survival. When the stress response is maintained without adequate treatment, it leads to energy reserve depletion, with severe consequences. It is therefore crucial to accurately assess the metabolic state of patients in ICU. Some of the causes of stress in critical patients are illustrated in Fig. 12.1, along with the relative resting metabolic rate. Patients undergoing hypermetabolism are frequently inadequately fed, but their clinical condition is different from the underfeeding provoked by short-term or long-term starvation.

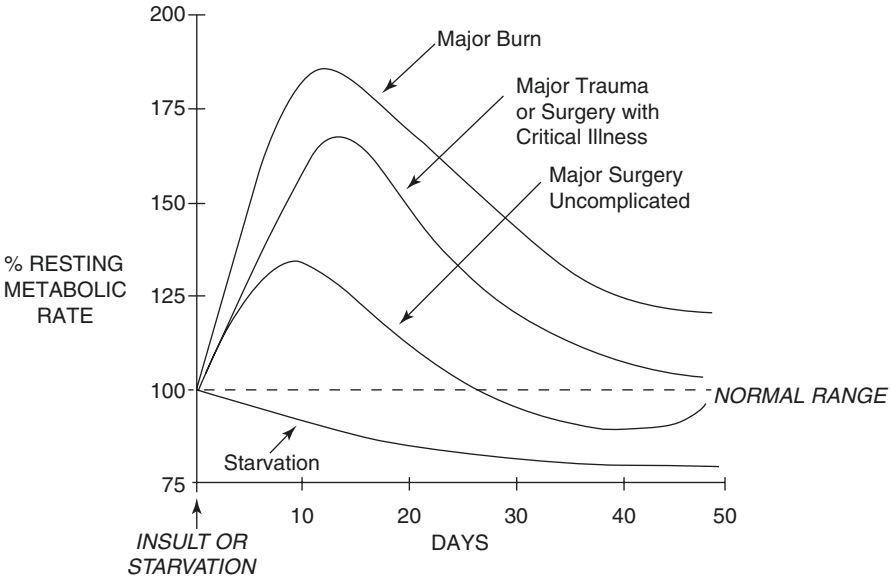

Fig. 12.1 Variation in resting metabolic rate in different types of critical patient. The graph was taken from [9]

Glucose transporters (GLUT) are a group of membrane proteins that facilitate the transfer of glucose across the cell membrane, from interstitial space into cytoplasm. These carriers are usually sequestered in cytoplasmic vesicles. In humans, seven types of glucose transporters have been identified, and each one of them has a different distribution depending on the tissue. In insulin-dependent tissues and in those who directly regulate glycaemia according to variations in the level of glucose, there are three types of glucose transporters:

- GLUT-4 (insulin-dependent glucose transporter)
- GLUT-2 (acts as an insulin-independent glucose sensor)
- GLUT-1 (responsible for the low level of basal glucose required by all cells)

In insulin-dependent tissues such as striated muscle (skeletal and cardiac muscle) and adipose tissue, the main glucose transporter is GLUT-4, which is strictly regulated by insulin concentration. The release of insulin increases both the synthesis of GLUT-4 and its translocation from the intracellular vesicles to the plasma membrane: the vesicles fuse with the membrane, and GLUT-4 transporters are inserted and become available for their function, augmenting glucose uptake from interstitial space into cytoplasm. Once glycaemia is reduced to basal concentration and insulin is cleared from the bloodstream, endocytosis sequesters GLUT-4 in vesicles. GLUT-4 concentration can also be influenced by other factors: hypercortisolaemia reduces it, while stress, physical exercise and any mechanism causing a decrease in the ATP/ADP ratio or an increase in levels of calcium ion

(Ca^{2+}), augmented blood flow and reduced levels of glycogen determine raising in GLUT-4 activity.

