UNIVERSITÀ DEGLI STUDI DI FOGGIA

DOTTORATO DI RICERCA IN
"MEDICINA TRASLAZIONALE ED ALIMENTI: MANAGMENT, INNOVAZIONE E SICUREZZA"
(XXXII CICLO)

COORDINATORE: PROF. DEL NOBILE

TESI CLINICO-SPERIMENTALE

Impact of protein intake on weaning from mechanical ventilation in ICU patients

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Abstract

Background: In mechanically ventilated ICU patients enteral nutrition started 24 to 48 hours of ICU admission, shown to reduce infectious complications and duration of hospitalization. Due to acute respiratory failure 30% of patients admitted to ICUs require mechanical ventilation. Delayed weaning increases costs, risks of nosocomial pneumonia, cardiac-associated morbidity, and death. Early weaning often results in reintubation, and associated complications due to prolonged ventilation. Nutritional management poses a vital challenge to the intensivist in the ICU. Malnutrition causes widespread organ dysfunction, associated with poor healing, reduce immune competence & poor weaning from ventilator (decreasing the diaphragmatic contractility and depressing the hypoxic drive & ventilatory drive to CO_2). The extent of muscle wasting and weight loss in the ICU is inversely correlated with long-term survival of the patients. In this thesis will be discussed the role of the nutritional support in the critical care setting when associated to weaning from mechanical ventilation.

Objectives:

1. Assessment of Clinical And Anthropometric nutritional status.
2. Differences in outcomes measuring weaning duration, harm (adverse events) and resource use (ICU and hospital length of stay, cost).

Material and methods: Patients >18 y-o, admitted to the ICU from November 2016 to November 2018 were enrolled. Anthropometrics, nutritional status such as BMI and weight, nutritional support such as enteral or parenteral nutrition, albumin and total proteins levels, clinical parametrs such as P/F were recorded for the entire ICU stay.

Results: 30 consecutive patients (12 female) were enrolled. The average duration of each admission to the ICU was 24.58 ± 14.7 days. The 84% of patients was enterally fed. Albumine and total proteins were not significantly different throughtout the ICU stay. Different enteral nutrition mixtures influence clinical response (better P/F). Calories estimated and provided were adequate to the ventilatory phase associate. The nutritional support was adequate, since BMI and weight were the same at admission and discharge from the ICU.

Conclusions: through an optimal planning of the nutritional supply, in our ICU days of hospitalization were not increased, avoiding the incidence of difficult or prolonged weaning conditions and the consequences associated with it.

Introduction

The importance of food for the health of the human organism is recognized to have its roots in human history; however, it can be affirmed that scientific knowledge on the importance of adequate patient nutrition has been consolidated only more recently in clinical practice.

It is, in fact, only since the 1950s many researchers have been committed to recognizing the close relationship between nutrition and disease, in particular focusing on the consequences of poor nutrition on morbidity and mortality. Despite this, even today, in the hospital setting the prevalence of malnutrition among hospitalized patients is very high and equally undervalued.

The term malnutrition refers to a disorder of the nutritional state, characterized by a macro and / or micronutrient deficiency, which occurs when the caloric intake is lower than the energy demands of the organism, such as resulting in impaired metabolism , alterations in the function of different organs and body composition. Ultimately, malnutrition presents itself as a condition of impoverishment of the body's energy, protein and other nutrient reserves, which could significantly affect the individual's state of health. What emerges from many parts, is that an incorrect management of the patient hospitalized from the nutritional point of view, can determine a "disease in the disease", an expression coined precisely to emphasize the impact of malnutrition on the condition patient's clinic.

At European level, it is estimated that the prevalence of protein-calories malnutrition at the time of admission fluctuates between 20 and 60% (1) and at the national level it would settle at 30%; this incidence tends to rise to 30-55% in intensive care (2) due to the impact of "metabolic stress"; in addition to this, a fair percentage of critically ill patients at the time of admission to ICU are malnourished and others are at high risk of malnutrition due to hypercatabolism (3), which is characteristic of the patients who are in this department.

Not surprisingly, the nutrition of critically ill patients remains a challenge today, as it has to face multiple difficulties linked to the presence of heterogeneous groups of patients with different individual needs, concomitant pathologies and a complex pathophysiology of the metabolic stress response, to be taken into consideration .

This therefore makes it crucial for the physician in the critical area to tackle the subject of nutrition in a new perspective, which starts from considering how this type of medical intervention, as well as nourishing the patient, is addressed, together with all other therapeutic acts (both surgical and medical), to correct the metabolic alterations, so as to limit catabolism, primum movens of the complications extensively described in the literature (4) (5).

In particular, the nutritional aspect must also be considered in relation to the management of the patient's respiratory assistance, especially as regards weaning or weaning from mechanical ventilation.

The transition from a situation in which the patient's breathing is completely controlled by the machine to the resumption of his respiratory autonomy (the weaning precisely) requires energy according to the muscular effort performed in these phases, a commitment that is maximum precisely during the return to breathing spontaneously; this energy must be compensated through an adequate supply of nutrients by artificial means, so as to cover the energy needs functional to the needs of the patient. Not surprisingly, metabolic factors such as inadequate nutrition can interfere with weaning. In fact, in a state of malnutrition, the body tends to consume endogenous proteins, especially those of muscle tissue, thus reducing muscle strength (particularly of the respiratory muscles), aggravating respiratory work and the possibility of situations arising difficult or prolonged weaning (6).

The purpose of this paper is to assess how the intake of calories, provided to the sample of patients studied, influences the phase of weaning, as well as assessing how the choices in terms of nutrition carried out at the University Intensive Care

Unit of Foggia, structure in which the sample has been recruited, also conditioned other parameters taken into consideration in the study.

General principles of physiopathology of nutrition in the critical patient.

Because of its integrity, the human body has constant need for energy and nutritional elements. Only the perfect coupling of the processes of synthesis (anabolism) and degradation (catabolism), which together constitute the metabolism, makes it possible for adults to maintain organic functions in physiological conditions. In particular, the energy that the cells need depends on the continuous availability of substrates used to generate energy compounds, first of all the ATP (adenosine triphosphate), from the hydrolysis of which will be obtained the energy necessary for cellular activities.

The energy required for anabolic processes is therefore derived from catabolic reactions: the use of substrates such as carbohydrates and lipids provides the energy necessary for the synthesis of macromolecules such as proteins, nucleotides and others, in the form of ATP. In a schematic way, such reactions start from the oxidation of substrates (carbohydrates, lipids or proteins) to lead to the formation of energy, partly dispersed also in the form of heat, and other compounds such as water and carbon dioxide.

Carbohydrates, lipids and proteins under physiological conditions are obtained through the ingestion of food, and as such are subjected, following absorption, to different metabolic reactions. Obviously, a part of the food income, not used immediately by the body, is stored in the form of energy reserves, from which the body can draw in conditions of need.

From a bioenergetic point of view, the share of energy produced in conditions similar to normality, will therefore be represented by the share of energy expenditure necessary for the maintenance of the organism (basal metabolism or Basal Energy Expenditure, BEE) to which it is necessary to reach, for obtaining the so-called total energy expenditure (Energy Expenditure), these energy supplies: the energy expenditure induced by the digestion and absorption processes (Diet induced thermogenesis) - which, though small, is evident in continuous artificial nutrition - and that dependent on the activity physical performed by the subject.

It is interesting to note that these physiological mechanisms are profoundly altered during a "stress response", a set of chain reactions that involve the nervous system, the endocrine system and the immune system, thus acting on the whole organism, induced by trauma, severe infection, extensive burns, etc. (7) . In general, under these conditions, the energy required for the metabolic needs of the individual cannot be obtained from the voluntary supply of nutrients from the outside and therefore the organism will tend to use its own energy reserves, which however will be destined to an inevitable exhaustion.

To this, it should be added that, from a bio-energetic point of view, to those physiological levels previously seen, the increase in energy expenditure induced by the disease is added, a very frequent occurrence in intensive care units.

In fact, serious traumatic insults (physical, surgical or phlogistic) or infectious induce altered metabolic responses in the organism that can profoundly subvert body metabolism, undermining body composition with potential serious deterioration of the subject's nutritional status.

In fact, all the metabolically active tissues are involved in these alterations, under the pressure of hormones and cytokines, which act as real modulators of these processes.

The metabolic responses are carried out on several fronts, but classically we will have:

- A hyperdynamic circulatory state in relation to both the neuroendocrine state and increased energy demands;
- An increase in energy expenditure due to a marked state of hypermetabolism;

- A marked destruction of visceral and structural proteins with a framework of prevalent body proteolysis (protein hypercatabolism);
- Marked gluconeogenesis with hyperglycemia, associated with insulin resistance status (stress diabetes), due to the release of hormones that antagonize the insulin action such as growth hormone (GH), adrenaline and cortisol.

The initial agents that trigger the process of neuroendocrine-hormonal-metabolic modification are represented by various peripheral stimuli (pain, hypovolemia, necrotic tissues), sympathetic afferents and activation of the neurovegetative system and the hypothalamic-pituitary system.

With the activation of the hypothalamic-pituitary axes, we are witnessing the increased increase of hormones such as ACTH, GH, catecholamines and the sympathetic stimulation of pancreatic glucagon augmentation. The metabolic responses resulting from this hormonal arrangement will essentially be represented by the increase in cortisol, glucagon and to a lesser extent thyroid hormones and insulin, whose action is however reduced by the prevalence of hormones counterinsular (8).

One of the typical characteristics of the stress response is the increase in energy expenditure, defined as hypermetabolism. The increase in the rate of heat production by the tissues is an indication of an increased oxidation of energy substrates, so that the extent of the increase in body oxidative metabolism proved to be proportional to the gravity of the pathological process.

Metabolic alterations actually modify the intermediate metabolism, both glucidic and lipidic, with the aim of increasing the proportion of metabolic substrates useful for repair processes, but which inevitably conditions its depletion, especially if we consider the protein proportion.

The main changes in intermediate metabolism will be:

- Increased production and consumption of glucose, through glycogenolysis and hepatic gluconeogenesis; however, the amount of glucose removed from the circulation is lower than that produced and, despite the increased glucose turnover, "stress" hyperglycemia is constant;
- Increased availability of free lipids due to accelerated lipolysis and increased use by tissues: in fact fatty acids become the preferential energy substrate of many organs, during stress response;
- Peripheral mobilization of amino acids from skeletal muscle, which are used for the synthesis of acute phase proteins (PCR, fibrinogen, prealbumin, fibronectin, opsonins, ...), enzymes and structural repair proteins; a large part of these liberated amino acids, however, is degraded to produce energy and support gluconeogenesis;
- The increased flow of amino acids from peripheral liver tissues is secondary to increased proteolysis. The protein hypercatabolism sees the skeletal muscles particularly involved, which operate a protein hydrolysis that causes a part of amino acids to be used locally (use of the branched BCAA amino acids directly by the muscle for energy purposes), the other is abandoned in a circle. Once they reach the hepatic level, these are destined to the synthesis of neo-proteins and, in higher altitudes, to degradation for energy or gluconogenetic purposes.

The increased oxidative catabolism of the amino acids leads to an acceleration of the synthesis of urea at the liver level, which will be eliminated at the urinary level, contributing in fact to the increase of urinary excretion of nitrogen in urea. Indeed, azoturia can be considered a marker of protein hypercatabolism induced by metabolic stress (9).

What is set up is a complex picture of metabolic alterations in which the high energy requirements and the marked protein catabolism lead to a serious state of malnutrition, should an adequate nutritional therapy not be established. These evidences are the result of the interest of various scholars, who over the years have been interested in the pathophysiology of the metabolic response to stress (10). Worthy of note, in particular, is the description provided by Cuthbertson in 1942 (3) (11), which was the first to divide the metabolic response to stress (specifically Cuthbertson conducted his studies on post-traumatic patients) in 3 phases :

1. Ebb phase (literally phase of outflow) or early phase of reduction of the metabolism: body temperature is reduced and the use of oxygen in order to limit the depletion of energy substrates. This phase is very short so as to be almost never clinically observable.

2. Flow phase or catabolic phase: this phase of hypercatabolism involves accentuation of metabolic processes, activation of the immune and endocrine system and induction of acute phase hepatic response. This phase is the one that most accompanies the onset of most complications in the patient.

3. Convalescent phase or anabolic phase, in which the synthesis of new macromolecules is progressively established. (Figure 1)

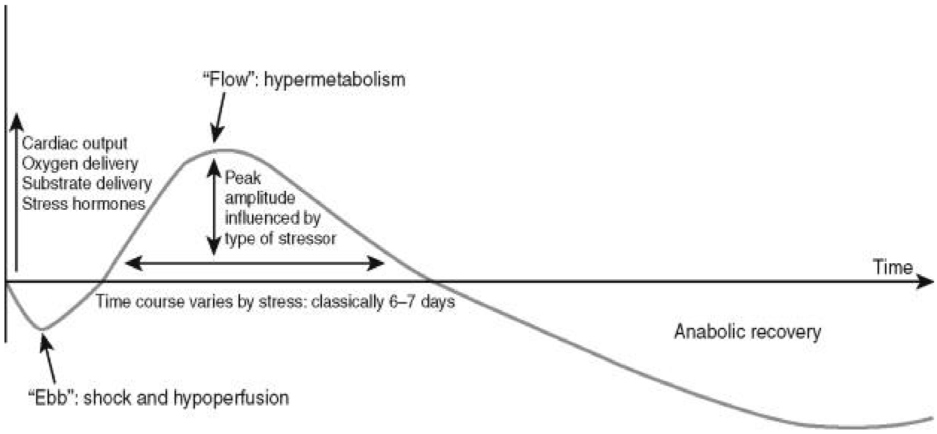


Fig.1. Ebb and Flow phase, adapted from "How Does Critical Illness Change Metabolism?", Mark E. Nunnally, Evidence-Based Practice of Critical Care 2010, Pages 447-451

Among these phases is that of flow to have a fundamental role. In fact, although this phase is essential for the survival of the subject especially in the acute phase, what emerges is that if prolonged and unchallenged, it will take on the characteristics of a harmful process for the organism: the response to stress, if not adequately addressed, will lead to inevitably to the consumption of all those substrates that participate in the constitution of muscles and adipose tissue, with negative reflexes from a clinical point of view.

Understanding this aspect is fundamental, since to prevent this, if on one hand it is necessary to reduce the cause of the response to stress - for example to intervene on the infectious process, on the traumatic one, as far as this is possible - on the other, it is fundamental to establish a valid nutritional support to compensate for hypercatabolism and other metabolic changes that occur in the patient, so as to reduce, in perspective, also the possible short and long term complications.

Consequences of inadequate patient nutrition in intensive care unit.

The inadequate intake of nutrients leads, in a more or less prolonged period of time, to weight loss and loss of body constituents, therefore to the appearance of malnutrition.

We can define malnutrition, as a state of depletion of the body's reserves of energy, with an acute, chronic or subacute course, which can in itself influence the evolution or prognosis of a disease state of the subject (12).

