Nutritional Support in the Perioperative Period

Topic 17

Module 17.1

The Stress Response and its Effects on Metabolism

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Learning Objectives

- Understand the mechanisms behind the stress response in surgical patients and how this may relate to impaired or enhanced recovery after surgery;
- How does the surgical stress response lead to hypermetabolism;
- What does this mean for protein metabolism;
- How can certain aspects of the stress response and its effects on protein metabolism be avoided and how can it be treated;
- Insights into the relationship between hypermetabolism, alterations in protein metabolism and complications in surgery.

Contents

Key Messages

- The stress response after surgery is a useful phenomenon;
- However, if uncontrolled, it leads to auto-cannibalism;
- Reduction of magnitude of surgical impact or its effects may be useful (small incisions, epidural);
- The counter regulatory hormones and inflammatory response to surgery cause insulin resistance;
- Insulin is the main anabolic hormone;
- To avoid catabolism, insulin resistance must be avoided;
- Patients should not be fasted unnecessarily. Modern fasting guidelines recommend patients to drink clear fluids up until 2 hours and allow solids 6 hours before anaesthesia and surgery;
- Depleted patients should be replenished;
- Albumin is not a measure of nutritional status.

1. What is meant by the surgical stress response?

In modern medicine, elective and acute surgical procedures are a more and more common phenomenon. Particularly for elective surgery it can be said that this constitutes a predictable form of trauma, and we now know that such trauma elicits a series of events called the "stress response", that may adversely affect the patient's health and capability to recover.

Unlike accidental trauma, however, the moment when the organism is affected can be anticipated and therefore, if we know the details of the "stress response", adequate measures could be taken to streamline the physiological response of the organism to surgical trauma.

The "stress response" is a phenomenon extensively studied since the thirties of the past century and includes changes in the metabolism of all nutrients including the macro-nutrients fat, carbohydrate and protein.

It is initiated and orchestrated by a multitude of neuro-endocrine and cytokine mediators and release of stress hormones, such as catecholamines, cortisol and glucagons, and induces a catabolic response leading to a negative nitrogen balance (1) (Fig. 1, Fig. 2).

This negative nitrogen and energy balance indicates that the body loses protein and this occurs for 50% in muscle and 50% in fat (2) (Fig. 3).

The loss of muscle mass does not only interfere with muscle function, but also with the ability of the organism to raise substrate to fuel host response, necessary in the defence against disease (3).

In the following, we will stipulate why this stress response is detrimental on the one hand and useful on the other.

Effects of major surgical trauma on homeostasis of the organism – fresh wounds

- **Wound causes pain, resulting in stress**
- **Stress is accompanied by neurohumoral changes: fight or flight**
- **Open wound: fluid loss**
- **Healing: anabolism**

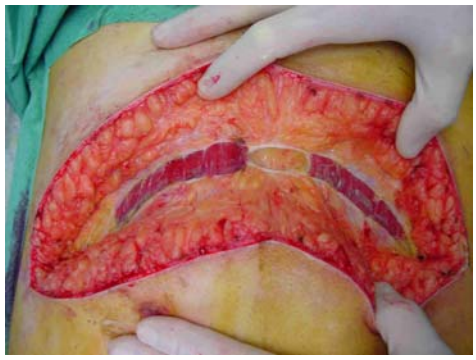


Fig. 1

Effects of surgical trauma on homeostasis of the organism

Surgical trauma is accompanied by a negative nitrogen balance

Nitrogen balance is more negative than during pure fasting

Fig. 2

weight loss following surgical trauma

- Where?
  - Muscle
  - Fat
- Why?
  - Reduced food intake
  - Increased energy expenditure and nitrogen loss
  - Metabolic 'Error' in Protein/Fat metabolism