In skeletal muscle, GLUT-4 uptake of glucose is more intense in type I fibres (also called red fibres). Striated muscles usually take 60% of the glucose available in the bloodstream, while other tissues take the rest, and only a very small fraction goes to the adipose tissue. It has been shown that at least 80% of glucose consumption, induced by insulin, takes place in the skeletal muscle, while adipose tissue only uses 5–10% of it.

Glycogenolysis

Every day, the human organism needs to regulate a lot of different reactions and functions to preserve its balance. One of the parameters that needs to be controlled is glycaemia. When hypoglycaemia occurs, glucagon is released in the bloodstream, causing a raise in plasmatic glucose levels. Glucagon acts as a signal to the liver, leading to an increased production and release of glucose into plasma. Adrenaline induces an augmentation in glycaemia too, but, unlike glucagon, it influences mostly the muscle tissue. When these hormones bind to their receptors (both in the liver and muscle tissue), protein kinase A is activated: this enzyme starts up phosphorylase kinase. This kinase converts glycogen phosphorylase b in its activated form (glycogen phosphorylase a) by phosphorylation (while glycogen phosphorylase can be inactivated by a protein phosphatase). Glycogen phosphorylase is the first enzyme in glycogenolysis. It removes terminal glucose residue from a glycogen branch, producing glucose-1-phosphate. The latter is converted by phosphoglucomutase into glucose-6-phosphate. This can either be used for glycolysis, in muscle tissue, or be released in the bloodstream, in the liver (in hepatocytes there is a particular enzyme, glucose-6-phosphatase, which can remove the phosphate group from glucose 6-phosphate).

12.3 Starvation vs Stress [17, 20]

Unlike stress-induced metabolic alterations, the *metabolic response to fasting* consists in a reduction of energy expenditure (*metabolic rate* is reduced to 20–25 kcal/kg/day). During the first hours, the glucose stored in the liver as glycogen is depleted; after that, 90% of energy is produced by lipolysis, while proteins are used as a substrate for gluconeogenesis to synthetize glucose. This would result in a decreased protein biosynthesis, if it were not for the *protein-sparing* response which minimises the loss of muscle mass. Starvation induces adaptive responses that, in time, can result in malnutrition.

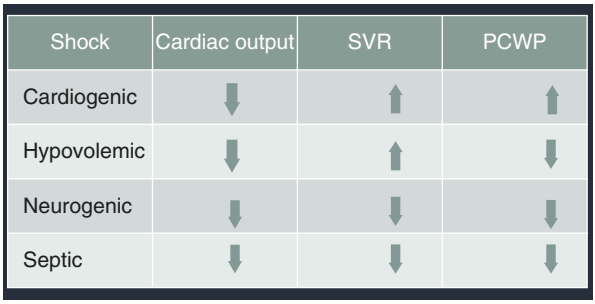

Fig. 12.2 Haemodynamic changes associated with different types of shock. Systemic vascular resistance (SVR). Pulmonary capillary wedge pressure (PCWP)

12.4 Hypermetabolism and Hyperdynamic Circulation

Biochemical and metabolic alterations are not the only changes caused by hypermetabolism. Also *haemodynamics is altered*. The augmented oxygen consumption in peripheral tissues leads to an increased cardiac output (CO) and a reduction in systemic vascular resistance (SVR). Typical clinical conditions presenting with hyperdynamic circulation are sepsis (when vasoplegia causes hypotension or dysoxic septic shock), intense adrenergic stimulation (e.g. due to postoperative pain), hyperthyroidism and hyperthermia. In a patient with hyperdynamic circulation, we should always consider underlying hypermetabolism.

In hyperdynamic circulation, the most common changes in haemodynamic parameters are *increase of cardiac index and systolic volume index*, possibility of hypertension or hypotension (depending on the level of vasoplegia) and reduction of systemic vascular resistance, central venous pressure and wedge pressure (changes in haemodynamic parameters in different types of shock are shown in Fig. 12.2).