Regardless of the different forms of protein-calorie malnutrition that can be reconstituted in clinical practice, we recall that the form of greater response, in the hospital setting, is the state of protein-calorie malnutrition.

Several studies have shown that it has a high incidence among hospitalized patients, with relevant rates also in the intensive care setting. To the high diffusion of this condition, several factors contribute, including: fasting periods for performing radiological, endoscopic or surgical procedures, drugs that alter appetite or nutritional status, lack of training for health professionals on the subject of nutrition, lack or lack of assistance during meals, and as regards the ICU (Intensive Care Unit) especially the increased nutrient losses and the altered metabolism of the same, associated with increased nutritional requirements (13) (3).

Protein malnutrition is among the most important problems in ICU, as the presence of malnutrition causes a profound modification of the organism's ability to react to the state of illness responsible for hospitalization; so much so that the expression "disease in the disease" has been coined, to underline the negative impact of the same on the patient's organism. Consequently, the intensivist must be able to take care of every patient currently and / or potentially suffering from nutritional deficiencies, which require the use of artificial nutrition.

On the other hand there are many consequences of malnutrition on the main biological functions and on the bodily apparatus, among which we recall (14):

- Cardiovascular system: there is a reduction in myocardial mass and a tendency to hypotension and bradycardia, with loss of the ability to increase stroke volume in response to an effort;
- Renal system: the renal mass is reduced and blood flow and glomerular filtration are reduced, in addition to the creatinine clearance capacity, the ability to concentrate urine to water deprivation is also reduced;
- Gastrointestinal system: the enteric mucosa tends to atrophy, the content of digestive enzymes is reduced and motility decreases; the transmucosal transport capacity is reduced and its permeability is increased; in the liver there is the disappearance of glycogen deposits and the hepatocytes show reduced enzyme assets and the protein synthesis and toxic metabolism, including drugs, are depressed;
- Immunocompetence: the lymphatic tissue is hypoplastic, the number of circulating lymphocytes decreases, the chemotactic and phagocytic functions performed by macrophages and polymorphonuclear are depressed, the ability to produce immunoglobulins is reduced, as well as the cell-mediated immunocompetence is globally depressed, with the risk of contracting infections;
- The ability to repair wounds is greatly altered and depressed, as well as overall convalescence from a disease;
- Respiratory system: pulmonary morphology is reduced in an emphysematous sense, the content of alveolar surfactant is reduced, the ventilatory response to hypoxia and hypercapnia is reduced and the respiratory muscles are hypotrophic and hypoactive. The reduction of muscle mass extensively affects the diaphragm and the other muscles involved in respiratory dynamics: due to this in response to an effort, the ventilatory capacity will be reduced and will be associated with the

appearance of a muscular fatigue. This will be particularly evident in the weaning phase: malnourished patients, in fact, tend to show higher failure weaning failure rates from the MV (15).

These pathological changes induced by malnutrition, in the field of intensive medicine, have found their place in a clinical entity that is commonly remembered as **ICUAW**.

The ICU acquired weakness (ICUAW) is a syndrome frequently encountered in critically ill patients. With this term, in reality, in recent years we refer to a spectrum of interesting neuromuscular disorders, both the sensorimotor axons, configuring the so-called "Critical illness polyneuropathy", and the muscular structures giving rise to a myopathy indicated with the expression "Critical illness myopathy ”. These entities and more generally the ICUAW, both manifest clinically with weakness, which will involve both skeletal and respiratory muscles. Although described as two different entities, CIP and CIM very frequently coexist in mixed forms, in very complex clinical pictures and with a poorer prognosis than just the presence of neuro- or my-patia, which among other things show different prognosis, such as emerged from an important Italian multicenter study, in which it was recorded that the CIM has a more favorable prognosis than the CIP (16).

It should also not be surprising how such neuromuscular disorders have been renamed in the literature as "the modern technology diseases" (15), emphasizing when the ICUAW is an emerging problem of great importance for the intensivist also in light of its incidence in the departments of TI (would affect more than a third of critically ill patients, and this percentage would tend to increase in the presence of specific risk factors) (17).

In recent years, in fact, it has become increasingly important to talk about ICUAW, this being a condition that can influence the patient's outcomes (outcome) both in the short and long term (18).

Among the short-term outcomes, the role of ICUAW and weaning difficulties in mechanical ventilation in inpatients in ICU was evaluated, given that the neuromuscular problem involves in various ways the phrenic nerve, the diaphragm, the intercostal muscles and the other respiratory muscles; in fact, the appearance of acute respiratory insufficiency of neuromuscular origin can be the cause of readmission to ICU or unexpected death after transfer to the ward; the ICUAW would also be associated with a dysfunction of the pharyngeal muscles and therefore increased risk of tracheal aspiration.

Subsequently, therefore, the isolated or in combination CIP / CIM increases the time of hospitalization and the morbidity related to the permanence in TI and hinder the patient's weaning from mechanical ventilation (MV) (19).

Also interesting are the evidence relating to long-term outcomes that examined the persistence of a muscle weakness that would tend to improve over time or result in disability (more frequent in patients who develop CIP) (20). As a result, many patients continue to complain, even after several months or even years, of a reduced ability to adapt to physical exercise that significantly affects their quality of life.

The neuromuscular dysfunctions associated with intensive care units were the subject of study as early as the end of the last century, when the CIP was first described by Bolton in 1984 (21). Over the years the interest in this topic has increased more and more, so much so that it has come to describe the main risk factors and pathophysiology.

There are numerous factors incriminated in the etiopathogenesis of the two components of this complex neuromuscular dysfunction (CIP and CIM) and specifically sepsis, trauma, tumors, hyperglycemia, catecholamine administration, renal failure, liver failure, l use of neurotoxic antibiotics, immobilization (due to forced bed rest, sedation, curarization), not least malnutrition. The association with other factors such as hyperpiressia, hypoalbuminemia, hypoxia, hypotension, hypo / hypercalcaemia, female sex and advanced age are less evident.

To date, the most accredited etiopathogenetic theory recognizes that both CIP and CIM are the result of a channelopathy involving sodium channels at the level of the nerve and muscle membrane (22). To maintain the normal resting membrane potential, the muscle and nerve consume energy, as well as to propagate the action potential. If the production of ATP is reduced, the first effect will be that of an altered conduction of the electrical stimulus (electrophysiological alterations); if the energy deficit persists, the muscle and nerve begin to lose the ability to construct intracellular proteins and components of the cell membrane (histological damage visible at the biopsy); finally, if the cellular damage continues involving a significant number of axons or muscle fibers, the clinically evident weakness appears.

To this it should be added that at the cellular level there is, with the loss of the function of the sodium potassium pumps, a bioenergetic damage that also alters the intracellular environment with an increase in ROS production, mitochondrial dysfunction and induction of cellular apoptosis. In addition to the metabolic alterations referred to, probably even the microvascular ones, such as the increased expression of E-selectin, increased capillary permeability with consequent extravasation and endoneural edema would have a pathogenetic role: this mechanism would be particularly evident in the ICUAW associated with sepsis. Also relevant in the genesis of ICUAW is the marked cell-induced proteolysis by cytokines released during a systemic inflammatory response: these cytokines would upregulate lysosomal proteolysis, the ubiquitin-proteasome pathway and the TGFβ / MAPκ pathway leading to an interesting protein breakdown above all myosin and other fibrillar proteins, which make up muscle fibers. The final result, result of known processes and others still not well characterized, is a picture of alterations that configure the two pathogenetic entities called into question.

The clinical management of an inpatient in ICU, even more if in the presence of anamnestic risk factors, should include a clinical evaluation for the ICUAW. In addition to the application of a score for the risk stratification of poly / myopathy

(23), the intensivist can use, in association with biochemical investigations, such as the evaluation of creatine kinase (an index of muscle necrosis absolutely non-diagnostic per se), at electrophysiological study. It has a great diagnostic value because it highlights the reduction of action potentials, alterations of nerve conduction and variable patterns of fibrillation potentials. To date, the gold standard diagnostic test for CIM / CIP remains the execution of the muscle biopsy, which at the expense of its invasiveness, allows the histological diagnosis of certainty.

In light of what emerges from the scientific literature, also in terms of outcome, it is fundamental to manage these neuromuscular disorders clinically. To date there are no specific therapies for ICUAW, although it is possible to resort to effective supportive and preventive measures. In addition to a therapy aimed at resolving the cause responsible for the acute event that led the patient to admission to ICU, it is fundamental to concentrate on some aspects that have been associated in the literature with the reduction in the appearance of ICUAW (24):

- Early awakening and dose reduction and duration of use of neuromuscular blockers and corticosteroids.
- Narrow glycemic control (glycemic target 80-110 mg / dl): studies have shown how insulin therapy of hyperglycemia reduces the duration of VM duration, reduces hospital stay, has antioxidant effects and on the prevention of microcirculation alterations (25).
- Adequate caloric intake that meets the metabolic needs of the patient, in order to counteract the protein hypercatabolism, which could alter the muscular reserves.
- Early mobilization and physical therapy.

In conclusion, it must be kept in mind that, from the medical point of view, much can be done during the admission of the patient in intensive care to reduce the difficulties encountered by them during hospitalization and during discharge, without neglecting the fundamental role of nutrition in planning patient care.

Elements of Artificial Nutrition

Artificial nutrition refers to a replacement therapy that allows the supply of one or more energy sources (carbohydrates, lipids or proteins) together with electrolytes, trace elements, vitamins and water in quantities sufficient to satisfy the nutritional needs of the patient. The techniques of artificial nutrition are more properly divided into:

- Enteral nutrition (EN): performed by digestion, thus using the intestine as a route of administration and absorption of nutrients;
- Parenteral nutrition (TPN): instead it uses the venous system to administer nutrients.

The subjects for which recourse to the AN is necessary are:

a) malnourished patients who cannot satisfy their energy demands through oral feeding;
b) patients at risk of malnutrition, that is, well-fed patients who have not been able to satisfy their energy demands through oral feeding for 5 days;
c) patients at risk of malnutrition, that is, well-fed patients who in the next 5 days will not be able to satisfy their energy demands through oral feeding;
d) patients, to be subjected to major elective surgery, malnourished or at risk of malnutrition, as a pre-post operative treatment.

ENTERAL NUTRITION

General information, advantages and contraindications

"Enteral nutrition" is defined as the nutritional support technique that provides the intake of nutrients both orally, if the reflex of swallowing is intact, and the "feeding tube" (FT) or the use of nasogastric probes, naso-enteral or percutaneous. Enteral nutrition is certainly a more "physiological" method: the entral approach, in fact, promotes the integrity of the digestive tract by preserving the "tight junctions" between the enterocytes, with trophic effect at the local level. Thus the integrity of the intestinal villi is not lost and the local production of IgA remains; promotes normal intestinal motility and guarantees the maintenance of the stimulus for the release of cholecystokinin, gastrin and bile acids. In this way it is avoided that the intestinal mucosa loses its functional integrity with secondary increased permeability and consequent passage of bacteria and toxins in circulation with phenomena of systemic inflammatory response.

From here, the rationale in the use in the first instance of this mode of nutrition: observational studies of patients admitted to intensive care and nourished prematurely by entral seem to confirm these considerations (26); moreover, the metanalytic revisions appear to agree in highlighting a benefit of this type of nutrition in the initial stage as regards infectious complications and the time spent in intensive care (27).

Enteral nutrition is therefore indicated as the first choice, in all cases in which the intestine is functioning.

It is generally contraindicated, instead, in patients with: sub-occlusion / intestinal obstruction, intractable vomiting, paralytic ileus and / or severe diarrhea that makes metabolic management of the patient difficult, presence of proximal entero-cutaneous fistulas ("high") and / or high flow rate, chronic intestinal ischemia, short bowel syndrome. In such situations, parenteral nutrition is used.

There are many access routes to the gastro-enteric tract, the most frequently used are:

- Nose-gastric or naso-duodenal tube (NGT-NDT);
- Percutaneous endoscopic gastrostomy / jejunostomy (PEG / PEJ);
- Surgical gastrostomy and jejunostomy.

The stronghold of the EN is, to date, the gastric nose tube (NGT). This protection, in fact, although it is not always well accepted by the patient, due to its ease of positioning, low cost and limited complications, it is still the first choice in the administration of EN for treatments that do not go beyond 30 days, in the absence of risk of aspiration of the mixture in the airways and of severe impassable stenoses of the upper digestive tract. In anticipation of periods longer than 30 days, it is advisable to consider PEG, PEJ or the creation of a surgical stoma.

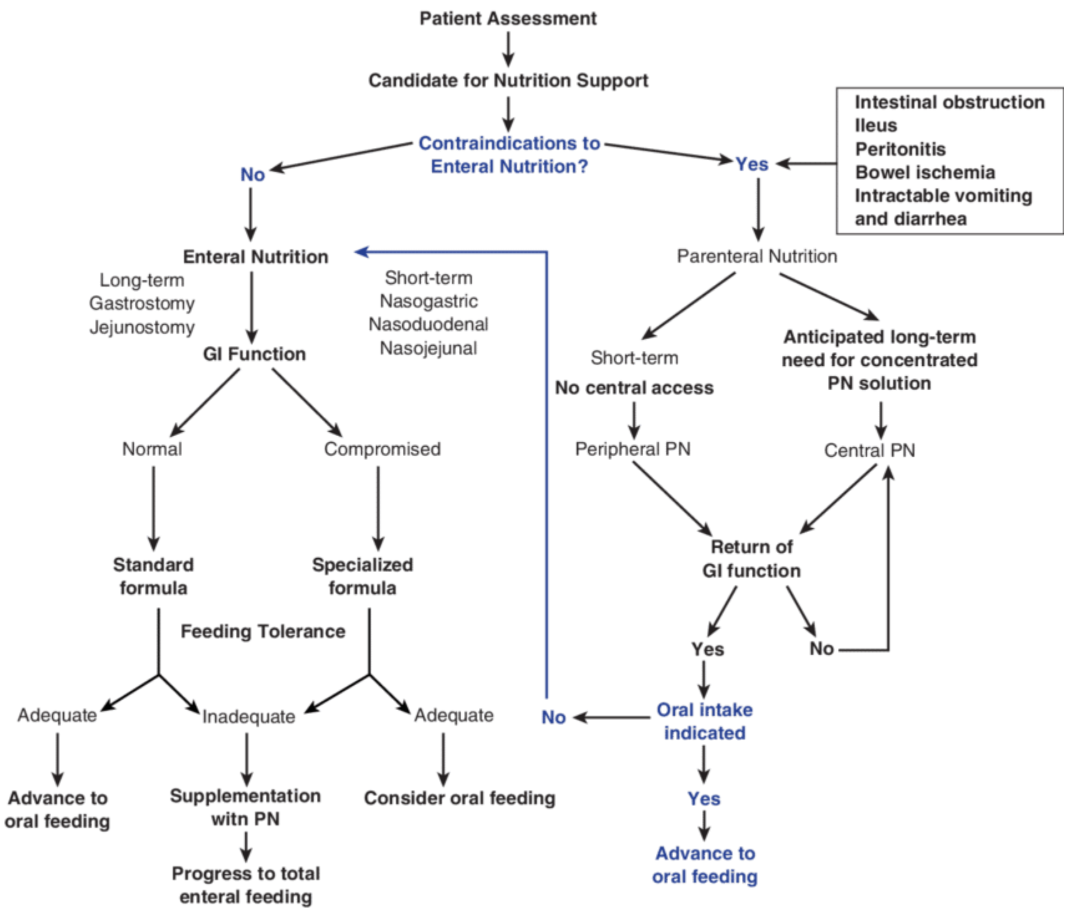


Fig 2. Route of administration algorithm (adapted from clinical pathways and algorithms for delivery of parenteral and enteral nutrition support in adults). GI, gastrointestinal; PN, parental nutrition.