Fig. 3

2. Clinical symptoms

Effects of major surgical trauma on homeostasis of the organism – chronic wounds

Shift in fluid compartmens

Fluid losses in wounds

Generalized edema

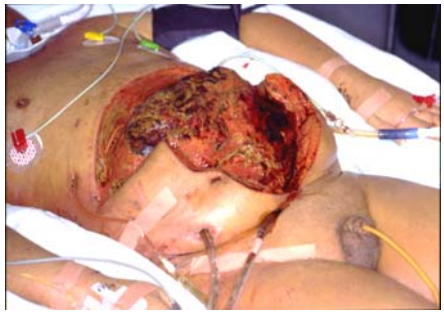


Fig. 4

Changes in body composition following major surgical trauma

ECW = extracellular water

BCM = body cell mass

EFM = estimated fat mass

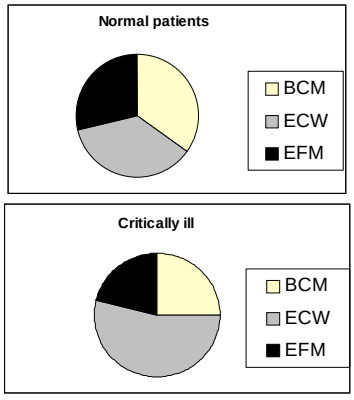


Fig. 5

Changes in body composition following trauma

Decrease in total body protein and potassium (TBP and TBK)

Decrease in intracellular water (ICW) and intracellular potassium (ICK)

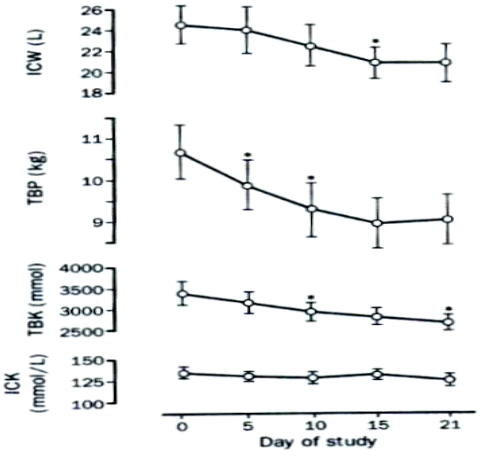


Fig. 6

Two different phases have classically been distinguished by Sir David Cuthbertson after most forms of trauma, including surgery: an initial short hypodynamic 'ebb' phase and a later hyperdynamic 'flow' phase (4).

The clinical picture accompanying the hyperdynamic phase consists of several characteristics: tissue edema (representing shifts in the body fluid compartment) (Fig. 4), increased cardiac output, hyperthermia, hypermetabolism, catabolism leading to muscle atrophy, biochemical alterations and an ongoing acute phase response:

- Tissue edema results from vasodilatation and increased capillary leakage. This implies that more fluid, plasma proteins, leukocytes, macrophages and electrolytes leave the vascular compartment and accumulate in the tissues. Increased capillary leakage is probably mediated by pro-inflammatory cytokines. Vasodilatation implies that intravascular volume decreases, which induces shock if adequate resuscitation is not achieved. Meanwhile intracellular volume decreases and this furnishes part of the volume necessary to replenish intravascular and extravascular extracellular volume (Fig. 5, Fig. 6).
- Increased cardiac output is induced by vasodilatation.
- Hyperthermia leads to, but is also caused by increased energy expenditure, oxygen uptake and substrate utilization during the stress response. This requires increased delivery by increased cardiac output, or increased extraction.
- Changes in protein breakdown and synthesis lead to net catabolism, but tissue edema may hide muscle atrophy.
- Biochemically the expansion of total body water leads to dilution of solutes including important electrolytes, but is also reflected in a low haematocrit.

- The ongoing "acute phase protein response" is illustrated by rises in CRP and fibrinogen (positive acute phase proteins), and a drop in albumin (negative acute phase proteins) (5, 6).

3. How does hypermetabolism result from the surgical stress response?

Surgical trauma and the resulting stress response leads to an increase in energy expenditures of about 15-25% above predicted healthy resting values. The increase in energy expenditure is caused amongst others by an upward resetting of thermoregulation that mediates an increase in energy production through enhanced activity of the sympathetic nervous system. Also, an increase in sympathetic activity may stimulate metabolic rate by enhancing substrate cycling between non-esterified fatty acids and trialglycerol and glucose and glucolytic products. The wound is also an area of increased metabolic activity (Fig. 7), and contributes to substrate cycling.

Lactate produced in the wound is transported to the liver where it is converted to glucose in the Cori cycle, an energy consuming process. Activated inflammatory cells in the wound have a high oxygen consumption and release of a number of cytokines (e.g. Il-1β and TNF-α) which mediate central upward resetting of metabolic activity. Finally, increased protein breakdown via energy-consuming pathways may contribute.

