

## **The metabolic response to trauma**

### **THE GRADED NATURE OF THE INJURY RESPONSE**

The response to injury is graded: the more severe the injury, the greater the response.

This concept not only applies to physiological/metabolic changes but also to immunological changes/sequelae. Thus, following elective surgery of intermediate severity, there may be a transient and modest rise in temperature, heart rate, respiratory rate, energy expenditure and peripheral white cell count. Following major trauma/sepsis, these changes are accentuated, resulting in a systemic inflammatory response syndrome (SIRS), hypermetabolism, marked catabolism, shock and even multiple organ dysfunction (MODS).

Not only is the metabolic response graded, but it also evolves with time. In particular, the immunological sequelae of major injury evolve from a pro-inflammatory state driven primarily by the innate immune system (macrophages, neutrophils, dendritic cells) into a compensatory anti-inflammatory response syndrome (CARS) characterised by suppressed immunity and diminished resistance to infection. In patients who develop infective complications, the latter will drive on-going systemic inflammation, the acute phase response and continued catabolism.

### **MEDIATORS OF THE METABOLIC RESPONSE TO INJURY**

The classical neuroendocrine pathways of the stress response consist of afferent nociceptive neurones, the spinal cord, thalamus, hypothalamus and pituitary.

- ✚ Corticotrophin-releasing factor (CRF) released from the hypothalamus increases adrenocorticotrophic hormone (ACTH) release from the anterior pituitary. ACTH then acts on the adrenal to increase the secretion of cortisol.
- ✚ Hypothalamic activation of the sympathetic nervous system causes release of adrenalin and also stimulates release of glucagon.
- ✚ Intravenous infusion of a cocktail of these 'counter-regulatory' hormones (glucagon, glucocorticoids and catecholamines) reproduces many aspects of the metabolic response to injury.
- ✚ Alterations in insulin release and sensitivity,
- ✚ Hypersecretion of prolactin and growth hormone (GH). Of note, GH has direct lipolytic, insulin-antagonising and pro-inflammatory properties.
- ✚ Inactivation of peripheral thyroid hormones and gonadal function.
- ✚ The innate immune system (principally macrophages) interacts in a complex manner with the adaptive immune system (T cells, B cells) in co-generating the metabolic response to injury.
- ✚ Pro-inflammatory cytokines including interleukin-1 (IL-1), tumour necrosis factor alpha (TNF alpha), IL-6 and IL-8 are produced within the first 24 hours and act directly on the hypothalamus to cause pyrexia. Such cytokines also augment the hypothalamic stress response and act directly on skeletal muscle to induce proteolysis while inducing acute phase protein production in the liver. Pro-inflammatory cytokines also play a complex role in the development of peripheral insulin resistance. Other important pro-inflammatory mediators include nitric oxide [(NO) via inducible nitric oxide synthetase.

- ✚ Within hours of the upregulation of pro-inflammatory cytokines, endogenous cytokine antagonists enter the circulation [e.g. interleukin-1 receptor antagonist (IL-1Ra) and TNFsoluble receptors (TNF-sR-55 and 75)] and act to control the pro-inflammatory response.
- ✚ A complex further series of adaptive changes includes the development of counterinflammatory response [regulated by IL-4, -5, -9 and -13 and transforming growth factor beta (TGF beta)] which, if accentuated and prolonged in critical illness, is characterised as the CARS and results in immunosuppression and an increased susceptibility to opportunistic (nosocomial) infection.
- ✚ There are many complex interactions between the neuroendocrine, cytokine and metabolic axes. For example, although cortisol is immunosuppressive at high levels, it acts synergistically with IL-6 to promote the hepatic acute phase response. ACTH release is enhanced by pro-inflammatory cytokines and the noradrenergic system. The resulting rise in cortisol levels may form a weak feedback loop attempting to limit the pro-inflammatory stress response. Finally, hyperglycaemia may aggravate the inflammatory response via substrate overflow in the mitochondria, causing the formation of excess free oxygen radicals and also altering gene expression to enhance cytokine production.

### **Systemic inflammatory response syndrome (SIRS) following major injury**

- Is driven initially by pro-inflammatory cytokines (e.g. IL-1, IL-6 and TNF)
- Is followed rapidly by increased plasma levels of cytokine antagonists and soluble receptors (e.g. IL-1Ra, TNF-sR)
- If prolonged or excessive may evolve into a counterinflammatory response syndrome (CARS)

### **THE METABOLIC STRESS RESPONSE TO SURGERY AND TRAUMA: THE 'EBB AND FLOW' MODEL**

In the natural world, if an animal is injured, it displays a characteristic response, which includes immobility, anorexia and catabolism. In 1930, Sir David Cuthbertson divided the metabolic response to injury in humans into 'ebb' and 'flow' phases.