Complications of enteral nutrition.

The control and monitoring of artificial nutrition complications is mandatory in ICU patients, given that metabolic and nutritional disorders are frequent and can modify the patient's outcome. Complications related to EN can be summarized as follows:

- Mechanical complications: radiological checks for correct positioning of the probe should be performed routinely and possibly repeated every week, especially in comatose patients. It is important to remember that serious complications may occur if the probe is malpositioned, a partially reduced condition if the head is positioned at 30-45 ° to the bed edge. For what concerns the naso-gastric probe it is possible to have accidental removal or deposition, angles and obstructions, haemorrhages, perforations or decubitus ulcers. As far as the ostomy is concerned, it is possible to have an infection or decubitus of the skin, the appearance of early peritonitis or mechanical obstructions.

- Metabolic complications: the so-called Feeding Syndrome (Refeeding Syndrome) is particularly important, frequent following an aggressive nutrition in long-time fasted / malnourished patients; following the re-exposure to nutrients the cells sum up the molecules they lacked; the whole, associated with other metabolic alterations that have arisen, exposes patients to important risks such as heart failure, the appearance of peripheral edema, the development of convulsions, important glycemic alterations that can also lead to coma, hydro-electrolyte, neuromuscular and hematological disorders (28). The other complications reported in the literature are mainly related to micronutrient deficiencies and metabolic alterations, among which the hypothesis is hypo-or hyperglycemia; these, however, have been reduced thanks to a greater culture and attention to the topic, to the increasingly adequate and personalized choice of the prescribed formulations and to the application of protocols and check-lists to monitor the possible complications by the health personnel.
- Gastrointestinal complications: it is strongly recommended to periodically evaluate the tolerance to administration and the control of the residual gastric volume, in order to modulate the administration of the mixture and / or proceed with the administration of prokinetics; when enteral feeding is administered, the gastric residue must be measured which, if greater than 500 ml, will require a reduction in the infusion rate for about 1-4 hours, with possible administration of prokinetics, such as metoclopramide or erythromycin, to increase gastric emptying. Furthermore, in case of excessive speed, cramps, diarrhea and abdominal pain can occur (especially if the solutions are cold).

- Among the documented disadvantages is the increase in bacterial colonization, favored by the increase in gastric pH. This, associated with any deficiency of peristalsis due to, for example, opiate drugs or paralytic ileus, facilitates pulmonary microaspiration and increases the risk of aspiration pneumonia. One of the most used strategies to reduce these risks is the positioning of the patient with the chest raised preferably 45 ° with respect to the bed surface.
- Diarrhea during enteral nutrition is an occurrence that requires an important and often inconclusive diagnostic effort to define its etiology. The most frequent causes are related to the administration of excessively osmolar solutions and to infectious causes (especially Clostridium difficile), drugs or the type of mixture used.

PARENTERAL NUTRITION.

During parenteral nutrition nutrients are administered directly into the circulatory stream, without the action of the gastro-enteric tube. It is customary to distinguish the TPN in peripheral and central.

In peripheral parenteral nutrition the administration of nutrients in simple form takes place directly in a peripheral vein. The largest veins of the forearm (cephalic vein and basilica) are generally used. The peripheral veins, however, do not tolerate nutritional mixtures with high osmolarity: in fact, having a smaller diameter and a slower flow compared to the central ones, they suffer more from the irritative insult, tolerating therefore the infusion of mixtures with osmolarity up to 850 mOsm / liter for a limited time period. This involves a limited caloric intake that does not completely cover the patient's caloric needs, especially if this is hypercatabolic.

This type of nutrition is therefore indicated in those cases in which a high caloric intake is not required (integration with insufficient oral nutrition, intestinal subocclusions, low flow fistulas, chronic intestinal diseases in the acute phase) for a short period of time (15-20 days).

In the case of parenteral nutrition greater than two weeks or with high caloric needs where hyperosmolar nutritional mixtures are required (> 850 mOsm / l) central venous catheters are required.

Central venous access means a device which, once implanted, allows infusion into the superior or inferior vena cava or, in any case, near the right atrium. Among the numerous indications for central venous catheterization, there is also that of infusing nutrients. Today there is a considerable variety of central venous catheters (CVC), mono-bi-trilumen, in polyurethane and silicone, heparinized (heparin coating) or impregnated with antibiotic (sulfadiazine, chlorhexidine). In most cases, venous access is now positioned by percutaneous venipuncture, using the Seldinger method.

Complications of artificial nutrition with central venous access

In patients undergoing parenteral nutrition with central venous access, it is essential to take into account the complications related to it, which are classically divided, as shown in Figure 3.

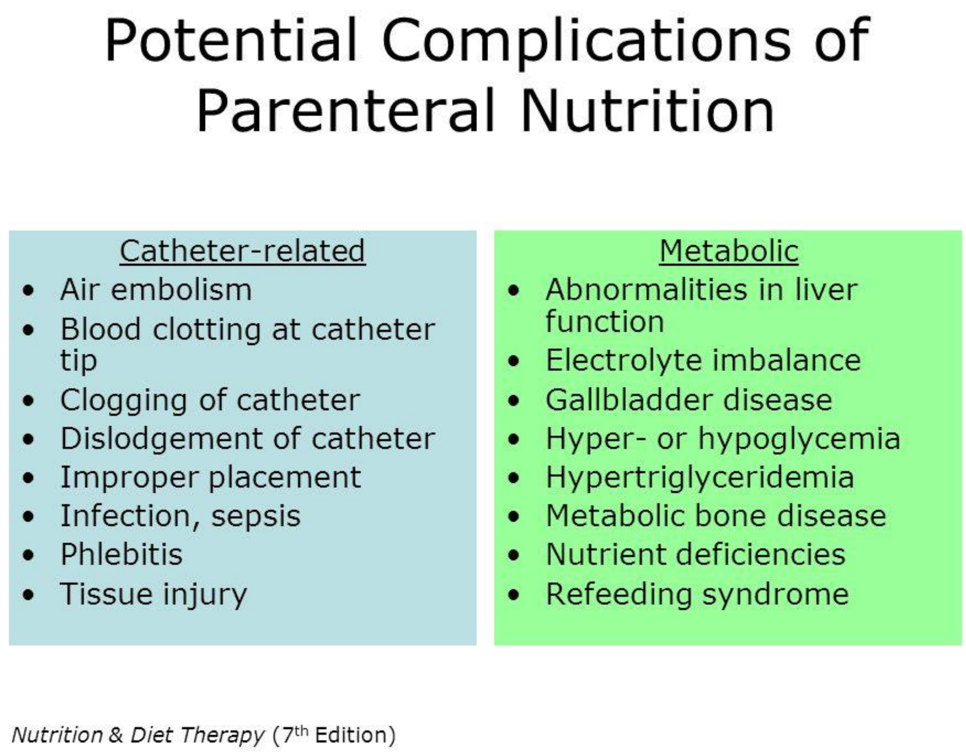


Fig. 3. TPN potential complications.

Guidelines for critical patient nutrition.

The choices made by the ICU doctor regarding the nutrition of the critical patient are inspired by the current ESPEN Guidelines (European Society for Clinical Nutrition and Metabolism), which arise from the revision of the previous editions of the same dated 2006 and 2009, relative, respectively , to enteral and parenteral nutrition.

Today they represent the reference standard for what concerns the management of nutritional support of the patient in ICU.

The ESPEN recommendations arise from rigorous evidence, the result of the systematic review of the scientific literature on patient nutrition, conducted by a panel of experts in the sector, respecting the quality standards required of the Scientific Societies in drawing up the guidelines. The most significant aspects of the current edition of the guidelines will be discussed below (29).

NUTRITIONAL STATE ASSESSMENT.

The Guidelines indicate to carry out a general assessment of the risk of malnutrition that includes a clinical investigation with the collection of the anamnesis, looking in particular for an unintentional loss of body weight, associated with the physical examination, to the evaluation of body composition and muscle mass and strength (when possible).

Several studies suggest using more tools for assessing nutritional status, as only the association of several parameters allows a complete overview of the patient's condition. Also because weight changes are difficult to evaluate in ICU, because they suffer from many variables such as fluid administration. It is useful to assess the presence of sarcopenia, which must be sought in all patients (30). What numerous studies have shown, however, is that sarcopenia is an extremely widespread syndrome even in an intensive environment and that greatly conditions the patient's prognosis.

Laboratory tests are also important: for example albumin and pre-albumin, they are not specific markers for malnutrition, because they could be reduced independently of this. However, albumin has been shown to be a marker of severity of malnutrition, evidence derived from the study by Mogensen et al. (31) in which survival at 30, 90 and 365 days was shown to be significantly reduced in the group of malnourished patients with intense reduction of dosed albumin.

The thorny issue remains the use of scores for the evaluation of nutritional status in ICU, especially as a screening tool to be implemented at the entrance of the patient in the ICU considering also the great heterogeneity of patients coming to this environment, often already malnourished before their entry into the hospital environment. Several publications have tried to compare the various scores as Sheean et al (32) did when comparing the Mini Nutritional Assessment Test, extremely widespread in the geriatric field, with the Nutritional Risk Screening 2002 (based on parameters such as weight loss, BMI, reduction of caloric intake and disease severity). Recently the use of the Malnutrition Universal Screening Tool (MUST score) and the NUTRIC, a score based on variants such as age, degree of severity of the disease calculated with APACHE II or SOFA score, comorbidities, days of ICU stay were evaluated. and interleukin-6 dosage (for the evaluation of the inflammatory state). This latter score has shown an excellent ability to demonstrate how patients with a high NUTRIC score, to whom adequate nutritional support is given, have a reduced mortality rate (33).

However, at present none of the proposed scores have been validated for its use in ICU, so further studies will be needed in this regard.

ENERGY NEEDS ASSESSMENT.

As far as the patient's energy needs are concerned, it is essential that it be calculated before the start of nutritional support in order to administer an adequate quantity of calories. It can be calculated with the predictive equations (ex. Harris-Benedict or Mifflin equation) or measured with indirect calorimetry, a gold standard especially for mechanically ventilated patients (34). If this is not available, an alternative could be to use the VO2 (calculated with the catheterization of the pulmonary artery) or the VCO2 (obtained from the ventilator capnometer, the energy requirement is equal to the product of the VCO2 for 8.19). Given that predictive equations in themselves have shown poor accuracy, leading to situations of over- or under-estimation of needs, they must be used with caution (35; 36). Instead, good clinical efficacy has shown the use of simplistic formulas based on an estimate of 25-30 kcal / kg / day for the adult individual (37).

NUTRITIONAL SUPPORT.

The ESPEN Guidelines state that nutritional support must be considered for all patients who will remain in the ICU, especially if they are expected to stay for more than 48 hours, since each critical patient in the ICU for more than 48 hours must be considered at risk of malnutrition. In fact, all patients belonging to the ICU, who reasonably will not be able to feed sufficiently orally within 3 days, must receive adequate nutritional support.

Among the different types of nutritional therapy, an oral diet is to be preferred as the first choice for all patients able to feed themselves. If it is not possible to take nutrients orally, an enteral nutrition should be carried out, as it has considerable advantages compared to the parenteral one: it allows to avoid the atrophy of the intestinal mucosa, guaranteeing a normotropism, stimulating peristaltic recovery of the paralytic ileus, preventing the transmucosal translocation of the bacteria, reducing the risk of infectious processes, and is substantially more physiological than the parenteral method.

Therefore, in critically ill patients the EN must be initiated early, ie within the first 24-48 hours from admission to the ward, provided that a stable clinical picture of the patient has been reached and the vital balances have been corrected with adequate treatment. In fact, studies comparing early EN vs. delayed EN have shown a reduction in infectious complications for early EN (38) (39; 40).

An interesting step in the recommendations proposed by the ESPEN concerns the need, in the management of the nutrition of the critical patient, to consider timing for the beginning of the nutritional support, modality of administration and energy target in an integrated vision; in this way, after defining the start and the method of administration, the energy target should be reached progressively and not before 48 hours to avoid an "over-nutrition", taking care to proceed with caution in increasing the support nutritional progressively.

In line with this, the Guidelines state that it is important to administer a low-calorie nutrition (which does not exceed 70% of energy requirements) during the acute phase of the disease, and then proceed from the third day to increase the calorie intake up to cover 80-100% of the calculated requirement. Therefore, during the first week of admission, the administration of the EN must aim to cover a share greater than 50-60% of the planned one, to then progressively increase, admitting the possibility of associating an additional TPN to the EN, in the impossibility of covering within 7-10 days the total planned caloric quota.

With regard to enteral nutrition, the guidelines recommend the use of a continuous EN within 24 hours, rather than the administration thereof in boluses, as the meta-analysis conducted by ESPEN observed a significant reduction in the incidence of diarrhea and a significant gastric residue (41) (42) (43). Among the access routes to the EN, gastric access is preferable with naso gastric tube (NGT), in practically all critically ill patients and in most surgical patients; in the case of patients intolerant to gastric access not resolved by the use of prokinetic drugs (erythromycin, metoclopramide e.v.), one should proceed with post pyloric EN. The jejunal tube showed equal efficacy compared to the classic SNG; in general it finds greater application in patients with a high risk of aspiration and when endogenous enteral nutrition should be suspended for high stagnation.

In case of impossibility to perform an enteral nutrition (for example due to intestinal obstruction, mesenteric ischemia, abdominal compartment syndrome or impossibility of access to the gastrointestinal system), parenteral nutrition will be considered, only after having tried all the strategies to resort to to the EN. In light of the results of numerous studies showing that early parenteral nutrition is associated with increased mortality, prolonged ICU stay, increased incidence of infections, ESPEN recommends in patients at risk of malnutrition to start parenteral therapy only after 7- 10 days of impossibility to reach the required energy targets with only the EN. This recommendation derives from the observation that starting TPN before 7-10 from the beginning of hospitalization, preferring it to EN, would not improve the patient's outcome (44).

Speaking of parenteral nutrition, ESPEN states that all patients, for whom normal nutrition is not expected to resume within 3 days and for whom there are no contraindications to EN, should receive parenteral nutrition no later than 48 hours (45).