12.5 Hypermetabolism and Sepsis [5, 11, 18, 23]

Stress response is particularly emphasised in patients with sepsis: it can be induced by SIRS (systemic inflammatory response syndrome), hypermetabolism (with an increase in resting metabolic rate), hypercatabolism (protein breakdown takes place especially in muscle tissue), shock and *multiple organ failure (MOF)*. In this case the inflammatory response can be triggered by components of the bacterial cell wall (endotoxins or exotoxins) which induce a massive release of inflammatory mediators, increasing the stress action. Augmented energy expenditure can be also explained by fever. It induces a 10–15% increase in energy expenditure for each degree Celsius elevation of temperature, even though the relation between the two parameters in critically ill patients is complicated.

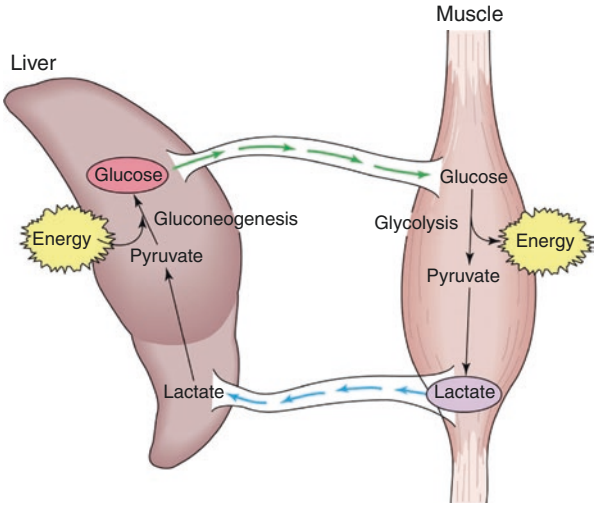

Fig. 12.3 The Cori cycle

We cannot address hypermetabolism and sepsis without mentioning lactate metabolism. *Hyperlactatemia*, due to hypoxia and hypoperfusion, is present in every low cardiac output condition, such as shock. Understanding lactatemia levels in septic shock has been shown to be a much more complex task though. In the early phase of septic shock, the clinical presentation is similar to that of cardiogenic and haemorrhagic shock. The administration of sympathomimetic drugs (adrenaline, noradrenaline, dopamine and dobutamine) causes an increase in lactatemia per se. A peculiar metabolic condition called "accelerated aerobic glycolysis" occurs in septic patients, and its main features are increased synthesis of glucose transporters across the cell membrane, augmented glycolysis (induced by endogenous and exogenous catecholamines) and inflammation. The rate of glycolysis exceeds the oxidative capacity of mitochondria: this imbalance, together with protein hypercatabolism, causes an increase in pyruvate concentration, especially in muscle cells. Pyruvate is then converted to lactate by fermentation. The increased lactate production acts as an adaptive mechanism in order to keep the carbohydrate metabolism from stopping when oxygen delivery is reduced. Lactate can be used both as an alternative fuel to glucose and a source of glucose itself. Cells keep it for producing energy and this protects from acidosis. Lactate is transported out of the cell by diffusional cotransport with protons (H^+ ions), thus regulating intracellular pH. In septic shock, lactate produced in myocytes is used as a substrate in the Cori cycle (illustrated in Fig. 12.3), an effective but highly energy-consuming pathway. Lactate is transported to the liver, where it is used for gluconeogenesis: it is first converted to pyruvate and then to glucose. In this way, lactate serves to deliver additional glucose that can be used by the organism. It is also important to point out that, when the patient undergoes stress, the heart and the brain are able to use lactate as main fuel: these organs can oxidise lactate instead of glucose during anaerobic conditions, leaving glucose for other cells.