#### **Ebb phase**

The ebb phase begins at the time of injury and lasts for approximately 24–48 hours. It may be attenuated by proper resuscitation, but not completely abolished. The ebb phase is characterised by:

- 1) Hypovolaemia,
- 2) Decreased basal metabolic rate,
- 3) Reduced cardiac output,
- 4) Hypothermia and lactic acidosis.

The predominant hormones regulating the ebb phase are catecholamines, cortisol and aldosterone (following activation of the renin–angiotensin system). The magnitude of this neuroendocrine response depends on the degree of blood loss and the stimulation of somatic afferent nerves at the site of injury. *The main physiological role of the ebb phase is to conserve both circulating volume and energy stores for recovery and repair.*

### **Flow phase**

Following resuscitation, the ebb phase evolves into a hypermetabolic flow phase, which corresponds to the SIRS. *This phase involves the mobilisation of body energy stores for recovery and repair, and the subsequent replacement of lost or damaged tissue.*

It is characterised by:

- 1) Tissue oedema (from vasodilatation and increased capillary leakage),
- 2) Increased basal metabolic rate (hypermetabolism),
- 3) Increased cardiac output,
- 4) Raised body temperature,
- 5) Leukocytosis,
- 6) Increased oxygen consumption and
- 7) Increased gluconeogenesis.

The flow phase may be subdivided into an initial catabolic phase, lasting approximately 3–10 days, followed by an anabolic phase, which may last for weeks if extensive recovery and repair are required following serious injury. During the catabolic phase, the increased production of counter-regulatory hormones (including catecholamines, cortisol, insulin and glucagon) and inflammatory cytokines (e.g. IL-1, IL-6 and TNFalpha) results in significant fat and protein mobilisation, leading to significant weight loss and increased urinary nitrogen excretion. The increased production of insulin at this time is associated with significant *insulin resistance* and, therefore, injured patients often exhibit poor glycaemic control. The combination of pronounced or prolonged catabolism in association with insulin resistance places patients within this phase at increased risk of complications, particularly infectious and cardiovascular.

Obviously, the development of complications will further aggravate the neuroendocrine and inflammatory stress responses, thus creating a vicious catabolic cycle.

### **Physiological response to injury**

The *natural* response to injury includes:

- Immobility/rest
- Anorexia
- Catabolism

The changes are designed to aid survival of moderate injury in the absence of medical intervention.

### **Purpose of neuroendocrine changes following injury**

The constellation of neuroendocrine changes following injury acts to:

- Provide essential substrates for survival
- Postpone anabolism
- Optimise host defence

*These changes may be helpful in the short term, but may be harmful in the long term, especially to the severely injured patient who would otherwise not have survived without medical intervention.*

### **KEY CATABOLIC ELEMENTS OF THE FLOW PHASE OF THE METABOLIC STRESS RESPONSE**

There are several key elements of the flow phase that largely determine the extent of catabolism. It should be remembered that, during the response to injury, not all tissues are catabolic. Indeed, the essence of this coordinated response is to allow the body to reprioritize limited resources away from peripheral tissues (muscle, adipose tissue, skin) and towards key viscera (liver, immune system) and the wound.

#### **Hypermetabolism**

The majority of trauma patients (except possibly those with extensive burns) demonstrate energy expenditures approximately 15–25% above predicted healthy resting values. The predominant cause appears to be a complex interaction between the central control of metabolic rate and peripheral energy utilisation.

In particular, the causes of increase patient energy expenditure are:

1. Central thermodyregulation (caused by the pro-inflammatory cytokine cascade),
2. Increased sympathetic activity,
3. Abnormalities in wound circulation [ischaemic areas produce lactate, which must be metabolised by the adenosine triphosphate (ATP)-consuming hepatic Cori cycle; hyperaemic areas cause an increase in cardiac output],
4. Increased protein turnover and nutritional support.

Counteracts of the hypermetabolism:

- 1) Standard intensive care (including bed rest, paralysis, ventilation and external temperature regulation).
- 2) The skeletal muscle wasting experienced by patients with prolonged catabolism actually limits the volume of metabolically active tissue.