Adequate timing at the beginning of parenteral nutrition is however a long-standing problem, not least in the light of what has emerged from two published studies on the subject. The results obtained by the two studies appear to be diametrically opposed, since from the first one emerges how to implement a wait-and-see conduct in starting nutrition that is favorable in terms of a faster recovery of the subject and lower complication rate (44). The other study (46) demonstrates the exact opposite, in favor of an early beginning of nutritional support. Unfortunately, both studies show significant methodological limitations and therefore, until further studies show more evidence in favor of one of the two approaches, the indications provided by ESPEN remain valid.

In the administration of parenteral nutrition, central venous access is generally used, especially if the mixtures to be infused have high osmolarity; a peripheral venous access can be used for those with osmolarity <850 mOsmol / L. The quantity of mixture to be supplied must be estimated on the basis of the calculation of the energy requirement or by referring to the formulas of 25 kcal / kg / day, increasing the target gradually over the next 2-3 days.

Aspects related to the mixtures composition.

In defining the nutritional plan for the critical patient, it is necessary to ensure a daily protein intake of 1.3 gr / kg to be progressively increased. This, in light of the fact that the patient in ICU presents a marked proteolysis and muscle loss which is well known to be associated with the onset of ICUAW (47). The administration of an adequate protein intake is therefore fundamental to reduce this; in fact the guidelines starting from the analysis of various studies, have found the remarkable benefits deriving from the administration of a high protein intake in relation to the reduction of mortality, increase in survival, reduction of the negative nitrogen balance (48) (49).

In both parenteral and enteral nutrition, attention must be paid to the amount of glucose (TPN) and carbohydrates (EN) which should not exceed 5 mg / kg / min, also accurately controlling the glycemic level, as hyperglycemia it is certainly a factor that undeniably contributes to the increased mortality of the patient in TI (50). In fact it is good to remember how carbohydrates represent the main metabolic substrate of the organism, so their presence in nutritional preparations is inevitable. On the other hand, however, in the critical patient there is a profound alteration of the glucose metabolism with marked insulin resistance hyperglycemia, which makes it essential to always pursue adequate glycemic control in the critical area patient.

Other constituents of emulsions for parenteral nutrition are lipids, essential for guaranteeing the supply of fatty acids for energy purposes and essential fatty acids (they are linoleic acid and alpha-linoleic acid, which are not synthesized by the body and must be introduced from outside). With regard to the administration of intravenous lipids, these should respect a range ranging from 0.7 gr / kg / day to 1.5 gr / kg / day, without exceeding this value (51). Particular is the finding that some categories of saturated fatty acids, such as omega-3, have the ability to modulate the inflammatory response in a negative sense, reducing the same with positive effects on improving the patient's condition. Consequently, in defining the lipid intake, we must consider not only the quantity of lipids to be added, but also their quality (52).

Particular attention must be paid to the supplement of vitamins (A, C, group B, K, E), trace elements (Se, Zn) and electrolytes (Mg, P) whose needs are increased and which must therefore be adequately replenished in order to avoid failures.

SPECIAL CONDITIONS.

Sepsis and septic shock.

The ESPEN conclusions basically recognize how, after the stabilization of the hemodynamic parameters, it is possible to proceed also in the septic patients to the precocious EN and. If the EN is contraindicated, the next step is parenteral nutrition. It is undeniable, in fact, as the metabolic response to stress in the septic patient, puts him at serious risk of malnutrition and that this makes him further vulnerable. In fact, the metabolic alterations that characterize sepsis are represented by:

- Increased energy expenditure;
- Hyperglycemia with insulin resistance;
- Increased lipolysis;
- Protein hypercatabolism.

In light of these changes in metabolism - associated with the inevitable entrapment, hyperthermia, metabolic effects of underlying diseases or associated pathologies, lack of nutrition - it is easy to understand how these patients, in the absence of nutritional support interventions, can easily and rapidly reach a state of depletion of the various body constituents and in particular of the lean mass.

Artificial nutrition (AN) obviously cannot prevent or inhibit the various metabolic alterations of these patients, but it nevertheless represents a symptomatic support necessary to slow down the extent of caloric protein depletion, thus allowing other therapies to act and to overcome the disease. This is confirmed by a study by Elke (53), in which increasing the calorie intake in the septic patient was associated with the reduction of 60-day mortality and reduction of days in the absence of MV.

When choosing between EN and TPN, even in the septic patient EN “wins” because of its undoubted advantages on preserving the integrity of the gastrointestinal barrier, for the down-regulation of the inflammatory response and of insulin resistance. In any case, it is essential to follow the same recommendations generally provided by ESPEN.

For patients with septic shock, there is not much evidence in the literature. Pathophysiological knowledge states that the altered splanchnic perfusion associated with hemodynamic instability makes it very difficult to pursue the path of enteral nutrition (54). Therefore, an assessment based on the patient's condition will be essential to guide the doctor's choices.

Trauma patients.

Trauma patients should be treated with early EN to be preferred to TPN; the meta-analysis has shown, with this approach, a reduction in the duration of hospitalization and mortality (55) (56).

Most of the traumatized patients are not malnourished when they enter the ICU, but they become so as a result of their hospitalization. In this perspective, it is essential to promptly recognize any states of energy-calorie deficiency to be able to treat them; as well as an excessive nutritional intake can lead to decompensation of cardio-respiratory, hepatic and renal function.

The protein and caloric needs of polytraumatized, follow the ranges defined by the ESPEN Guidelines. As for the total energy requirements, these should be equal to 25-30 Kcal / kg / day, ie 120-140% of the BEE calculated according to the Harris-Benedict equation.

Most of the studies agree that a large portion of the calories should be supplied as glucose (57). In selected cases it may be necessary to reduce the intake of carbohydrates to reduce the production of CO_2, this need is very limited if the total caloric intake is kept below 30 Kcal / kg. Some works suggest that containing lipid intake can reduce morbidity and improve outcome.

The metabolic response to trauma induces, among other effects, the mobilization of amino acids from muscle tissue. These amino acids are used both for energy purposes and to support protein synthesis dedicated to wound healing and immunocompetence.

The goal of early metabolic support is to maintain the immune response and preserve the lean mass. However, both enteral and parenteral nutrition presents risks, in the face of specific benefits for each of the routes.

A series of works testifies to the feasibility and effectiveness of enteral nutrition, as well as its superiority over parenteral nutrition, especially with regard to the incidence of septic complications in thoraco-abdominal traumas (58; 59). Even in medium-severe trauma, the enteral route should be preferred to the parenteral route, when possible.

The use of immuno-modulating formulas in severely traumatized patients, administered early and in adequate quantities, is able to reduce the incidence of organ failure, infectious complications and length of stay. However, in many of these studies there are no benefits on mortality (60) (61).

Traumatic brain injury patients.

The metabolic response to severe cranioencephalic trauma is characterized by a marked increase in energy expenditure and accelerated proteolysis with a significant increase in energy and nitrogen requirements; all associated with early onset of bodily deficiency, if adequate nutritional support is not established. These acquisitions have, on the one hand, revised the assumption that the state of coma is associated with a reduction in nutritional and metabolic needs and, on the other, have found new and established principles of neurointensivology (neurosedation, mechanical ventilation, analgesia, etc.) limit, without abolishing, the metabolic response to trauma, and how an early metabolic-nutritional support is needed to control it and prevent the onset of malnutrition and related complications. Even in recent years, multiple studies have confirmed and quantified in patients with severe head injury and coma (Glasgow Coma Scale, GCS ≤ 8), in the acute phase and in the subsequent evolutionary phases up to neurological recovery, the extent of consumption and needs nutritional (caloric and protein), documenting the evidence of the effectiveness of the recommended levels (quantity) of nutritional supplies, of the choice of artificial nutrition technique (preferentially enteral) and of the time to start treatment (precocity), detecting the positive effects on metabolic indices and nutritional efficacy, on the reduction of complications, infectious species, related to malnutrition and the best global clinical course.

At present, artificial nutritional support, early and adequate, is considered one of the mandatory components of post-traumatic good clinical practice care.

In fact, patients with severe cranio-encephalic trauma represent a particular category of traumatized patients with particular metabolic needs, due to a marked and prolonged phase of hypermetabolism with an average increase in energy expenditure (REE) of 40%, compared to energy expenditure predicted basal rate (according to the Harris-Benedict formula), an increase determined by the post-traumatic hormonal and metabolic flow (62; 63). Fever, neurovegetative and epileptic seizures, motor agitation and muscular hypertonus are the major causes of increased energy consumption (64). On average 25-30 Kcal / kg of current weight in patients results in a level of average caloric intake that is recommended in patients with coma head injury (GCS <8).

Regardless of the neurological evolution, the high energy requirements persist even for a long time (2-3 weeks) after the acute phase of the trauma and can further grow due to intercurrent hypermetabolic causes (infections, sepsis, motor agitation, physiotherapy).

Neurosedation, high-dose analgesics and myolution solution reduce expenditure and energy requirements, which suggests that much of energy hypermetabolism depends on muscle tone and activity (65).

Some studies have evaluated the relationships between levels of nutritional intake and clinical outcome, noting that hypoalimentation in the first two weeks post-trauma is associated with increased mortality, while early coverage of nutritional needs with artificial feeding reduces it, while it does not appear affect neurological outcome (66). Nevertheless, patients with severe head trauma have similar outcomes whether they are adequately nourished by entral or parenteral route, as both are effective, although each presents advantages and disadvantages. Significant studies, in addition, have shown that the route of administration is not associated with significant differences in peak values of intracranial pressure (ICP), efficacy of ICP control therapy, serum osmolarity, morbidity and mortality (67) (68).

Consequently, the enteral pathway, as in the other types of critically ill patients, has greater clinical-managerial advantages and lower costs and is to be preferred if or as soon as it is usable.

Several studies have investigated the incidence and causes of intolerance and gastro-enteric intolerance following severe brain trauma, noting how frequent a post-traumatic gastroparesis, sensitive to prokinetics, is related to levels of intracranial hypertension; delayed gastric emptying can last up to two weeks post-trauma in a high percentage of patients (69). The unavailability or delayed gastro-enteric tolerability, if different strategies are not implemented (early TPN or integrated entero-parenteral support), involves a delayed start of artificial nutrition with late achievement of coverage of needs, an event associated with a worse course clinical for intercurrent morbidity and longer duration of hospitalization (27).

Early nutritional support (started within the first 48-72 hours and a steady 5-day post-trauma period) compared to the one started and on a late schedule (between the seventh and ninth days) results in a reduction in the risk of death in patients with severe head trauma , of morbidity (especially for intercurrent infections), of neurological relics and is associated with shorter hospitalization in an intensive environment.

In the severe cranial trauma, therefore, enteral nutrition remains the technique of choice, due to its ease of use, low costs and enteric protective effects; if conditions exist that impose recourse to TPN this must be precociously established and adequate for the purposes and clinical-nutritional purposes of the metabolic-nutritional support of the critical patient.

In the phases of oral re-feeding, the high frequency of neurogenic dysphagia and post-traumatic cognitive-motor disorders that limit swallowing ability and increase the risk of hypophagy and pulmonary inhalation complications must be taken into account; this disorder must be constantly suspected and investigated and the relevant rehabilitative and dietary actions must be undertaken (70).

Mechanical ventilation

Mechanical ventilation is used to guarantee gas exchange at the alveolar level through partial or total assistance in the respiratory cycle; its use becomes necessary in the case of alterations in the correct functioning of one of the components of the respiratory system: CNS-transmission pathways- pulmonary parenchyma-muscles.

Unlike normal respiratory physiology, in which muscle contraction promotes the expansion of the thoracic cage by increasing the negative pressure of the pleural space, modern mechanical ventilators blow gas through the airways, stretching the lungs and the rib cage. In fact, there is talk of positive pressure ventilation to distinguish it from the negative pressure ventilation of the "steel lung", which is no longer used today.

Mechanical ventilation can also be divided into invasive and non-invasive ventilation, depending on the interface used: in the first case it will be an endotracheal tube or a tracheostomy tube, in the second an external interface to the airways such as a mask or a helmet.

Depending on how the fan delivers the flow, we can also distinguish:

- Controlled modes, in which the patient is totally dependent on the ventilator who starts, guides and ends each breath;
- Assisted modes, in which the patient is partially able to interact with the ventilator that supports the respiratory act: the patient can, in fact, start the inspiratory act (trigger) and his muscles generate a level of pressure in the airways, which is supported by the machine.

Both assisted and controlled modes can be volume or pressure controlled. In volumetric modes, the independent variable (ie independent of the patient and controlled by the ventilator) is the volume, the dependent one is the pressure. In pressure mode, vice versa, pressure is the independent variable that determines a variable volume (71) (72) (73).

In particular, the beginning of the inspiratory act of the patient subjected to controlled MV is set to time (timed trigger), as the duration of the inspiration, the eventual inspiratory pause and the beginning of expiration is regulated in time. The possibility of adjusting these times and other parameters, such as the respiration rate, occurs during the setting of the fan, taking into account that in the controlled volume mode a tidal volume must be set, while in the pressure mode a pressure must be defined (74).

In the case of assisted modalities, instead, the inspiratory act is initiated by the patient and the ventilator reads the signal in different ways (pressure, flow or neural triggers as in NAVA) to synchronize with his respiratory activity (75). The respiratory rate and the different times of a respiratory cycle are decided by the patient and in most assisted modalities, the ventilator supplies an inspiratory flow that implements that produced by the activity of the patient's respiratory muscles. This pressure support can be constant, as in pressure-controlled ventilation (PSV, Pressure Support Ventilation) or titrated on patient's requests as in NAVA (Neurally Advanced Assisted Ventilation) or PAV + (Proportionally Assisted Ventilation Plus) (76).

Common modes of MV

Volume controlled ventilation (VCV)

The VCV is a controlled flow-rate ventilation system; in particular it is a mode in which the independent variable is the flow, which being controlled guarantees the achievement of a specific volume. Being a controlled ventilation it needs complete control over the patient's respiratory activity. In controlled volume mechanical ventilation, the following parameters must be set on the fan:

- FiO_2;
- Breath frequency;
- Tidal volume (amount of air blown with each inhalation);
- PEEP or positive end-expiratory pressure;
- The inspiratory trigger, which initiates the inspiratory phase;
- The respiratory time ratio;
- Speed and flow profile.

In this type of ventilation, therefore, it is the pressure in the airways that represents the dependent variable, correlated to the characteristics of the thoraco-pulmonary system and to the equation of motion of the respiratory system.

Advantages. The VCV allows the exact control of the respiratory volume by act and by minute, independently of the variations of pulmonary or thoracic compliance, and also of the PaCO2, with indirect evaluation of the blood pH. In fact it is preferred when you want to control CO2 carefully (as in a cranial patient) or when you want to perform protective ventilation (eg ARDS).

Disadvantages. Increased airway impedance leads to reduced compliance and increased resistance, increasing the risk of pulmonary pressure injury (barotrauma) or volume (volotrauma) due to the rise in breathing pressure (77).

Pressure controlled ventilation (PCV)

PCV is a controlled pressure-controlled ventilation mode; this VM mode has a time trigger, a time cycle and a pressure limit. During the inspiratory phase, airflow is delivered with a certain pressure during inspiration. Therefore, in the controlled pressure ventilation the following parameters must be set on the fan:

- FiO_2;
- Upper pressure level in the airways (pmax);
- PEEP;
- Breath frequency;
- Respiratory time ratio.