Septic patients are extremely frail, both during the early and the late phase of illness. *SIRS* is a pro-inflammatory syndrome: its aim is to remove the organism responsible for the infection by increasing the activity of the immune system. When this response goes out of control or is overly prolonged, it damages the patient. Studies on septic patients have shown the existence of an anti-inflammatory response, usually occurring after SIRS, called *CARS* (*compensatory anti-inflammatory response syndrome*). CARS consists in a suppression of the immune system in order to restore homoeostasis after a severe inflammatory state. SIRS and CARS are the two sides of the same coin: each one is characterised by a particular set of cytokines, and, although they are separate responses, most of the times one follows the other (even though often they take place simultaneously with different relevance). Like SIRS, CARS can be dangerous too if it is not regulated or it fails to restore homoeostasis, making the patient vulnerable to infections. Some of the clinical features of CARS are cutaneous anergy, leucopenia, hypothermia, susceptibility to infections and failure to clear infections.

12.6 Hypermetabolism in Cancer Patients [21]

In neoplastic patients, especially at advanced stages, cachexia is frequently associated with an increased *resting energy expenditure* (REE). The condition is even more complicated due to the presence of symptoms such as anorexia, pain and depression, which can often cause malnutrition, both in quantitative and qualitative terms. Malnutrition affects the metabolic state of the patient, which is already impaired.

12.7 Hypermetabolism in Postoperative Patients [7, 13]

Patients undergoing surgery are an ideal model for the study of hypermetabolism caused by stress response. Surgery is in fact a clear example of a stressful event: even though anaesthesia reduces afferent neural transmission to pain centres, the organism interprets surgery as a threat. The activation of different hormonal axis causes the release of stress hormones such as cortisol, catecholamines, glucagon and growth hormone. These hormones are responsible for the condition of hypermetabolism, whose biochemical aspects have been previously discussed. This mechanism takes place in elective operations, but even more in emergency surgery, major surgery and when postoperative complications occur. The stress response purpose is the survival of the critically ill patient, by using the energy reserves and retaining water. The response becomes a harmful condition when prolonged in time. Regional and local anaesthesia has been shown to be an important factor in both reducing the stress response to surgery and influencing the postoperative outcome by bringing beneficial effects on organ function.

12.8 Hypermetabolism in Trauma Patients [4, 6, 7]

In trauma patients, the systemic inflammatory reaction is similar to the one previously described. The splanchnic region appears to be the main source of hypermetabolic response. The increased energy expenditure is not adequately matched by an implementation in blood flow, especially right after the trauma, when the patient is often hypovolaemic due to loss of blood. Hypovolaemia causes splanchnic vasoconstriction which is an important risk factor for inadequate perfusion of splanchnic region.

12.9 How Can Energy Expenditure Be Accurately Determined [1, 2, 24, 25, 26]?

Once the complex condition of the critical patient in hypermetabolic state has been analysed and understood, it is essential to think about the correct way to manage the administration of nutrients. That is important to satisfy needs and prevent negative consequences of catabolism and malnutrition. First of all, it is crucial to accurately determine energy expenditure (EE).

Historically we know two different ways to solve this problem: the use of predictive equations and the calorimetry procedure (whether direct or indirect).

Predictive equations are really manageable since no measuring instrument is required and the results can be comfortably calculated at a desk; the required data are easily available and at no great expense, either! It should not, however, be forgotten that they represent only a mere approximation of the energetic consumption of the individual being examined. Even in the analysis of healthy subjects, it is well known that predictive equations are not particularly accurate. Each of the available formulas was derived from a cohort of individuals who, potentially, could have had extremely different features from the patient that we want to examine. Let us consider, for example, the Harris-Benedict (which, when the correction factor 1.2 is applied, is the least discordant among the calorimetric measures for the male sex). This formula was worked out, in 1919, from the study of a specific population of 239 *healthy* adults. It is evident that the physical features of the subjects examined were dramatically different from those of people living nowadays. Changes in lifestyle, working conditions, services and facilities available, alimentary regimen and disposition to physical exercise are only some of the differences we can find between these two different groups.