Healing wounds

Inflammatory response

Immune system activation

Anabolism at the wound site

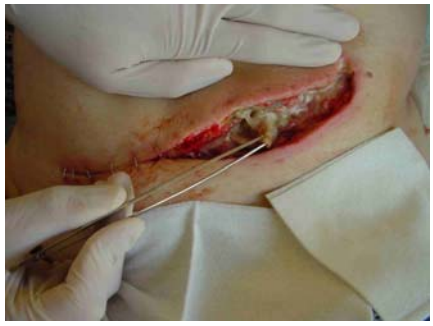


Fig. 7

The stress response is always accompanied by catabolism at the whole body level

Normally, following surgical trauma, the body is in negative nitrogen balance, reflecting loss of body protein (7-9) (Fig. 2). Body weight drops and muscle atrophy becomes apparent, even when the patient has been receiving adequate nutrition. Interestingly, the response to surgical trauma is quite different from that to pure starvation. During pure starvation all organs lose mass (10). Following surgical trauma however some organs (muscle, adipose tissue, skin) are catabolic (11) (protein degradation exceeds synthesis). Other organs, however, such as the wound itself are anabolic (12). The whole immune system is anabolic including the liver.

This is achieved by an increase in muscle protein degradation whereas muscle protein synthesis hardly changes. "Centrally" increased uptake of amino acids is achieved in liver by an increase in protein synthesis, whereas protein degradation increases to a lesser extent. Thus, during the stress response, only peripheral tissues (muscle, adipose tissue, skin) are catabolic whereas central tissues (liver, immune system, wound) are anabolic (13, 14) (Fig. 8).

Surgical trauma – Protein kinetics

- Immobilization
- Muscle protein breakdown
- Protein synthesis in liver, wound and immune system
- Anabolism and catabolism occur simultaneously
- Overall result: Body weight loss

Fig. 8

Stress response - Protein

- Ongoing acute phase protein response
- Accelerated protein synthesis in liver
- Amino acid mismatch
- Disproportionate muscle breakdown by ATP-consuming pathway
- Body weight loss

Fig. 9

Protein metabolism

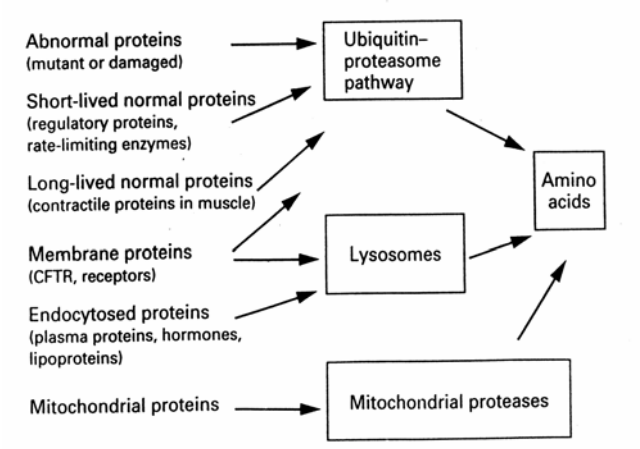


Fig. 10

Mitch WE and Goldberg AL, NEJM 1996;335:1897-1905

Proteolytic pathways

- Lysosomal: Cathepsin B, D, H, L
- Non-lysosomal
  - Energy dependent
    - Ubiquitin dependent: 26S protease
    - Ubiquitin independent: 600-kDa protease
  - Energy independent
    - Ca^{2+}-dependent: Calpain I, II

Hasselgren PO et al, Ann.Surg 1997;225:307-316

Fig. 11

As the amino acid composition of the protein synthesized centrally differs considerably from the ones broken down in muscle, this contributes to nitrogen loss. In this context, it has been calculated that seven grams of muscle protein would have to be broken down to furnish the amino acids for hepatic synthesis of 1 gram of fibrinogen (15) (Fig. 9).

However, the atrophying action of the stress response on muscle has been viewed as a useful adaptive process, meant to furnish fuel and building blocks to organs that play a vital role in the healing process after trauma and disease (14).

It is remarkable that muscle catabolism can hardly be inhibited by furnishing nutrition as long as the stress response continues. However, emerging evidence suggests that if the stress response is minimized, metabolism supported towards anabolism and nutrition is provided, healing of wounds can be accomplished at least as well while recovery is enhanced (see Modules 17.2 and 17.6).