If the independent variable is the pressure, which must be delivered constantly, the dependent one will be represented by the flow, which will respond to variations in the characteristics of the thoraco-pulmonary system, to which ventilation is applied.

Advantages of PCV. With this method the risks of increasing the pressure exerted above a predefined value are reduced. Setting a low pressure (usually below 35 mbar) reduces the risk of pressure injury and excessive pulmonary distension. If there is a leak in the system (airways and conduction systems) adequate pressure and ventilation levels are maintained within defined limits. Furthermore, the continuous pressure level has a positive effect on the honeycomb opening, compared to the pressure value established in the controlled volume and constant flow ventilation. It also allows for easier patient weaning.

Disadvantages of PCV. The inspired volume depends on the thoraco-pulmonary compliance and the patient's resistance. Therefore, in accordance with the motion equation, impedance reductions and increased compliance may favor a greater inspired volume, with a risk of hyperventilation and respiratory alkalosis.

On the contrary, increased impedance and reduced compliance can lead to hypoventilation resulting in hypercarbia and respiratory acidosis.

Pressure support ventilation (PSV)

PSV is the most commonly used assisted ventilation mode. It requires a normal competence of the patient's respiratory drive which triggers the respiratory act (thus acting as a trigger); in fact, the patient's inspiration is helped by the ventilator up to an established and always equal pressure value (support pressure). The PSV is, therefore, a ventilation method with pressure control, triggered and guided by the patient, limited by the ventilator as the patient begins the inspiratory act and receives support for his spontaneous activity, until a pressure level is reached defined.

PSV advantages. In most intensive care patients, breath regulation is not primarily impaired; therefore, complete controlled ventilation is not necessary and this leaves room for the use of a pressure-assisted mode.

With regard to PSV, this has the following advantages:

- The patient maintains his own rhythm and breathing cycle and can determine the duration of the inspiratory phase;
- Synchronization with the fan is better;
- There is less use of drugs that oblige to complete artificial respiration (muscle relaxants, sedatives);
- The average pressure in the airways reaches normal values and this results in minor effects on the cardiovascular system.

In the weaning phase, the PSV allows a reduction of the support by the fan, allowing for a reduction in time, ease and greater safety.

Disadvantages. The lack of artificial breath control can determine the onset of hypoventilation and apnea. The danger of breath stoppage can be avoided in modern fans, thanks to the setting of so-called "apnea-ventilation" as a safety function (Back up-Modus, a controlled mode that interrupts the apnea period).

Synchronization with the ventilator, in patients with severe respiratory activity impairment, even in PSV mode, may be inadequate and result in hyperventilation and asynchrony of the patient with the respirator.

In the case of high inspiratory resistance in the airways, high inspiratory flow and cycle variables can promptly terminate inspiration, resulting in lower volume inspiration. However, setting a lower initial flow, which is possible in modern fans, can facilitate the use of this mode even in patients with high resistance. It is also disadvantageous that, even when the patient's ventilatory needs are changed, the mechanical support of each inspiratory act remains the same. Occasionally, in patients with partial respiratory failure, pressure support may be offset by the use of accessory respiratory musculature. The contraction of these muscles involves more work, with energy expenditure, even when the patient is able to breathe independently without mechanical help. The consequence is a longer weaning time. Especially in the event of increased ventilation requirements, the constant and insufficient pressure support cannot compensate for the additional work determined by the endotracheal tube. These problems have led to the development of new ways, such as automatic tube compensation (ATC) and assisted proportional ventilation (PAV). In fact, modern fans allow the association PSV with ATC.

In recent years, PSV has become increasingly popular and is frequently used as a ventilation modality in patients in intensive care: PSV, alone or in association, occupies second place as the most widely used method in intensive care. However, there is no clear evidence to show the prevalence of PSV against other partial ventilation methods. This applies to both ventilation and weaning times. However, due to the advantages listed, the method is increasingly used (71) (78).

Weaning from mechanical ventilation

The term "Weaning" refers to the process that involves the transition from mechanical ventilation support to spontaneous respiration, with consequent recovery of the patient's respiratory autonomy (79).

This process consists of two components:

- Switch to spontaneous breathing;
- extubation.

For the doctor of Intensive Care, when he starts to improve the condition that led to the need for intubation and VM, the problem arises of understanding the right time to proceed with extubation and the suspension of mechanical ventilation. Choosing the right timing for weaning is an extremely difficult process, as weaning inevitably exposes you to two possible risks:

- Early extubation, with a patient not yet able to breathe independently, necessitating a new intubation and VM, which, according to one study, would be associated with mortality, in re-incubated patients, between 25 and 50% (80) ;
- Delayed extubation with prolongation of the duration of respiratory support and all the related complications (81).

To avoid these risks and not make mistakes, when weaning, the conditions necessary to suspend mechanical ventilation and extubate the patient will be taken into consideration, as discussed below.

WEANING CONDITIONS

For the success of the weaning process, the following conditions must be met:

a) **Sufficient oxygenation**:

- It is possible to start the weaning process only when the patient with an inspiratory oxygen concentration decreased and reduced need for artificial respiratory measures (eg PEEP <5-8 cmH2O), manages to maintain a sufficiently high PaO2. As a fundamental criterion, an oxygenation index (PaO2 / FiO2) greater than 200 is considered.

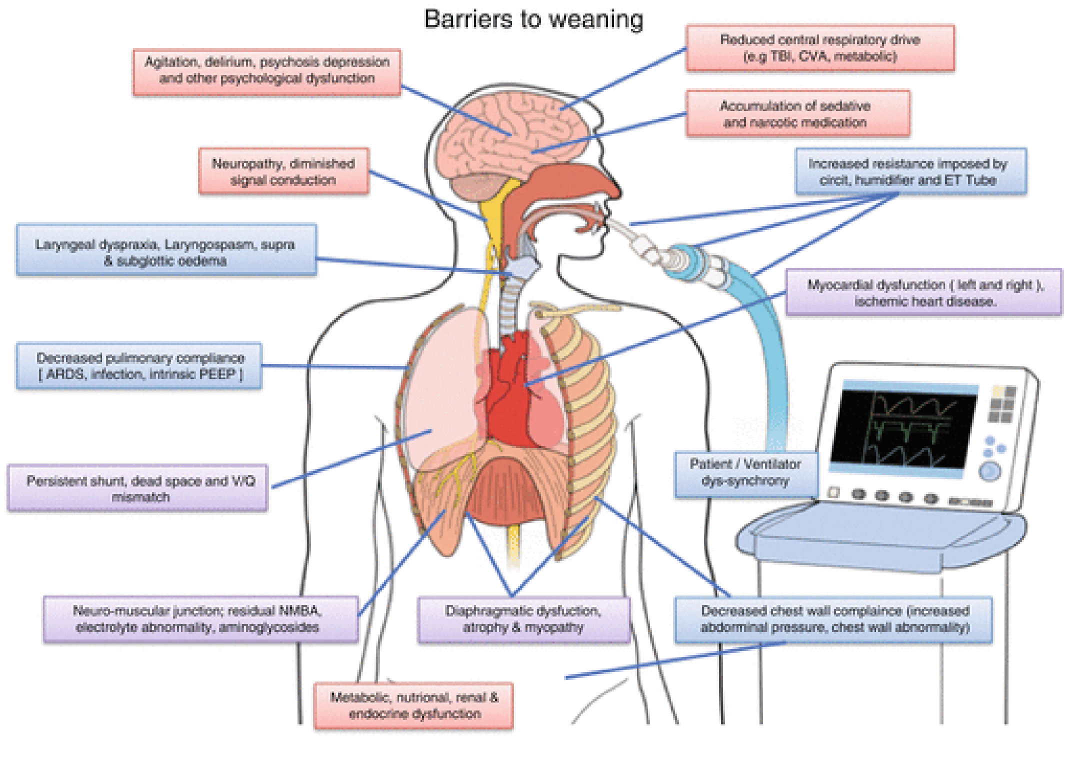
b) **Satisfactory ventilation, ie spontaneous breathing without fatigue**.

While a paO2 greater than 60 mmHg, under the conditions described above, can be considered as sufficient oxygenation, it is not possible to define a valid criterion that indicates an acceptable alveolar ventilation of the patient breathing spontaneously. The ability to breathe spontaneously depends on the following factors:

1. Respiratory trigger;
2. Endurance load of respiratory muscles;
3. Functionality of the respiratory muscles.

A condition that confidently defines whether the functionality of the respiratory muscles can sustain the respiratory need for a long time and therefore perform the appropriate respiratory work cannot be assessed on the basis of measurable parameters. Basically, all the factors that negatively affect the conditions listed above must be evaluated; for example by evaluating the presence of ventilation alterations that make weaning from the respirator more difficult, such as those shown in the figure.

Fig. 4 Barriers to weaning .



The Barriers to weaning patients with ARDS include factors causing increased workload, decreased respiratory drive and/or decreased respiratory efficiency

1. **Respiratory impulse**. An important condition for successful weaning is the preservation of the respiratory impulse. Breath-suppressing drugs should be avoided or reduced in dosage. A possible cause of the reduction of the respiratory impulse can be a metabolic alkalosis, which can often develop after a long-term intensive treatment. In severe alterations of the regulation of breath or spinal cord, without alteration of the innervation of the diaphragm, it is possible to place a "pacemaker" that stimulates its activity.

2. **Endurance load of the respiratory muscles**. High airway resistance, a reduction in compliance, a high intrinsic PEEP, increase respiratory work and must be avoided.

3. **Functionality of the respiratory muscles**. If there is fatigue in the respiratory muscles, the causes must be ascertained and resolved before weaning. It is

necessary to ensure sufficient spraying of the diaphragm. In fact, in conditions of shock, weaning must not be carried out. Furthermore, it must be possible to state with certainty that the effect of muscle relaxants has disappeared. The use of corticosteroids, associated with a previous or concomitant administration of muscle relaxants, can lead to a persistence of respiratory muscle weakness (so-called ICU or ICUAW myopathy); however, the nutritional status must also be considered among the causes of reduction in muscle strength.

c) **Airway safety even after extubation**.

It is necessary to verify if the conditions exist for extubating the patient. The answers to the following questions prove a sufficient capacity for spontaneous breathing of the patient, without tube and mechanical support:

1. Is the patient awake?
2. Can the patient swallow?
3. Does the patient have a good expectoration?
4. Is there a high production of secretions?
5. Are there anatomical alterations of the oral cavity or throat that can obstruct the upper airways (wounds, tumors, edema, surgical outcomes)?

If it is possible to answer affirmatively to the first three questions and negatively to the last two, you can be sure of a successful outcome of weaning from the respirator. In a very practical way, it can be stated that for hypersecretory subjects and with ineffective expectoration, weaning should be postponed to more appropriate times.

WEANING CRITERIA

Below, the criteria necessary to undertake the weaning process from the ventilator are listed:

- Volume at rest less than 10 liters / min per minute;

- Vital capacity greater than 10 ml / kg of body weight;
- Respiratory rate less than 35 per minute;
- Volume per act greater than 5 ml / kg of respiratory body weight;
- Maximum inspiratory force greater than 20 mbar;
- $PaO_2 > 60$ mmHg;
- $PaCO_2 < 55$ mmHg;
- pH value> 7.25- 7.3;
- Hemodynamic stability;
- Airway closure pressure below 6 mbar.

WEANING INDICES

The need to obtain preventive information about patients' ability to tolerate weaning from mechanical ventilation has generated great interest in the study of parameters and indices to be used for this purpose. For a better prediction of the success of weaning, several indices have been defined. Among them, those most widely used in clinical practice are listed below:

1. Airway closure pressure (p.01);
2. Rapid-shallow-breathing-Index (RSBI);
3. CROP-Index.

1. Airway closure pressure (p.01)

It is a parameter of measurement of the respiratory impulse. The p.01 represents the negative pressure developed in the respiratory system during spontaneous respiratory activity, measured in the first 100 thousandths of a second. Indicates the actual inspiratory attempts of the patient. The new ventilators allow the measurement during the spontaneous breathing of the intubated patient. The normal value is between 0 and -2.

For the interpretation of values it can be stated that:

- p.01 <-6 cmH2O is an indication of an unlikely success of weaning,
- A high negative value indicates a patient with excellent muscular performance, capable of generating high negative pressures, which will respond well to weaning.

2. Rapid-shallow-breathing-Index (RSBI)

This index is calculated as the ratio of the respiratory rate (acts / minute) and the tidal volume (ml / breath). A patient who is not ready to weaning from the ventilator will tend to have rapid (high RR) and superficial (low tidal volume) breaths, with a consequent increase in the RSBI which will consequently indicate an ineffective weaning.

The RSBI can be calculated before extubation and with patient in spontaneous breathing. This evaluation must be performed without pressure support, as the PSV falsifies and makes the value obtained insignificant. It represents the simplest predictive index of an effective weaning, remembering that:

The range, which allows to discriminate between an effective and an ineffective weaning attempt, is equal to 105 with normal values between 60÷105.

RSBI below 60 indicates effective extubation in 80% of cases

RSBI greater than 105 indicates extubation failure in 95% of cases.

3. CROP-Index.

The acronym includes the parameters "Compliance", "Oxygenation", "Rate" and "Pressure". It then combines oxygenation parameters (PaO2 / PAO2), with actual compliance (C), respiratory rate (f) and maximum inspiratory pressure in the airways (Pimax): CROP $= [C + P_{imax} + (paO_2/pAO_2)] /f$

Values higher than 13 ml / inspiratory act, suggest an effective weaning.

Although in recent years the use of these indexes has become increasingly widespread, it is also true that these have not been supported by studies that validate them exhaustively.

Weaning techniques

Basically, two methods of weaning from the fan are used:

- Discontinuous Weaning;
- Continuous Weaning.

Discontinuous weaning consists of phases of complete mechanical ventilation and spontaneous breathing phases, without mechanical support.

If the conditions for effective weaning are met, ventilation is interrupted intermittently and the patient breathes spontaneously, through the artificial nose or T system. A variant of this procedure is discontinuous weaning with a “Continuous-flow-CPAP system ". The system certainly does not offer respiratory support during spontaneous phases, but favors oxygenation and can reduce respiratory work in obstructive respiratory disease.

Specifically, to assess whether a patient can be safely extubated, the spontaneous breathing trial is performed, ie the VM is suspended, for a patient who is still intubated, for a short period of time; the aim is to assess whether the subject will be able to withstand the respiratory load, without more mechanical support. If the patient does not show signs of discomfort (listed below) during the test, it will be extubated.

To perform the spontaneous breath test, the following methods can be used:

- T-tube: the VM is connected to the tracheal tube, with a T-fitting, to a continuous flow of humidified and oxygen-enriched gas.
- PS-0 PEEP-0: keeping the patient connected to the VM, the support pressure and the PEEP are set at zero.
- CPAP <5 cmH2O.
- Pressure support 5-8 cmH2O.
- ATC without inspiratory support: the ventilator only applies the pressure necessary to cancel the resistive load of the tracheal tube.