Secondly, even when resorting to these formulas, we have to choose which one, from the large number available, is the most suitable for our patient. There are indeed differences that may reach 20–30% of the estimated value when choosing one rather than another (Table 12.1). It has been proven that the use of these equations can frequently lead to *underfeeding* (in formulas that underestimate the EE) or to *overfeeding* (in equations that overestimate the EE) the patient concerned. This can, obviously, compromise the patient's prognosis. Considering the extreme

Table 12.1 Comparison of REE values obtained by indirect calorimetry and with the different predictive equations in 49 elderly male subjects who were being mechanically ventilated

Predictive equation	REE (kcal/24 h)	ICC	95% CI	*P* value
Indirect calorimetry	1701.9 ± 387.4	–	–	–
Lührmann	1579.6 ± 267.68	0.574	0.353–0.735	<0.001
Fredrix	1569.4 ± 268.7	0.597	0.384–0.750	<0.001
Ireton-Jones	1590.5 ± 178.4	0.465	0.216–0.658	<0.001
Mifflin St-Jeor	1470.9 ± 265.0	0.446	0.193–0.644	0.001
Harris-Benedict × 1.2	1707.6 ± 339.7	0.668	0.480–0.798	<0.001
ESPEN minimum	1553.3 ± 424.9	0.579	0.360–0.738	<0.001
ESPEN average	1747.5 ± 478.0	0.617	0.410–0.764	<0.001
ESPEN maximum	1941.7 ± 531.1	0.505	0.265–0.686	<0.001

The table was taken and adapted from [24]
REE resting energy expenditure, *ICC* intraclass correlation coefficient, *CI* confidence interval, *ESPEN* European Society for Clinical Nutrition and Metabolism

variations of energy expenditure in the different conditions of stress that can occur in a critical patient, it is obvious how only the correct measurement of how much energy (EE) the patient *actually consumes*, and not the estimate of how much the patient *should theoretically consume*, can represent the baseline for the institution of a correct caloric supply.

This is especially true when treating critical patients and, in particular, hypermetabolic ones. Using predictive equations with these subjects, their real energetic consumption is almost always underestimated. We will determine how much energy they *should theoretically* consume and not what they are *really* wasting, in energetic terms, to support the hypermetabolic state in which they are. The arrangement of artificial nutrition, based on energy expenditure obtained using predictive equations, will lead to a negative energetic balance that will inevitably deteriorate the state of intensive catabolism. Literature supports how "hospital malnutrition" is associated with unfavourable prognostic factors such as an increased risk of contracting nosocomial infections, prolongation of hospitalisation and, not least, increased risk of mortality. An absolutely necessary goal in the management of artificial nutrition must be the strict recording of the patient's daily energy expenditure. This represents best practice with the aim of identifying the correct calorie intake to prevent a negative energy balance in the critical patient.

In the light of all this, we can understand how calorimetry acquires overriding importance. This is the reference tool for the measurement of energy expenditure. Unfortunately, this method is still not widely practised. Considering how cumbersome the early instruments were and how difficult they were to use, it is understandable why such instrumental investigation was rarely resorted to in the past. Nowadays, thanks to the portability of the equipment and its ever-increasing simplicity of use, there is no longer any justification for omitting to measure this sort of data at the patient's bedside. This is actually even easier, as we shall see later, where patients are being ventilated through an endotracheal tube or a tracheostomy cannula.

Calorimetry assessment is, therefore, the real issue of the metabolic and nutritional study of critically ill patients.

In current scientific literature, *the calorimeter* is the "gold standard" reference tool for the measurement of *energy expenditure*. Yet, today, the use of these instruments is limited to only a few artificial nutrition centres and even fewer intensive care units. The rather high cost of the equipment, together with the fact that they are still hardly user-friendly and that certain measurements—especially the more accurate ones—take a long time to calculate, still seems to be a problem.