#### **Hypermetabolism following injury:**

- Is mainly caused by an acceleration of futile metabolic cycles
- Is limited in modern practice on account of elements of routine critical care

#### **Alterations in skeletal muscle protein metabolism**

Under normal circumstances, synthesis of muscle protein equals breakdown and muscle bulk remains constant. Physiological stimuli that promote net muscle protein accretion include feeding (especially extracellular amino acid concentration) and exercise. Paradoxically, during exercise, skeletal muscle protein synthesis is depressed, but it increases again during rest and feeding. During the catabolic phase of the stress response, muscle wasting occurs as a result of an increase in muscle protein degradation (via enzymatic pathways), coupled with a decrease in muscle protein synthesis. The major site of protein loss is peripheral skeletal muscle, although nitrogen losses also

occur in the respiratory muscles (predisposing the patient to hypoventilation and chest infections) and in the gut (reducing gut motility). Cardiac muscle appears to be mostly spared. Under extreme conditions of catabolism (e.g. major sepsis), urinary nitrogen losses can reach 14–20 g day<sup>-1</sup>; this is equivalent to the loss of 500 g of skeletal muscle per day. It is remarkable that muscle catabolism cannot be inhibited fully by providing artificial nutritional support as long as the stress response continues. Indeed, in critical care, it is now recognised that ‘hyperalimentation’ represents a metabolic stress in itself, and that nutritional support should be at a modest level to attenuate rather than replace energy and protein losses.

Clinically, a patient with skeletal muscle wasting will experience asthenia, increased fatigue, reduced functional ability, decreased quality of life and an increased risk of morbidity and mortality. In critically ill patients, muscle weakness may be further worsened by the development of critical illness myopathy, a multifactorial condition that is associated with impaired excitation–contraction–coupling at the level of the sarcolemma and the sarcoplasmic reticulum membrane.

### **Skeletal muscle wasting**

- **Provides amino acids for protein synthesis in central organs/tissues**
- **Can result in immobility and contribute to hypostatic pneumonia and death if prolonged and excessive**

### **Alterations in hepatic protein metabolism: the acute phase protein response (APPR)**

The liver and skeletal muscle together account for 50% of daily body protein turnover. Skeletal muscle has a large mass but a low turnover rate (1–2% day<sup>-1</sup>), whereas the liver has a relatively small mass (1.5 kg) but a much higher protein turnover rate (10–20% day<sup>-1</sup>). Albumin is the major export protein produced by the liver. The transcapillary escape rate (TER) of albumin is about 10 times the rate of synthesis, and short-term changes in albumin concentration are most probably due to increased vascular permeability. Albumin TER may be increased threefold following major injury/sepsis. In response to inflammatory conditions, including surgery, trauma, sepsis, cancer or autoimmune conditions, circulating peripheral blood mononuclear cells secrete a range of pro-inflammatory cytokines, including IL-1, IL-6 and TNF alpha. These cytokines, in particular IL-6, promote the hepatic synthesis of positive acute phase proteins, e.g. fibrinogen and C-reactive protein (CRP). The APPR represents a ‘double-edged sword’ for surgical patients as it provides proteins important for recovery and repair, but only at the expense of valuable lean tissue and energy reserves. In contrast to the positive acute phase reactants, the plasma concentrations of other liver export proteins (the negative acute phase reactants) fall acutely following injury, e.g. albumin. However, rather than represent a reduced hepatic synthesis rate, the fall in plasma concentration of negative acute phase reactants is thought principally to reflect increased transcapillary escape, secondary to an increase in microvascular permeability. Thus, increased hepatic synthesis of positive acute phase reactants is not compensated for by reduced synthesis of negative reactants.

### Hepatic acute phase response

The hepatic acute phase response represents a reprioritization of body protein metabolism towards the liver and is characterised by:

- **Positive reactants (e.g. CRP): plasma concentration** ↑
- **Negative reactants (e.g. albumin): plasma concentration** ↓