The guidelines on weaning from VM recommend the use of support pressure at 5-8 cmH2O, compared to other methods, as this strategy increases the number of successfully extubated patients (82) (84).

The duration of the spontaneous breathing phases is established by virtue of the patient's abilities. In most cases, these trials last about 2 hours. If they occur effectively, the patient can be extubated. According to new studies, even 30 minutes are sufficient to predict an effective return to spontaneous breathing (85). If the trial fails, mechanical ventilation must be resumed by adjusting the level of respiratory assistance to the patient's needs (86).

Observation must be very careful during the spontaneous breathing phases. In fact, if the patient shows signs of respiratory failure, the mechanical ventilation must be reinserted and the attempts postponed to the following day; the signs of failure of spontaneous breathing attempts to be sought are:

- Tachypnea exceeding 35 acts / minute;
- Tachycardia greater than 140 bpm;

- Systolic blood pressure> 180 mmHg;
- Systolic pressure <90 mmHg;
- Reduction of arterial oxygen saturation below 90% with PaO2 <50-60 mmHg and / or PaCO2> 50mmHg;
- Agitation, anxiety;
- Reduction of the state of consciousness;
- Asynchronous respiratory movements, use of accessory muscles.

Continuous weaning can be undertaken with SIMV, PSV and other partial ventilation methods: the part of mechanical ventilation is gradually reduced and the spontaneous part is progressively increased.

With SIMV, the basic idea is that the patient can breathe and activate the respiratory muscles during spontaneous breathing, while he is at rest during the mandatory breathing. Generally the mandatory frequency is reduced by 1-2 acts / min and a PS is introduced to help the patient. The problem with this method is that, often, the patient breathes even during the mandator acts and in doing so generates an important asynchrony with the ventilator. For this reason the role of SIMV in weaning has been strongly reduced (87).

PSV is a method widely used in ICU which allows the patient to breathe independently, controlling the frequency, duration and depth of each breath, offering him the necessary blood pressure. With the progressive improvement of the respiratory capacity, in the weaning phase the pressure support is reduced, up to minimum values, necessary to overcome the resistances of the respiratory tubes. In 2014, a review by the Cochrane group compared the use of PSV and T-tube in terms of efficacy and safety for the weaning of mechanically ventilated patients; the results allowed to demonstrate sufficient efficacy tests in favor of the use of PSV compared to the T-tube for patients with simple weaning (88).

Clinical uses of different weaning techniques

There is no clear evidence to show that the continuous weaning techniques are faster and safer than discontinuous ones. Instead, there are recommendations in favor of weaning through a T system. Several studies have shown that the SIMV mode compared to the PSV and the T system leads to lengthening of the intubation times (89).

According to current knowledge, at least the last phase of weaning must take place with spontaneous breathing attempts in a T system, CPAP mode, PSV mode or with the ATC.

Regardless of the method used, the clinical experience of medical and nursing staff in intensive care units is decisive; always in compliance with the weaning protocols and defined algorithms, so as to have a faster and safer weaning.

In weaning attempts - regardless of the procedure - particular attention must be paid to the associated medical therapy. Only the patient who does not receive significant coverage with opiates or analgesics can be successfully weaned. A progressive reduction in the administration of these drugs accelerates weaning (90).

Weaning: when to start

In controlled ventilation, the beginning of weaning can be clearly defined: the process begins when artificial respiration is replaced by partial ventilation or the patient mentions spontaneous acts, so that extubation or decannulation can be taken into consideration. After a long-term ventilation, one passes first to partial modes, in which spontaneous respiration is only sustained, then a real weaning will take place (91).

It should be remembered that weaning, carried out with special precautions, is necessary only after long-term ventilation (greater than 48 hours).

On the contrary, after short-term ventilations, mechanical respiration can end by proceeding with extubation, when the patient has sufficient spontaneous breathing.

To ensure the effectiveness of weaning, especially after long-term ventilation, respiratory therapy and gymnastics are required. Add to this:

- Removal of secretions through nasotracheal aspiration or bronchoscopy;
- The administration of oxygen through nasal tubes or facial masks;
- The use of intermittent CPAP-Mask or other non-invasive ventilation procedures;
- Mobilization.

Difficult weaning

While most patients can be successfully extubated (70%), in others difficulties may arise.

Classically, in fact, next to the "simple weaning" in which the extubation takes place at the first attempt, there are also the "difficult weaning", which requires 1-3 attempts in less than 7 days, and the "prolonged weaning" , characterized by at least 3 failed attempts and a weaning time of more than one week (92).

The efficacy of weaning can be compromised above all in patients suffering from chronic respiratory disease with acute decompensation, as well as in the final stage of irreversible respiratory pathologies, in which weaning from the respirator is not always possible and opting for a home respiratory therapy (93).

The most important causes of a complicated weaning are:

- Persistence of changes in ventilation of the respiratory pump;
- Persistence of severe oxygenation disorders;
- Persistence of significant heart failure;
- Psychic dependence on the ventilator.

The persistence of respiratory failure, that is the inability of the respiratory pump to perform adequate respiratory work, is the most important event of difficult weaning. Some associated pathologies can further complicate the process:

- COPD;
- Pulmonary fibrosis;
- Tetraplegia;
- Irreversible neurological disorders of the cervico-thoracic cord, and / or of the respiratory musculature.

If difficulties arise in weaning, other factors must be considered, such as:

- Avoid additional respiratory work and alteration of the respiratory impulse;
- During nocturnal rest, the practice of respiratory support is recommended, to rest the muscles involved;
- It is necessary, where possible, to establish a communication relationship with the patient, to explain as clearly as possible the various phases of weaning and the expected respiratory gymnastics after extubation, so as to obtain his collaboration;
- Fear (to suffocate), pain and delusional conditions, can make the weaning process difficult. In these cases it is advisable to use anxiolytics, analgesics and delirolytics, paying attention to the possible depressive effect on breathing. Neuroleptics (haloperidol, promethacin) and clonidine are indicated. Benzodiazepines, due to

their muscle relaxant effect, should be avoided or given at minimal doses. Even a continuous administration of minimal doses of Propofol, can accompany weaning, since even in long-term uses, the accumulation phenomena are irrelevant.

On the other hand, it is also necessary to remove the possible causes that can make weaning difficult (for example, the persistence of the long-term effect of benzodiazepines and opiates).

Furthermore, adequate nutrition with sufficient caloric intake is necessary for regeneration and maintenance of respiratory muscles, especially after long-term ventilation. In fact also the way of setting the nutrition can influence the weaning process: high amounts of amino acids and proteins stimulate the center of the breath, while the fats reduce the production of carbon dioxide and the need for ventilation. Therefore, it will be the responsibility of the ICU doctor to carefully choose the nutritional plan most suited to the patient's condition (94-96).

Weaning failure

The ineffectiveness of weaning is evidenced by the progression of respiratory failure, whose clinical signs are:

- Tachypnea;
- Shortness of breath;
- Thoracic-abdominal paradoxical breath;
- cyanosis;
- Increased activity of the auxiliary respiratory musculature (sternocleidomastoid muscle);
- Intercostal depression;
- Tachycardia;

- Cold sweating;
- Increase in patient agitation or panic.

Even with arterial blood gas analysis, it is possible to recognize the development of respiratory failure, considering these conditions:

- accentuation of hypoxia;
- Increase in acidosis;
- Significant increase in $PaCO_2$.

The aggravation of respiratory failure requires the interruption of the weaning process, before acute decompensation. Respiration must therefore be re-sustained using the SIMV, PSV or other method.

If the patient has already been extubated, the failure of non-invasive methods must extend to reintubation. The reintubation rate, after weaning attempts following long-term ventilations, amounts, according to the data, to 13%. However, we must consider how the re-intubation and mortality rate are closely related (97-99).

A summary of the procedure recommended for weaning and shown in the diagram presented in Fig.5.

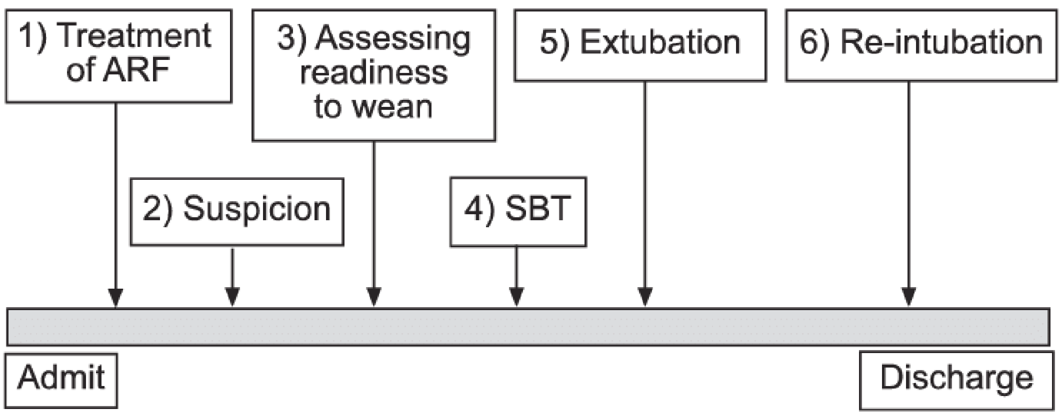


Fig. 5. Schematic representation of the different stages occurring in a mechanically ventilated patient. ARF: acute respiratory failure; SBT: spontaneous breathing test.

Aim of the study

The complexity of ICU patients is remarkable and this constantly requires the presence of specific skills on the part of the ICU doctor, not least as regards the nutritional aspect. In fact, adequate caloric support is a fundamental part of the patient care process. The purpose of this experimental work is to evaluate how much the caloric intake, provided to patients, influences the laboratory parameters examined, as well as examine how the nutritional choices adopted influence the dynamics of ventilatory assistance, during the weaning of the patient from the mechanical ventilation. A reduction of days of ventilation and a more appropriate caloric intake, directly proportional to the patient's requirements in the healing phase, will allow a higher percentage of success at discharge and a reduction of costs of hospitalization.

Materials and methods

The patients of this study were recruited at the Intensive Care Unit of the Ospedali Riuniti University Hospital of Foggia from November 2016 to November 2018.

For the purposes of the study, the selected patients were followed and monitored as regards ventilatory assistance, in its various modalities and phases up to weaning from the MV, and nutritional support implemented as enteral nutrition (EN), parenteral (TPN) or both (TPN + EN), respecting the recommendations of the current ESPEN Guidelines adapted to the specificities of the clinical case

Inclusion criteria

All patients admitted consecutively to the Intensive Care Unit for Respiratory Failure, Politrauma, Post-operative Urgency and Election, Sepsis or Septic Shock.

Exclusion criteria

No particular exclusion criteria were used, as the purpose of this paper is to evaluate the impact of nutrition on weaning from the critical patient's MV. Since both nutritional support and adequate management of ventilatory assistance up to the resumption of spontaneous breathing of the patient, are two conditions that can be found in almost all patients in ICU patients, it was decided to include in the experimental observations all subjects belonging to the ICU of Foggia with age over 18 years.

Data recording

Of the enrolled patients, data such as:

- Age;
- Sex;
- Cause of admission;
- Hospitalization time;
- Anthropometric parameters such as height, weight and daily BMI;
- Type of nutrition (EN, TPN or EN + TPN) and mixture used;
- Calories estimated with the Mifflin-St. Equation Jeor:

Women: (9.99 x weight in kg) + (6.25 x height in cm) - (4.92 x age) – 161

Men: (9.99 x weight in kg) + (6.25 x height in cm) - (4.92 x age) + 5

- Calculation of calories introduced with the mixture used for AN;
- Type of ventilation used;
- P / F obtained from the arterial blood gas analysis;
- Laboratory parameters such as albumin and total proteins.

Statistics analysis

The values obtained were analyzed in terms of mean ± SD. The statistical analysis was carried out with the statistical software Statgraphics 18. For the comparison of the different data it was decided to use, among the tools of inferential statistics, the ANOVA one way, setting the significance level P-value <0.05.

Results

The analyzed sample consists of 30 patients, of which 12 are females and 18 are males. The average age of the sample was 57.81 ± 19.15 years. Politrauma, respiratory failure and cerebrovascular events were the causes of hospitalization found in patients. The average duration of each admission to the ICU was 24.58 ± 14.7 days. Further demographic characteristics and information useful for understanding the results obtained are shown in Table 1 and 2.

Patient	Sex	Age	BMI admission	BMI discharge	Cause of Admission in ICU
1	F	54	23,19	23,19	Respiratory Failure
2	M	41	24,44	21,96	Respiratory Failure
3	F	19	19,31	20,55	Seizures
4	M	71	21,55	15,02	Ischemic Stroke
5	F	83	24,35	22,89	Intracranial Hemorrage
6	M	80	24,22	19,03	Traumatic Brain Injury
7	M	47	25,42	22,79	Politrauma
8	F	19	20,28	20,61	Politrauma
9	M	60	24,81	24,08	Subdural Hemorrage
10	F	82	23,04	22,07	Subdural Hemorrage
11	M	50	21,6	20,67	Hemolitic Uremic Syndrome
12	M	32	18,33	14,18	Hemorragic Shock
13	M	37	24,02	22,23	Politrauma
14	M	32	32,14	31,4	Politrauma
15	M	75	27,61	24,96	Intracranial Hemorrage
16	M	54	39,38	38,09	Respiratory Failure
17	M	78	25,3	23,51	Subarachnoid Hemmorage
18	M	52	32,57	32	Politrauma
19	F	81	40,77	38,56	Stroke
20	M	48	27,68	24,91	Stroke
21	F	82	24,56	24,97	Subarachnoid Hemmorage
22	M	51	20,9	21,55	Respiratory Failure
23	F	77	31,18	30,12	Intracranial Hemorrage
24	F	76	19,53	21,28	Respiratory Failure
25	F	71	19,53	18,16	Stroke
26	M	77	30,07	29,1	Subarachnoid Hemmorage
27	M	77	25,63	23,67	Respiratory Failure
28	F	71	31,85	27,99	Respiratory Failure
29	M	77	22,03	19,83	Subdural Hemorrage
30	F	77	27,73	24,6	Subdural Hemorrage
SD		19,15	6,94	5,65	
Mean		57,81	25,16	23,54	

Table1.Demographics

Table 2: Principal parameters investigated.

	EN	PN	EN+PN	P-value
Leght of ICU stay (in days)	22,10 ± 15	26,90 ± 15,6	24,75 ± 19	0.8
Albumine (g/dL)	3,17 ± 0,04	3,26 ± 0,05	3,26 ± 0,03	0.99
Proteins (g/dL)	6,32 ± 0,23	6,25 ± 0,04	6,21 ± 0,07	0.00
P/F	338 ± 7,77	302 ± 24	296 ± 76	0.03
CMV[1,2]	190	33	11	0.07
AMV[1,3]	340	39	7	0.9
SB[1,4]	57	18	0	0.75

[1] Number of events observed.
[2] CMV (Controlled Mechanical Ventilation) including PCV e VCV.
[3] AMV (Assisted Mechanical Ventilation) including PSV, NAVA.
[4] Spontaneus Breathing, including CPAP 0-5 cmH2O, O2 high-low flow therapy.