We are confident, however, that the main obstacle to the use of calorimetry at the critically ill patient's bedside is *a less than perfect understanding* of the importance of these figures which obviously do not only tell us about calorie consumption but also provide an assessment of the metabolic or hypermetabolic state of the critically ill patient.

12.10 Which Calorimetry [8, 12, 16, 19]?

Direct calorimetry measures the heat produced by the metabolic processes to quantify total energy expenditure. For this survey to be carried out, the subject must be transferred into a whole room calorimeter. This is, undoubtedly, the most accurate method to determine the consumption of substrates for energetic aims. The costliness, lack of availability and the complexity of performance have limited the chances of widespread use of this method, so direct calorimetry is out of the question for critical patients.

With *indirect calorimetry*, on the other hand, energy expenditure is defined by the analysis of respiratory gases based on the principle of respiratory thermochemistry: the organism gets energy through the oxidation of energetic sublayers held in food; these are metabolised according to known stoichiometric reactions in which oxygen is consumed and carbon dioxide is produced. Indirect calorimetry can be carried out using two different types of circuit. In closed circuit, the patient inspires and expires from the same chamber the gases, after a certain period, will be analysed. In this case only the consumption of oxygen is measured, and energy expenditure is estimated considering a thermal equivalent per litre of oxygen (i.e. 4.82 Kcal/L).

In open-circuit indirect calorimetry, the inspiratory air is supplied one way, while the expiratory gases are collected by another separate one for examination. So we can observe both O_2 consumption and CO_2 production. In this way we can define energy expenditure and respiratory quotient (which is useful for detecting nutritious substances that the patient is burning). This is the preferred method for clinical and diagnostic use because it is easy to perform either on ventilated patients or on patients that are in spontaneous breath. In this second class of patients, the gases are collected by using helmets, masks or nozzles—applying a nasal clamp to prevent any gas dispersion.

In patients with orotracheal intubation or with tracheotomy, the analytic circuit should simply be inserted between airway and ventilator (the latter can be set on just

any ventilation mode). With these subjects, furthermore, there is far less chance of gas leaks leading to any misrepresentation of the results of the analysis.

Accuracy of execution is fundamental. Aspects that could distort the determination are:

- Concomitant use of anaesthetic gases
- Gas leaks along the circuit
- Absence of appropriate calibration and validation of the equipment
- The failed achievement of a patient's steady state characterised by continuous changes in FiO_2 administration, in alimentary regimen and in drug prescription
- Fractions of inspired oxygen above 60%

Oversights in these fields can lead to imprecise metabolic measurements and data that are clinically absolutely useless.

As mentioned above, the determination of energy expenditure is possible through *the analysis of oxygen consumption (VO_2) and carbon dioxide production (VCO_2)*. It is obvious how any factor that continuously alters the dynamic of O_2 consumption and/or CO_2 production falsifies a quick reading (limited in time to 20–30 min) as an estimation of daily energy expenditure.

It is helpful to make sure the patient has reached a steady state before calorimetry is carried out and, then, to check that the same is maintained during measurement. This is important if we are to achieve reliable and clinically useful data using this method.

To verify the stability of the patient's energy consumption, it is enough to check temporary progress of VO_2 values. This parameter, after energy consumption variations, will settle on its new value in a maximum time of 2–3 min—unlike CO_2 that can take up to 30 min. If during calorimetric measurement the excursion of VO_2 values does not exceed 10%, it would be reasonable to assume that the patient is in stable metabolic conditions. Otherwise, it is worth considering a 24-h respiratory gas analysis.

The use of *sedatives and/or neuromuscular blocking agents* has been seen to lead to a reduction of energy expenditure. That being said, it is easy to understand how, whenever we introduce or remove these drugs, it is necessary to carry out the calorimetric determination once more in order to adjust artificial nutrition to the new metabolic attitude.

