Body Response to Injury

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Introduction :

The inflammatory response to injury or infection occurs as a consequence of the local or systemic release of "pathogen associated"

or "damage-associated" molecules, which use similar signaling pathways to mobilize the necessary resources required for the restoration of homeostasis.

Basic Concepts :

- Homeostasis is the foundation of normal physiology
- 'Stress-free' perioperative care helps to preserve homeostasis following elective surgery
- Resuscitation, surgical intervention and critical care can return the severely injured patient to a situation in which homeostasis becomes possible once again

THE GRADED NATURE OF THE INJURY RESPONSE :

It is important to recognize that the response to injury is graded , the more severe the injury, the greater the response. there may be a transient and modest rise in temperature, heart rate, respiratory rate, energy expenditure and peripheral white cell count. resulting in a systemic inflammatory response syndrome

(SIRS) , hypermetabolism, marked catabolism, shock and even multiple organ dysfunction (MODS) .

MEDIATORS OF THE METABOLIC RESPONSE TO INJURY:

The classical neuroendocrine pathways of the stress responseconsist of afferent nociceptive neurones, the spinal cord, thalamus, hypothalamus and pituitary .Corticotrophin releasingfactor (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. There are, however, many other players, including alterations in insulin release and sensitivity, hypersecretion of prolactin and growth hormone (GH) in the presence of low circulatory insulin-like growth factor-1 (IGF-1) and inactivation of peripheral thyroid hormones and gonadal function.Of note, GH has direct lipolytic, insulin-antagonising and proinflammatory properties.

In summary :

The neuroendocrine response to severe injury/critical illness is
biphasic:

_ **Acute phase** characterised by an actively secreting pituitary and elevated counter-regulatory hormones

(cortisol, glucagon, adrenaline). Changes are thought to be
beneficial for short-term survival

- **Chronic phase** associated with hypothalamic suppression
and low serum levels of the respective target organ hormones. Changes contribute to chronic wasting.

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 Proinflammatory cytokines including interleukin-1 (IL-1), tumour necrosis factor alpha (TNF_), 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. Proinflammatory cytokines also play a complex
role in the development of peripheral insulin resistance.
Other important proinflammatory mediators include nitric oxide
((NO) via inducible nitric oxide synthetase (iNOS)) and a variety
of prostanoids (via cyclo-oxygenase-2 (Cox-2)). Changes in
organ function (e.g. renal hypoperfusion/impairment) may be
induced by excessive vasoconstriction via endogenous factors
such as endothelin-1.
results in immunosuppression and an increased susceptibility

to opportunistic (nosocomial) infection.

Systemic inflammatory response syndrome following major injury

_ Is driven initially by proinflammatory 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.

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

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.

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 hypovolaemia, decreased basal metabolic

rate, reduced cardiac output, 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.

Following resuscitation, the ebb phase evolves into a hypermetabolic flow phase, which corresponds to 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 tissue oedema (from vasodilatation and increased capillary leakage), increased basal metabolic rate (hypermetabolism), increased cardiac output, raised body temperature, leukocytosis, increased oxygen consumption and 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 TNF_) 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.

KEY CATABOLIC ELEMENTS OF THE FLOW PHASE OF THE METABOLIC STRESS RESPONSE :

Hypermetabolism:

The majority of trauma patients (except possibly those with extensive burns) demonstrate energy expenditures approximately 15–25 per cent above predicted healthy resting values.
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Alterations in skeletal muscle protein Metabolism :

Muscle protein is continually synthesised and broken down with a turnover rate in humans of 1–2 per cent per day. Under normal circumstances, synthesis equals breakdown and muscle

bulk remains constant . 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; 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.

Skeletal muscle wasting

_ Provides amino acids for the metabolic support of central
organs/tissues

Alterations in hepatic protein metabolism: the acute phase protein response :

The liver and skeletal muscle together account for >50 per
cent of daily body protein turnover. Skeletal muscle has a large
mass but a low turnover rate (1–2 per cent per day), whereas
the liver has a relatively small mass (1.5 kg) but a much higher
protein turnover rate (10–20 per cent per day).
In response to inflammatory conditions, including surgery,
trauma, sepsis, cancer or autoimmune conditions, circulating
peripheral blood mononuclear cells secrete a range of proinflammatory

cytokines, including IL-1, IL-6 and TNF_. These cytokines, in particular IL-6, promote the hepatic synthesis of positive acute phase proteins, e.g. fibrinogen and C-reactive protein (CRP).

Hepatic acute phase response

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

_ **Positive** reactants (e.g. CRP): increase plasma concentration _

_ **Negative** reactants (e.g. albumin): decrease 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 proinflammatory 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.

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
Critically ill patients admitted to the ICU with severe sepsis
or major blunt trauma undergo massive changes in body composition
. Body weight increases immediately on
resuscitation with an expansion of extracellular water by 6–10
litres within 24 hours. Thereafter, even with optimal metabolic
care and nutritional support, total body protein will diminish by
15 per cent 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.

AVOIDABLE FACTORS THAT COMPOUND THE RESPONSE TO

INJURY:

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 three-fold 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, leukocytes, 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 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 per day). This is achieved in the first 24 hours by mobilising
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 2 litres of intravenous
5 per cent dextrose as intravenous fluids for surgical patients who
are fasted provides 100 g of glucose per day and has a significant
protein-sparing effect. Avoiding unnecessary fasting in the first
instance and early oral/enteral/parenteral nutrition form the
platform for avoiding loss of body mass as a result of the varying
degrees of starvation observed in surgical patients. Modern
guidelines on fasting prior to anaesthesia allow intake of clear
fluids up to 2 hours before surgery. Administration of a carbohydrate
drink at this time reduces perioperative anxiety and thirst
and decreases postoperative insulin resistance.

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

Current understanding of the metabolic response to surgical injury and the mediators involved has led to a reappraisal of traditional perioperative care. There is now a strong scientific rationale for avoiding unmodulated exposure to stress, prolonged fasting and excessive administration of intravenous (saline) fluids .The widespread adoption of minimal access (laparoscopic) surgery is a key change in surgical practice that can reduce the magnitude of surgical injury and enhance the rate of patients' return to homeostasis and recovery. It is also decreases

tant to realise that modulating the stress/inflammatory response at the time of surgery may have long-term sequelae over periods of months or longer. For example, _-blockers and statins have recently been shown to improve long-term survival after major surgery. It has been suggested that these effects may be due to suppression of innate immunity at the time of surgery. Equally, the use of epidural analgesia to reduce pain, block the cortisol stress response and attenuate postoperative insulin resistance may, via effects on the body's protein economy, favourably affect many of the patient-centred outcomes that are important to postoperative recovery but have largely been unmeasured to date, such as functional capacity, vitality and ability to return to work.