First of all, from the analysis of the test sample, it is possible to observe how the majority of patients received enteral nutrition. This is in line with what is stated in the ESPEN Guidelines (29), in which enteral nutrition is recommended as a method to be implemented in all patients first, if there are no contraindications to its use.

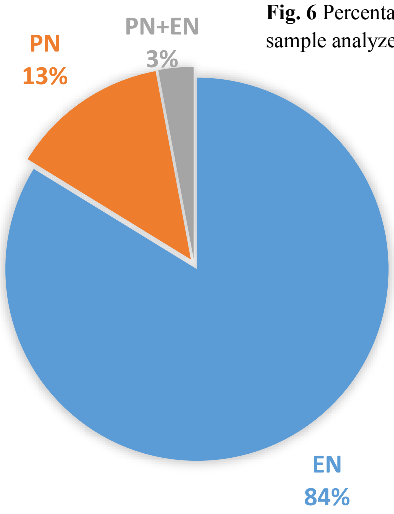
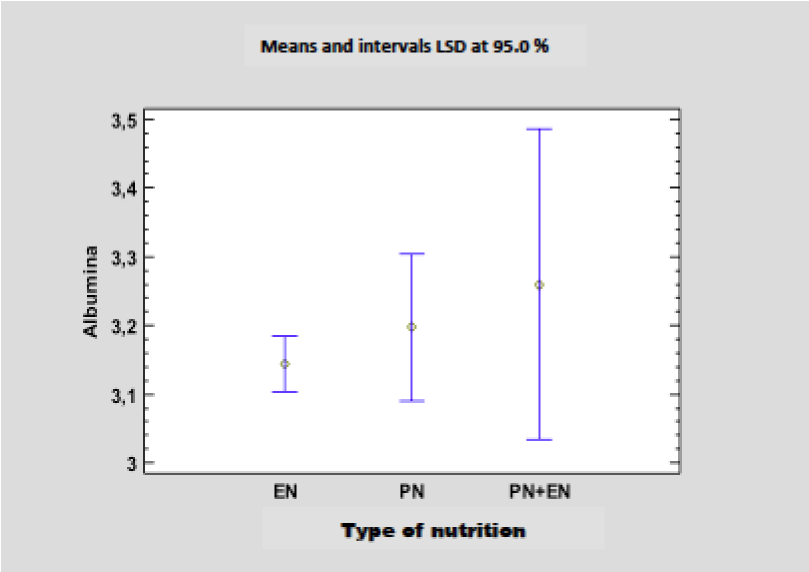


Fig. 6 Percentage of AN administered to the sample analyzed

Specifically, our analysis studied the variations of some parameters in the comparison between the three types of artificial nutrition, to which the patients of the sample were subjected.

For example we wanted to study the behavior of serum albumin variations with respect to the different modes of AN. Although from the graph it may seem that albumin has lower rates in patients in EN than in the other two groups, in reality the statistical analysis has returned a P-value of 0.99 in favor of a statistically insignificant difference between deviations standard with a 95.0% confidence level.

Fig. 7 Albumin levels in the three AN administered.



This graph (Fig. 7) must also be interpreted in light of the fact that the two groups of PN and EN + PN have a different number than that of EN, just as the clinical conditions that may have made albumin levels different among patients are different; in addition to this, that the non-significant change in albumin levels, supports the results of the observations that will be exposed later, in relation to the fact that the patients of our sample have been adequately nourished, during their stay, and consequently not have developed a condition of malnutrition, which can be detected using albumin as a laboratory marker (93).

The behavior of total proteins was different. From the analysis conducted, it was observed (Fig. 8) that EN allows patients to maintain better levels of total serum proteins. The statistics showed a P-value less than 0.05, thus demonstrating a statistically significant difference between the standard deviations of the three nutrition groups; furthermore, in a combined EN + PN regimen, as it is possible to observe, significantly more protein is administered than the other NA modalities.

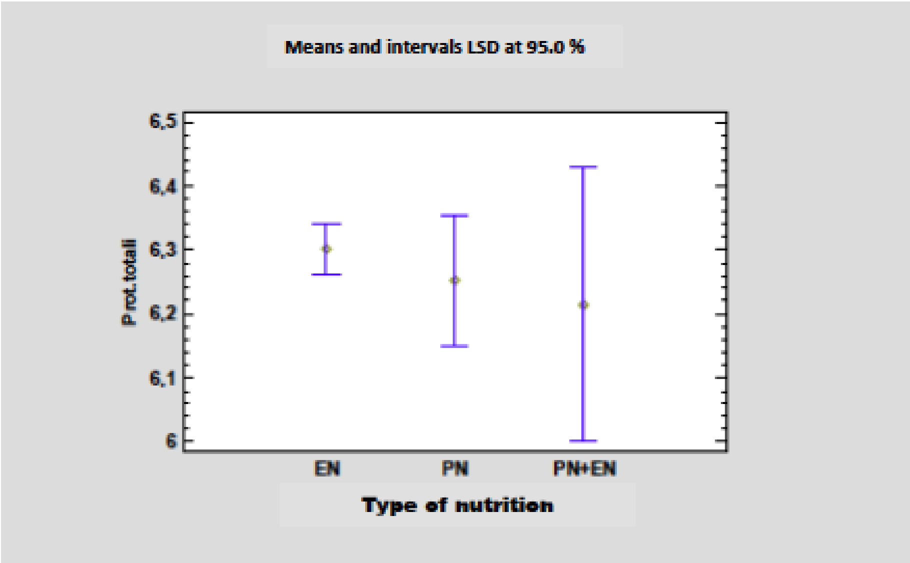
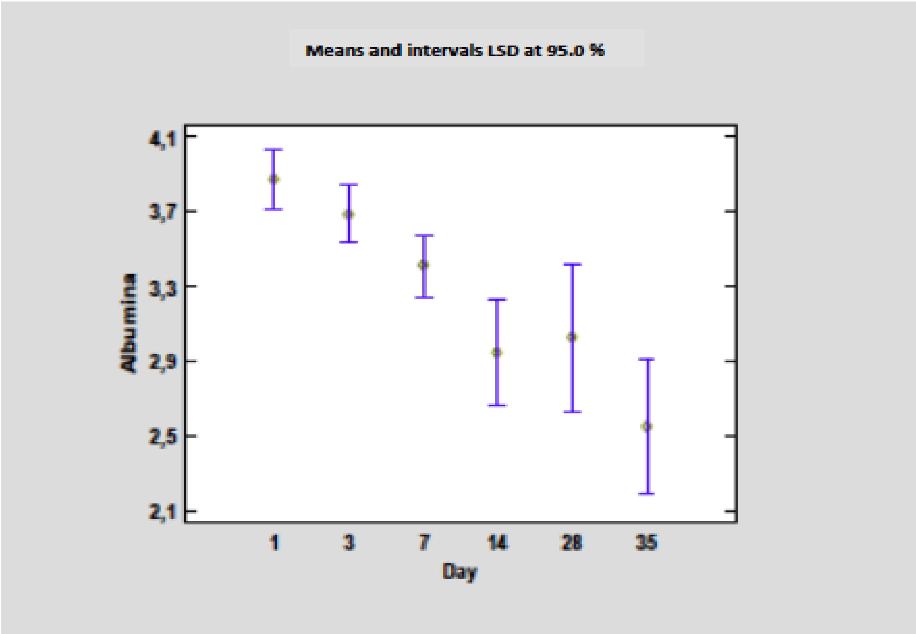


Fig. 8 Total proteins levels means and intervals LSD at 95% in the three AN administered.

This result confirms how the use of mixtures for EN with adequate protein content (such as those used in ICU in Foggia) is a fundamental choice in setting up an adequate nutritional therapy for the critical patient, who is notoriously hypercatabolic. In fact, due to the important changes that occur during the phase of metabolic stress, if not adequately nourished, the patient will inevitably encounter a depletion of body constituents including proteins. Providing adequate protein support with nutrition counteracts this important catabolism, also preventing the possible consequences associated with protein breakdown, especially in the muscle level (eg weakness of respiratory muscles and difficulty in weaning).

Fig. 9 Albumine levels during different days of observation.



The trend of both (Fig. 9-10) these parameters (albumin and total proteins), in the analysis by days of hospitalization (Day 1,3,7,14, 28 and 35) shows a progressive but not significant decrease, statistically speaking: this finding will have to be read in a positive perspective, as we will see below, while taking into account the fact that to compose the sample, there are patients with current pathological conditions (at the time of admission) and different pre-existing conditions, as well as specific factors of ICU that we know influence the onset of sarcopenia, including sepsis, immobilization and use of neuro-muscular blockers.

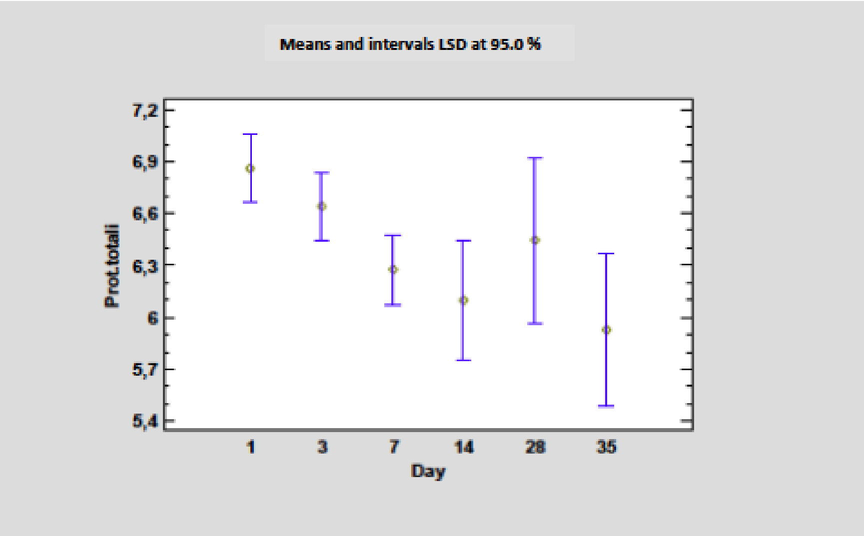


Fig. 10 Total proteins levels means and intervals LSD at 95% during different days of observation.

The result obtained by evaluating the P / F trend with respect to the type of nutrition used was very interesting (Fig 11).

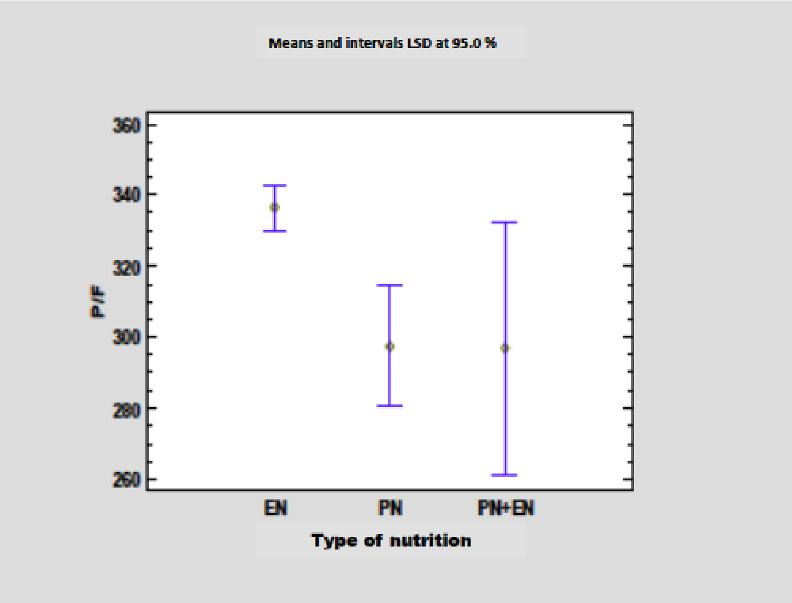


Fig. 11 P/F trends in the different type of nutrition administered

As can be easily seen from the graph below, patients fed enterally, in a statistically significant manner (P-value=0,03), better P/F.

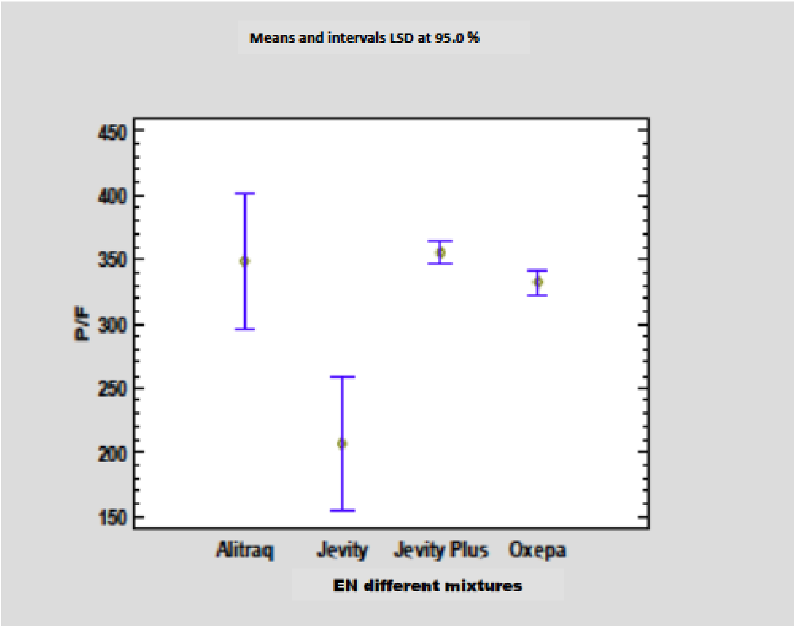


Fig. 12 P/F values among different EN mixtures

This is certainly influenced by the number of patients with EN, but it also reflects what has been shown by various studies in relation to the fact that the composition of the mixtures also influences the clinical response. Interestingly, among the mixtures used for the patients of our sample, the highest P/F were recorded with mixtures like Alitraq, Jevity Plus and Oxepa enriched with glutamine, arginine, EPA (eicosapentanoic acid), GLA (gamma-linoleic acid), compounds that have shown immunomodulatory and anti-inflammatory action (94; 95), (Fig. 12).