If we introduce these drugs and go on with caloric administration based on the indirect calorimetry already done, even if carefully, before the administration of sedatives and/or neuromuscular blocking agents, we will risk overfeeding our patient with deleterious consequences. Conversely, the nutritional provision might even prove wholly inadequate for the patient's needs.

Special consideration has to be given to patients undergoing *haemodialysis or continuous renal replacement therapy* (*CRRT*). Haemodialysis removes a large share of carbon dioxide from the venous circulation. This leads, inevitably, to a reduction in the proportion of CO_2 released from the lungs with consequent underestimation of VCO_2 and contemporary overestimation of VO_2. To these, one should add the side effects of the change in the acid-base balance, due to dialytic

depuration, that could further influence VCO_2. At this point it is to be recommended that patients undergoing intermittent haemodialysis do not have indirect calorimetry until 24 h after their last dialytic session. This will favour an accurate measurement of energy expenditure.

In patients undergoing CRRT, as well as those undergoing continuous venovenous haemodialysis (CVVHD), the gas removal rate depends on the dialysate flow rate.

The loss of CO_2 will lead to an underestimation of energy expenditure. Furthermore, these techniques often cause a reduction in body temperature with consequent decline in metabolic demands. At the present time, it is not yet entirely clear how CRRT affects the accuracy of indirect calorimetry. In the light of this, it is advisable to carry out a "temporary" indirect calorimetry to be repeated 24 h after the end of the dialysis cycle.

Since the 1990s, the biomedical industry has offered a contribution to spread clinical use of indirect calorimetry. The technological prerequisite is the availability of sensors for oxygen and carbon dioxide integrated in ventilators: it is therefore easier to measure the expiratory fraction of O_2 that in addition to the already known inspiratory fraction of CO_2 (equal to zero), expiratory fraction of CO_2 (measured by capnography) and inspiratory fraction of O_2 (imposed by the physician) provides a complete picture of the input and output of these two gases and therefore production and consumption of the same (VO_2 e VCO_2).

Many *respirators* from various companies offer the option to perform calorimetry: of particular interest is the opportunity to measure the change in energy expenditure during weaning from mechanical ventilation. Weaning that requires excessive energy consumption likely represents an attempt that it is better not to pursue.

12.11 Metabolic Calculations

Indirect calorimetry, performed at rest, quantifies the basal metabolic rate (REE) which, as we shall see, constitutes the bulk of daily energy expenditure. Energy expenditure is estimated from oxygen consumption (VO_2), production of carbon dioxide (VCO_2) and urinary excretion of nitrogen (uN_2). VO_2 and VCO_2 can be transformed into energy expenditure, corrected for protein metabolism (through uN_2), by applying the *Weir equation*:

$$M = 3.941\mathrm{VO}_2 + 1.106\mathrm{VCO}_2 - 2.17\mathrm{uN}_2$$

where M represents the metabolic energy expenditure expressed in kcal/min. Weir himself pointed out how, by neglecting the protein metabolism, you make an error of 1% each 12.3% of the proportion of calories provided by the same. If we accept an approximation of this order of magnitude, we can simplify *the Weir equation*:

$$M = 3.941\mathrm{VO}_2 + 1.106\mathrm{VCO}_2$$

Multiplying M to 1440 min/day, you get the REE expressed in kcal/day. These calculations are performed automatically by open-circuit indirect calorimeters that are used in clinical practice, accurately and in real time during the examination.

The *respiratory quotient*, which is the relationship between the CO_2 produced and the O_2 consumed, is a useful parameter to assess the metabolic mixture used during the investigation. The complete metabolisation of fats, proteins and carbohydrates leads to the production of different amounts of CO for the same values of O_2 consumed (the RQ of carbohydrates is equal to 1, for the lipids the value is 0.7, while for proteins is 0.8). In a fasting subject under physiological conditions, the expected RQ is around 0.82 (assuming as a physiological limit the range 0.707–1.000). Values below the lower physiological limit are associated with gluconeogenesis and ketogenesis, while values above the upper limit are associated with lipogenesis. Among the most frequent causes of *increase of RQ*, let us remember hyperventilation, metabolic acidosis, overnutrition, exercise and hyperthermia. Frequent factors that, conversely, *negatively affect the RQ* are hypoventilation, food deprivation, diabetic ketoacidosis, ethanol metabolism and hypothermia.