### **Insulin resistance**

Following surgery or trauma, postoperative hyperglycaemia develops as a result of increased glucose production combined with decreased glucose uptake in peripheral tissues. Decreased glucose uptake is a result of insulin resistance which is transiently induced within the stressed patient. Suggested mechanisms for this phenomenon include the action of pro-inflammatory cytokines and the decreased responsiveness of insulin-regulated glucose transporter proteins. The degree of insulin resistance is proportional to the magnitude of the injurious process. Following routine upper abdominal surgery, insulin resistance may persist for approximately 2 weeks. Postoperative patients with insulin resistance behave in a similar manner to individuals with type II diabetes mellitus and are at increased risk of sepsis, deteriorating renal function, polyneuropathy and death. The mainstay management of insulin resistance is intravenous insulin infusion. Insulin infusions may be used in either an *intensive* approach (i.e. sliding scales are manipulated to *normalise* the blood glucose level) or a *conservative* approach (i.e. insulin is administered when the blood glucose level exceeds a defined limit and discontinued when the level falls). Studies of postoperatively ventilated patients in the intensive care unit (ICU) have suggested that maintenance of normal glucose levels using intensive insulin therapy can significantly reduce both morbidity and mortality. Furthermore, intensive insulin therapy is superior to conservative insulin approaches in reducing morbidity rates. However, the mortality benefit of intensive insulin therapy over a more conservative approach has not been proven conclusively.

### **CHANGES IN BODY COMPOSITION FOLLOWING INJURY**

The average 70-kg male can be considered to consist of fat (13 kg) and fat-free mass (or lean body mass: 57 kg). In such an individual, the lean tissue is composed primarily of protein (12 kg), water (42 kg) and minerals (3 kg). The protein mass can be considered as two basic compartments, skeletal muscle (4 kg) and non-skeletal muscle (8 kg), which includes the visceral protein mass. The water mass (42 l) is divided into intercellular (28 l) and extracellular (14 l) spaces. Most of the mineral mass is contained in the bony skeleton. The main labile energy reserve in the body is fat, and the main labile protein reserve is skeletal muscle. While fat mass can be reduced without major detriment to function, loss of protein mass results not only in skeletal muscle wasting, but also depletion of visceral protein status. Within lean tissue, each 1 g of nitrogen is contained within 6.25 g of protein, which is contained in approximately 36 g of wet weight tissue. Thus, the loss of 1g of nitrogen in urine is equivalent to the breakdown of 36 g of wet weight lean tissue. Protein turnover in the whole body is of the order of 150–200 g day<sup>-1</sup>. A normal human ingests about 70–100 g protein day<sup>-1</sup>, which is metabolised and excreted in urine as ammonia and urea (i.e. approximately 14 g N day<sup>-1</sup>). During total starvation, urinary loss of nitrogen is rapidly attenuated by a

series of adaptive changes. Loss of body weight follows a similar course , thus accounting for the survival of hunger strikers for a period of 50–60 days. Following major injury, and particularly in the presence of on-going septic complications, this adaptive change fails to occur, and there is a state of 'autocannibalism', resulting in continuing urinary nitrogen losses of 10–20 g N day<sup>-1</sup> (equivalent to 500 g of wet weight lean tissue day<sup>-1</sup>). As with total starvation, once loss of body protein mass has reached 30–40% of the total, survival is unlikely. Critically ill patients admitted to the ICU with severe sepsis or major blunt trauma undergoes massive changes in body composition. Body weight increases immediately on resuscitation with an expansion of extracellular water by 6–10 l within 24 hours. Thereafter, even with optimal metabolic care and nutritional support, total body protein will diminish by 15% in the next 10 days, and body weight will reach negative balance as the expansion of the extracellular space resolves. In marked contrast, it is now possible to maintain body weight and nitrogen equilibrium following major elective surgery. This can be achieved by blocking the neuroendocrine stress response with epidural analgesia and providing early enteral feeding. Moreover, the early fluid retention phase can be avoided by careful intraoperative management of fluid balance, with avoidance of excessive administration of intravenous saline.

#### **Changes in body composition following major surgery/critical illness**

- **Catabolism leads to a *decrease* in fat mass and skeletal muscle mass**
- **Body weight may paradoxically *increase* because of expansion of extracellular fluid space**

#### **AVOIDABLE FACTORS THAT COMPOUND THE RESPONSE TO INJURY**

As noted previously, the main features of this metabolic response are initiated by the immune system, cardiovascular system, sympathetic nervous system, ascending reticular formation and limbic system. However, the metabolic stress response may be further exacerbated by anaesthesia, dehydration, starvation (including preoperative fasting), sepsis, acute medical illness or even severe psychological stress. Thus, any attempt to limit or control these other factors is beneficial to the patient.