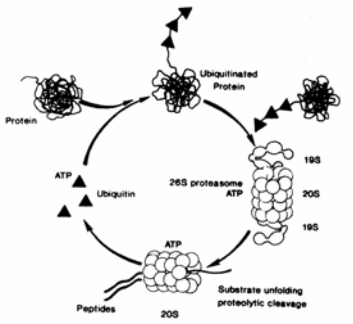
4. Protein kinetics

Proteins are continuously synthesized and broken down. Several authors have reported increased protein turnover after trauma, including an increase in whole body protein synthesis and an even more pronounced increase in protein breakdown (2, 16).

Protein breakdown can take place via at least three routes (Fig. 10, Fig. 11 and Fig. 12), but it is currently believed that the energy consuming ubiquitin proteasome pathway plays a crucial role in this respect, in concert with the calpain system (17, 18). This occurs also in the absence of food intake, but net whole body catabolism is more pronounced after surgical trauma than in the pure fasted state.

The continuous process of simultaneous protein synthesis and breakdown serves several useful purposes (19-21). Modest changes in protein synthesis or breakdown or both, allow for the net effect to be catabolic or anabolic. In addition, a high flux through pathways makes it possible to rapidly respond to changing needs.
As said, the sum of the central anabolic actions and the peripheral catabolic actions is negative in the sense that at the whole body level body protein is lost. This process is therefore inefficient in terms of nitrogen economy because the overall effect is net catabolism of the whole organism.

Ubiquitin-proteasome pathway



Steps requiring ATP

- Activation
- 26S assembly
- Degradation of ubiquitinated protein

Fig. 12

Hasselgren PO et al, Ann.Surg 1997;225:307-316

5. Does the gut play a role?

It has been proposed that temporary hypoperfusion of the splanchnic area may affect intestinal barrier function (Fig. 13).
This would then lead to increased permeability and translocation of bacteria or their products (Fig. 14), contributing to a systemic inflammatory response and/or sepsis.

Mechanism of sepsis/MOF

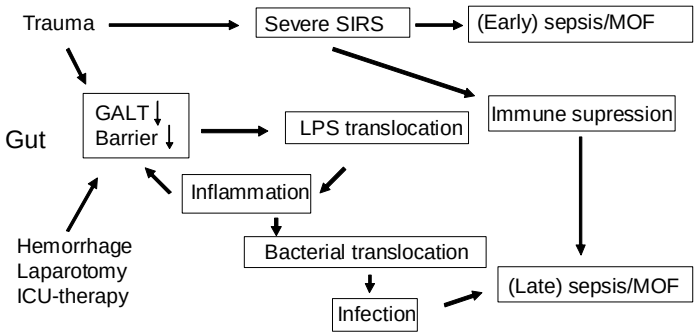


Fig. 13

Moore et al, Annals of Surgery 2000 Vol 231 No 1, 9-10

Changes in gut permeability

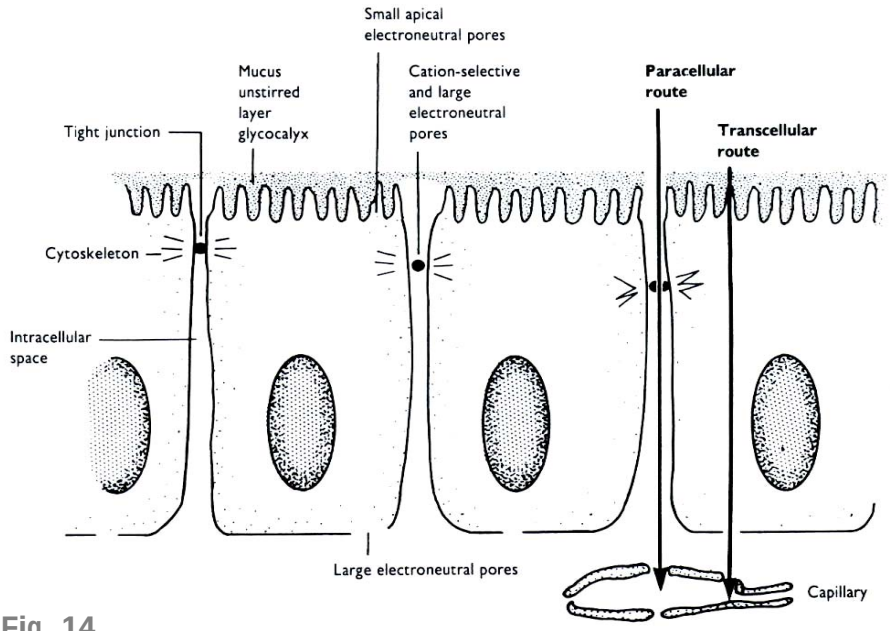
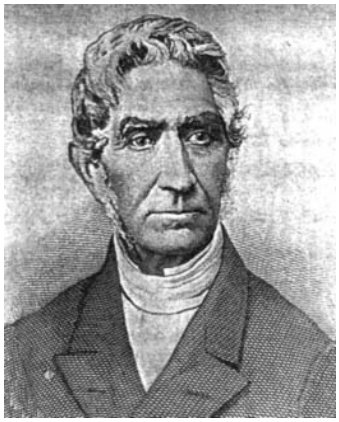