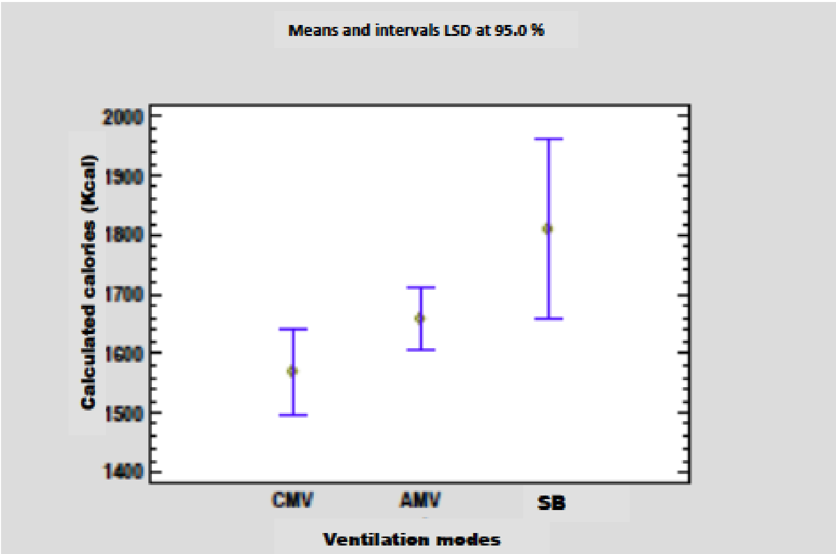


Fig. 13 Calculated calories given during the different ventilation modes. CMV controlled mechanical ventilation, AMV assisted mechanical ventilation, SB spontaneaous breathing.

Our analysis then focused on comparing the various parameters, considering the type of distinct ventilation in CMV, AMV and SB as independent variables. By adopting this sequence, it was possible to focus our attention on the impact of protein-caloric intake in the transition of the patient from a phase of total ventilatory support to the restoration of his respiratory autonomy (Fig. 13).

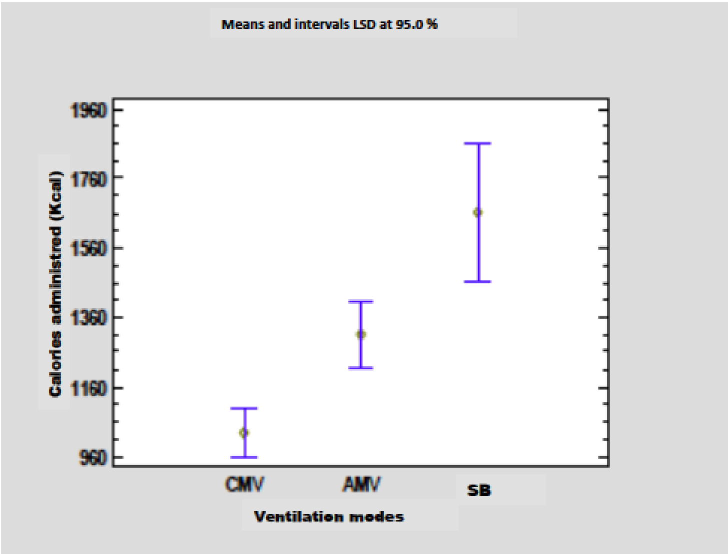


Fig. 14 Calories administrated during the different ventilation modes.

Both the estimate of caloric intake and the Mifflin-St. Equation Jeor, as the calculation of calories provided through the mixture for artificial nutrition, were not significant (Fig 14). This demonstrates the fact that the different phases of the "ventilatory" management of the patient are covered with an adequate caloric requirement, which progressively increases up to a maximum found in the SB phase, during which the muscular effort of the patient, necessary to allow the restoration of spontaneous breathing, it is compensated with a fair amount of calories.

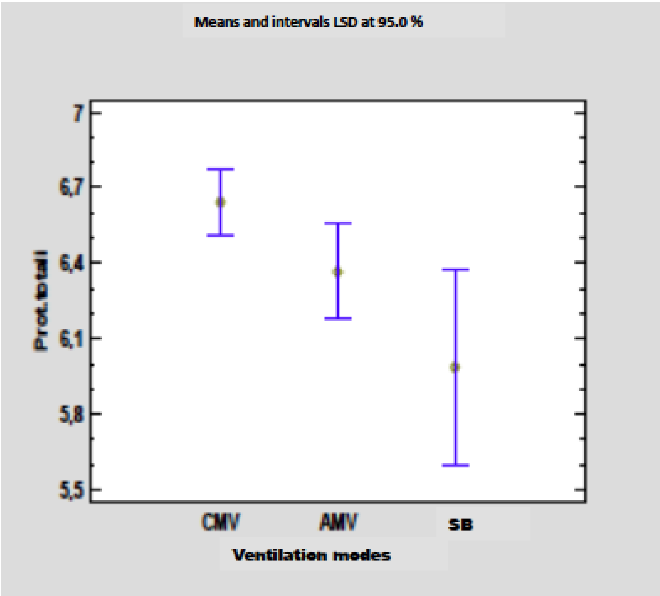


Fig. 15 Total proteins levels during the three ventilation modes.

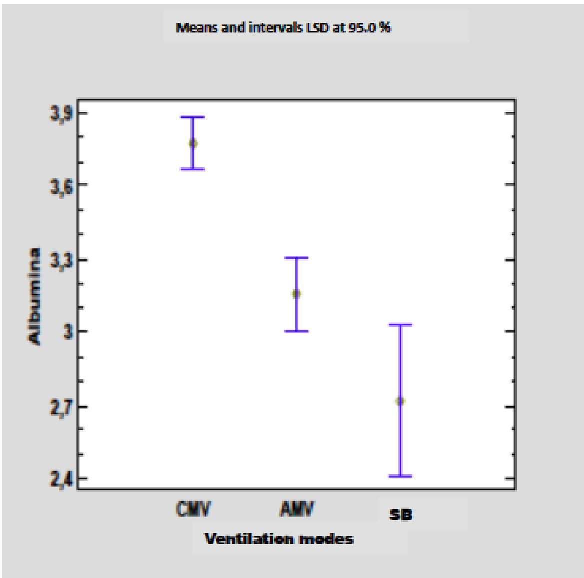


Fig. 16 Albumin levels in the three ventilation modes.

Similarly, the variations in total protein (Fig. 15) and albumin (Fig 16) during the three ventilation phases were not statistically significant. The analysis of the graph offers, however, an interesting starting point: it can be seen that these two parameters are progressively reduced, up to a minimum level in spontaneous breathing. In this phase, in fact, the patient makes a considerable muscular effort, to be able to "win" his dependence on the MV and return to breathe independently; in order to avoid this decrease in the two serum components, of which we are discussing, it should therefore, in the weaning phase, further implement the nutritional intake, in order to avoid the onset of a condition of sarcopenia related to the depletion of protein constituents used from the patients to derive the energy necessary to compensate for the greater use of the muscles during spontaneous breathing.

However, as we stated earlier, the analysis did not allow us to demonstrate statistical significance in the sample at our disposal.

At the end of the analysis and in support of the observations obtained, we wanted to observe how the weight and BMI varied in the different hospitalization phases, in particular in weaning from ventilatory support.

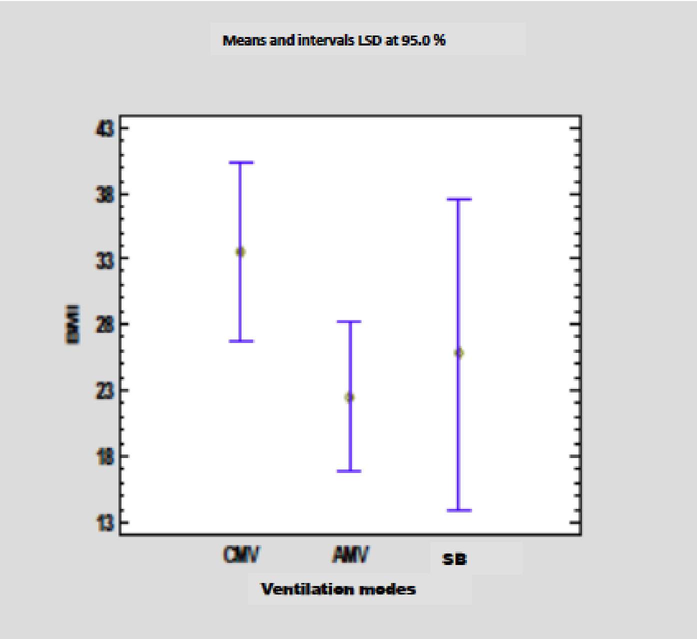


Fig 17 BMI levels during different ventilation modes.

The study of the graphs made it possible to highlight how, despite the fact that in the weaning phase patients show a reduction in BMI (Fig 17) and weight (Fig.18) (due to loss of muscle and / or fat mass, mobilized for energy purposes), in the last part of the ICU stay , in which spontaneous breathing is resumed, both of these parameters almost return to the initial values.

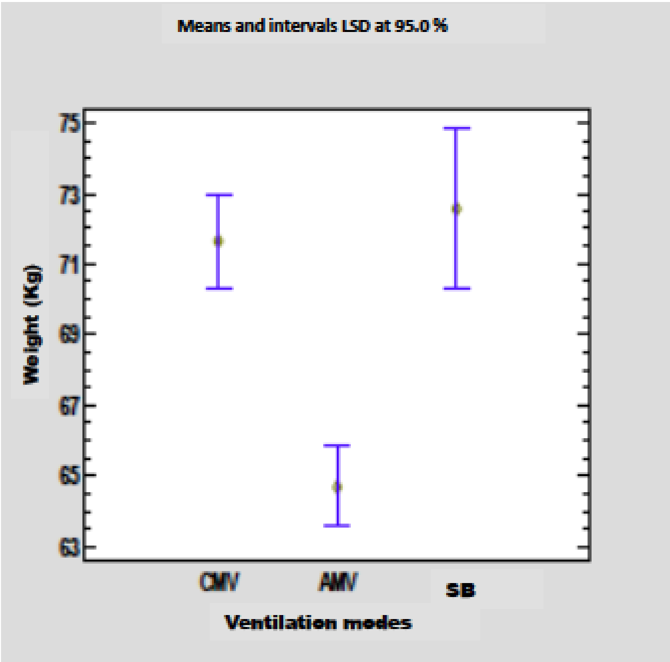


Fig. 18 Weight levels during different ventilation modes.

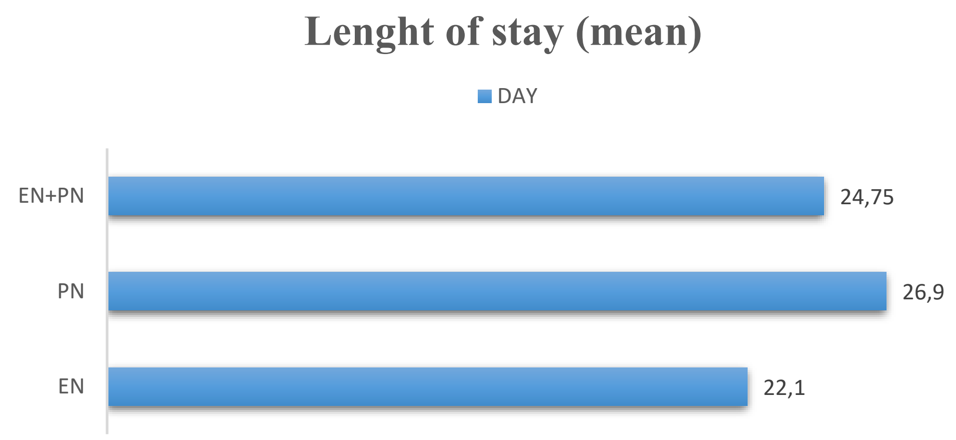
This supports the fact that recruited patients have received adequate nutritional support at every stage of hospitalization.

Discussion

Patients with chronic respiratory failure (over 21 days) are kept for long periods in the Intensive Care Unit, with high risk of developing nosocomial infections and deficits due to the relative lack of physiotherapy interventions. Several studies have shown that a vast amount of resources, which can be expressed as days of hospitalization in the intensive care unit, once the acute phase of the disease
is treated and resolved, is absorbed by the patient's mechanical dependence (100). Serious and longterm illness of intensive care patients, subject to prolonged mechanical ventilation and poor protein uptake, result in increased respiratory muscle weakness, which in turn extends hospitalization (101).
Despite the careful prescription of an appropriate caloric regimen, discrepancies between prescription and actual intake of nutrients administered via enteral were found. Nutrient breaks were attributable to interruptions caused by digestive tract intolerance (27.7%, daily wasted volume was 641 ml), airway management (30.8%, wasted on average a volume of 745 ml), and diagnostic procedures (26.6%, wasted volume averaged 567 mL) (102). Among the factors associated with low nutritional support, airway management and diagnostic procedures, together with nursing and broncho-gastro-aspiration, as well as gastrointestinal dysfunction, can limit the daily amount of calories absorbed through the gastrointestinal tract (103-104). In patients undergoing acute pathway recovery, nutrition, hemodynamics and respiratory support should be considered an integral part of patient outcomes, because an optimal nutrition support is important to limit the catabolic process and minimize the adverse events, such as prolonged mechanical ventilation. Respiratory muscle dysfunction is common in intensive care patients and is associated with adverse events, including prolonged mechanical ventilation. Risk factors for developing muscle weakness acquired in intensive care include disuse (105). Controlled mechanical ventilation can lead to diaphragmatic muscular atrophy within 24 hours of controlled mechanical ventilation. Assisted ventilation

mechanics can prevent the development of diaphragm dysfunctions associated with disuse (106). Therefore, to limit the development of diaphragmatic muscular atrophy, clinicians seek to use the assisted ventilation modes as soon as possible, if clinically appropriate. However, it must be recognized that even in assisted modes as pressure support, over-assistance episodes may occur, resulting in very low diaphragm muscular activity (107). Compared to what is already been published in literature, new findings correlating protein intake to the weaning phase, should be able to predict whether the percentage of weaning failure is directly correlated to debilitated patients. Furthermore, the application of a strategy where feeding and ventilator support are adapted on patients requirements and day by day monitoring of the criteria mentioned above, should results in increasing of weaning and discharge success from the ICU. The combination of nutrition and success of weaning has been highlighted by many studies. Nutrition becomes an indispensable aspect in the management of the critical patient, even in that delicate moment which is weaning from the MV. From this it is possible to detect that:

- The nutritional supply provided to the individual patient in the Foggia Intensive Care Unit is adequate for his metabolic needs; the adoption of the recommendations provided by the reference standards is fundamental, adapting the therapeutic choices to the needs of the individual (for example the choice of the mixture). The confirmation that the choices made regarding nutrition are appropriate is also highlighted by the study of weight variation and BMI.
- In patients in EN, the (average) days of hospitalization are reduced compared to the other two comparison groups; in this regime, therefore, the caloric intake responds better to the metabolic demands of the subject and in addition to this, by providing them with adequate caloric support, it is possible to wean them optimally.



In all the patients of the sample, the weaning phase was adequately.

Conclusions

- The combination of nutrition and success of weaning has been highlighted by many scientific papers (108-112). Nutrition becomes an indispensable aspect in the management of the critical patient, even in that delicate moment which is weaning from the VM.
- Our analysis showed that although the calories calculated and those provided are adequate for the patient's needs, total proteins and albumin show a decreasing trend, but in a statistically non-significant manner at any stage of admission to ICU.
- In light of what was found in the previous points, it can be stated that the costs of the University ICU of Foggia for this number of patients have been adjusted, since through an optimal planning of the nutritional supply, the days have not increased or of hospitalization or the incidence of difficult or prolonged weaning conditions and the consequences associated with it.

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