#### **Avoidable factors that compound the response to injury**

- **Continuing haemorrhage**
- **Hypothermia**
- **Tissue oedema**
- **Tissue underperfusion**
- **Starvation**
- **Immobility**

#### **Volume loss**

During simple haemorrhage, pressor receptors in the carotid artery and aortic arch, and volume receptors in the wall of the left atrium, initiate afferent nerve input to the central nervous system (CNS), resulting in the release of both aldosterone and antidiuretic hormone (ADH). Pain can also stimulate ADH release. ADH acts directly on the kidney to cause fluid retention. Decreased pulse pressure stimulates the juxtaglomerular apparatus in the kidney and

directly activates the renin–angiotensin system, which in turn increases aldosterone release.

Aldosterone causes the renal tubule to reabsorb sodium (and consequently also conserve water). ACTH release also augments the aldosterone response. The net effects of ADH and aldosterone result in the natural oliguria observed after surgery and conservation of sodium and water in the extracellular space. The tendency towards water and salt retention is exacerbated by resuscitation with saline-rich fluids. Salt and water retention can result in not only peripheral oedema, but also visceral oedema (e.g. stomach). Such visceral oedema has been associated with reduced gastric emptying, delayed resumption of food intake and prolonged hospital stay. Careful limitation of intraoperative administration of colloids and crystalloids (e.g. Hartmann's solution) so that there is no net weight gain following elective surgery has been proven to reduce postoperative complications and length of stay.

### **Hypothermia**

Hypothermia results in increased elaboration of adrenal steroids and catecholamines. When compared with normothermic controls, even mild hypothermia results in a two- to threefold increase in postoperative cardiac arrhythmias and increased catabolism. Randomised trials have shown that maintaining normothermia by an upper body forced-air heating cover reduces wound infections, cardiac complications and bleeding and transfusion requirements.

### **Tissue oedema**

During systemic inflammation, fluid, plasma proteins, leucocytes, macrophages and electrolytes leave the vascular space and accumulate in the tissues. This can diminish the alveolar diffusion of oxygen and may lead to reduced renal function. Increased capillary leak is mediated by a wide variety of mediators including cytokines, prostanoids, bradykinin and nitric oxide. Vasodilatation implies that intravascular volume decreases, which induces shock if inadequate resuscitation is not undertaken. Meanwhile, intracellular volume decreases, and this provides part of the volume necessary to replenish intravascular and extravascular extracellular volume.

### **Systemic inflammation and tissue underperfusion**

The vascular endothelium controls vasomotor tone and microvascular flow, and regulates trafficking of nutrients and biologically active molecules. When endothelial activation is excessive, compromised microcirculation and subsequent cellular hypoxia contribute to the risk of organ failure. Maintaining normoglycaemia with insulin infusion during critical illness has been proposed to protect the endothelium, probably in part, via inhibition of excessive inducible nitric oxide synthetase iNOS-induced NO release, and thereby contribute to the prevention of organ failure and death. Administration of activated protein C to critically ill patients has been shown to reduce organ failure and death and is thought to act, in part, via preservation of the microcirculation in vital organs.



### Starvation

During starvation, the body is faced with an obligate need to generate glucose to sustain cerebral energy metabolism (100 g of glucose day<sup>-1</sup>). This is achieved in the first 24 hours by mobilizing glycogen stores and thereafter by hepatic gluconeogenesis from amino acids, glycerol and lactate. The energy metabolism of other tissues is sustained by mobilising fat from adipose tissue. Such fat mobilisation is mainly dependent on a fall in circulating insulin levels. Eventually, accelerated loss of lean tissue (the main source of amino acids for hepatic gluconeogenesis) is reduced as a result of the liver converting free fatty acids into ketone bodies, which can serve as a substitute for glucose for cerebral energy metabolism.

Provision of at least 2 litres of intravenous 5% dextrose as intravenous fluids for surgical patients who are fasted provides 100 g of glucose day<sup>-1</sup> and has a significant protein-sparing effect.

### Immobility

Immobility has long been recognised as a potent stimulus for inducing muscle wasting. Inactivity impairs the normal meal-derived amino acid stimulation of protein synthesis in skeletal muscle. Avoidance of unnecessary bed rest and active early mobilisation are essential measures to avoid muscle wasting as a consequence of immobility.

### A proactive approach to prevent unnecessary aspects of the surgical stress response

- Minimal access techniques
- Blockade of afferent painful stimuli (e.g. epidural analgesia)
- Minimal periods of starvation
- Early mobilisation

*Mugdad fuad*