The RQ has been used, in the past, to guide the choice of the mixture of macronutrients to be administered as a nutritional support. It has been noted that such use of the RQ is inadequate. In fact, an increase in respiratory quotient may reflect an intolerance to excessive calorie intake which can lead to respiratory distress; that fact is especially common in debilitated patients, subjected to great stress, in hypermetabolic state or suffering from chronic obstructive pulmonary disease with reduced CO_2 elimination capacity.

12.12 How to Use Data Obtained [10, 15, 22]?

The total daily energy expenditure (TDEE) is given by three components: the basal metabolic rate (or *resting energy expenditure REE*) which accounts for 60–80%, the *diet-induced thermogenesis* (*SDA*, *specific dynamic action* of nutrients) which constitutes about 10% and the *energy consumption due to physical exercise (PAEE*, *physical activity energy expenditure*) that identifies the remaining 10–30% (Fig. 12.4). This is what happens in the healthy and autonomously mobile subject.

Calorimetry, performed in rest conditions, identifies, therefore, the *MREE* (*measured REE*). At this point it is worth thinking about the use of the data obtained. In particular, one might wonder if the value obtained from the calorimetric measurement needs an additional quota of calories to cover also the PAEE and SDA. With in-patients who are bedridden and immobilised, you can safely assume that the MREE is comparable to TDEE. Recovering from the sickness process, the resumption of mobilisation, deambulation and, then, routine daily activities affect the total daily energy expenditure. It is only at this point that, to define the TDEE, one must also add the PAEE to the MREE. In the past it was common practice to implement caloric administration in patients admitted to the ICU of a further 10% compared with MREE. This actually cannot help but lead to *overfeeding* of patients. It is now established that, if the determination is performed in the patient's steady state (or, alternatively, for 24-h investigation), the MREE closely approximates the total daily

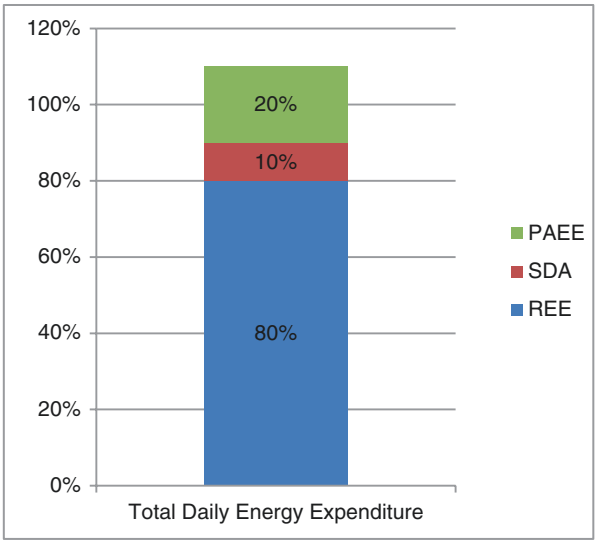

Fig. 12.4 Components of the total daily energy expenditure. The total daily energy expenditure is made up of the resting energy expenditure (REE), which accounts for approximately 70%, plus the share due to the specific dynamic action of nutrients (SDA) and physical activity energy expenditure (PAEE). In young individuals, the REE may be increased by active anabolic processes. The graph was taken and adapted from [15]

energy expenditure (even in conditions of hypermetabolism—the hypermetabolic processes are not interrupted while measuring takes place and thus contribute to the energy expenditure), and this should be the only reference value in determining the artificial nutrition dose to be administered.

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