Fig. 14

Travis et al. Clin Sci

A generalized systemic inflammatory response in itself may induce gut leakiness contributing to a vicious cycle detrimental to the host.

Adolphe Quetelet



Invented Body Mass Index (BMI) as a measure of nutritional state

Patients with BMI below 18 and recent weight loss are at risk

Fig. 15

http://www-groups.dcs.st-and.ac.uk/~history/PictDisplay/Quetelet.html

Changes in gut permeability

Depleted patients have increased gut permeability as measured by the lactulose/mannitol test

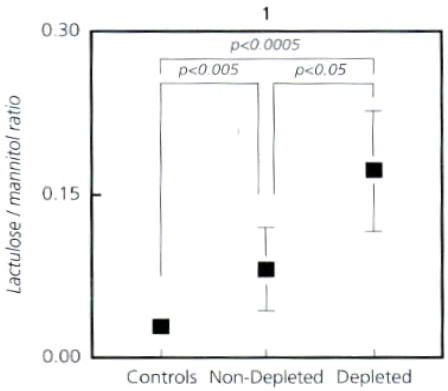


Fig. 16

Van der Hulst et al. Nutrition 1998; 14:1-6

Changes in gut permeability

Increased gut permeability following surgical trauma and/or shock may be prevented by early enteral feeding

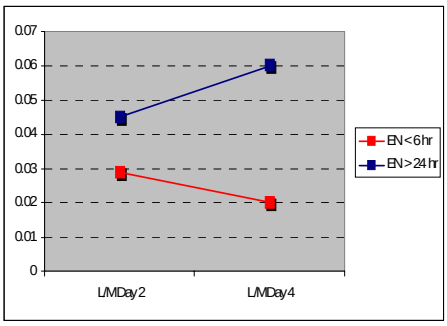


Fig. 17

Intensive Care Med 1999;25:157-161

Equally, a state of malnutrition as reflected by a low Quetelet index (Fig. 15) may lead to inappropriate gut permeability (Fig. 16). In this context, it should be stressed that albumin in itself is not a good marker of nutritional status.

Since early enteral nutrition has been shown to be safe and beneficial to the gut, it seems logical to administer food via the enteral route as soon as possible after surgery (Fig. 17). It may well be that high fat enteral nutrition or probiotics will turn out to have added value in this context (22, 23).

6. Proactive approach to prevent unnecessary aspects of the surgical stress response

From the above, the strategies to dampen the surgical stress response and its effects are self-evident:

- surgical trauma should be minimized (length of incision, technique);
- afferent painful stimuli should be minimized to prevent the stress response. The use of epidural analgesia and/or local wound infiltration with a local anesthetic may be useful;
- stressing the patient preoperatively should be avoided (no unnecessary starvation);
- the anabolic effects of insulin should be facilitated by reducing insulin resistance (see Module 17.2);
- depleted patients should be fed during 7-10 days preoperatively. Protein synthesis rates should be stimulated by nutritional support to synthesize new muscle protein and to meet the demand of crucial visceral protein and proteins in wounds, white cells and macrophages. So essentially, new therapeutic interventions should be more tailored to organ needs and thereby supply organs with their specific needs.

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