Surgery: a stressful business

Over the years the surgical stress response and the efforts to modify it have been the subject of a great deal of research. Most recently this has led to the development of 'enhanced recovery' programmes which are revolutionizing perioperative patient care across the UK.

The stress response is the term used to describe the widespread hormonal, metabolic and immunological changes observed in patients following trauma or injury. In modern medicine a traumatic trigger for the stress response is surgery.

How the body responds to injury has been of interest to scientists and clinicians for many years and there has been much research in this area. It was nearly 80 years ago that Sir David P Cuthbertson, a clinical biochemist, first described the metabolic disturbances he observed in patients with limb injuries (Cuthbertson, 1932). He demonstrated that following injury such patients exhibited an increased loss of nitrogen in their urine, which peaked at 3–8 days. By combining this finding with measurements of the urinary potassium, sulphur and phosphate levels he concluded that the increased nitrogen excreted could not have derived solely from the tissue damaged by injury. He surmised that the traumatic injury had stimulated a net protein catabolism and the increased nitrogen excreted derived from the breakdown of skeletal muscle. It was from his early work that the concept of 'ebb' and 'flow' developed, used to describe the initial decrease and subsequent increase in metabolic activity following trauma or surgery.

Over the following decades the endocrine and metabolic responses to many different types of surgery have been described. It has become widely accepted that the stress response probably developed to give injured animals the best conditions in which to survive their wounds and recover. However, it has been argued that this response is not necessary in the context of modern surgical practice and that it may in fact be detrimental. For this reason, there has been much interest in looking at ways of modifying or inhibiting the stress response to surgery – including the use of different surgical approaches, anaesthetic agents, regional techniques with neural blockade, nutrition and physiotherapy.

In the 1990s Professor Henrik Kehlet, a Danish gastrointestinal surgeon, postulated that by minimizing the stress of anaesthesia and surgery one might be able to speed up patients' postoperative recovery times and reduce their morbidity and mortality following colorectal surgery (Kehlet, 1991). He pioneered the concept of a 'multimodal surgical approach' involving the use of a programme of evidence-based interventions across the perioperative period with the intention of modifying the stress response and thereby improving patient outcomes (Kehlet, 1997). This approach has evolved and now forms the basis of today's 'enhanced recovery programmes' which have been proven to reduce postoperative length of stay and complications in patients undergoing elective colorectal surgery (Varadhan et al, 2010a) and are showing evidence of producing the same results in other specialties such as urological (Arumainayagam et al, 2008) and orthopaedic surgery (Husted and Holm, 2007).

In addition to the endocrine and metabolic elements of the stress response, research over recent years has investigated the immunological response to surgical trauma and the role of cytokines and leucocytes. Most recently, in oncological surgery, it has been postulated that the surgical stress response and in particular the changes in cell-mediated immunity may influence the incidence of metastases and recurrence, thus altering long-term survival rates (Gottschalk et al, 2010; Snyder and Greenberg, 2010). To date the evidence to support this theory is extremely limited and it is worth remembering the previous controversy over the role of allogeneic blood transfusions in cancer recurrence. It had been thought that patients who received perioperative allogeneic blood transfusion at the time of their curative resection surgery were at higher risk of recurrence because of the immunosuppressive effects of the transfusion. However, a meta-analysis of the evidence carried out in the late 1990s (McAlister et al, 1998) failed to support this. While further work is needed to investigate whether modification of the stress response can indeed decrease the tumour recurrence rates and improve overall survival from cancer, it is an exciting area of future research.

This article summarizes the main endocrine, metabolic and immunological changes that form the stress response and discusses how they are affected by different surgical and anaesthetic techniques.

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The neuroendocrine response to surgery

The surgical stimulus triggers two initial pathways: the release of cytokines and inflammatory mediators from the damaged tissues and the stimulation of afferent

neurones which carry information centrally. It is important to note that these two pathways are not distinct and there is significant interaction between them. Both pathways lead to activation of the central effectors of the stress response: the locus coeruleus–noradrenergic or sympathetic systems situated in the brainstem and the hypothalamic release of corticotrophin-releasing hormone (O'Connor et al, 2000). A positive feedback mechanism exists between these two systems such that activation of one leads to activation of the other.

The activation of the locus coeruleus–noradrenergic results in stimulation of the sympathetic nervous system and increased secretion of catecholamines from pre-synaptic nerve terminals and the adrenal medulla. This produces the characteristic tachycardia and hypertension seen in response to trauma. Circulating catecholamines also act on receptors situated in certain visceral organs to modify their function (Desborough, 2000).

One such organ is the pancreas, where increased α-adrenergic stimulation inhibits the secretion of the peptide hormone insulin from its β cells. Insulin is an anabolic hormone which promotes the uptake of glucose into muscle and adipose tissue and its subsequent conversion into glycogen. Insulin also inhibits the catabolism of protein and lipid.

Corticotrophin-releasing hormone and the hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal axis describes the complex set of interactions and feedback mechanisms that occur between the hypothalamus, the pituitary gland and the adrenal (or supra-renal) glands. It regulates many processes within the body and its activity is increased during the stress response (Desborough and Hall, 1993).

Via the mechanisms outlined above, surgical stress stimulates the hypothalamus to release increased amounts of corticotrophin-releasing hormone, which in turn stimulates the anterior pituitary gland to produce adrenocorticotrophic hormone (O'Connor et al, 2000). Adrenocorticotrophic hormone then acts on the adrenal cortex to increase the secretion of glucocorticoids, principally cortisol.

Plasma cortisol levels increase rapidly following surgical incision, peaking at 4–6 hours (Desborough, 2000). Under normal circumstances high plasma cortisol levels inhibit the secretion of adrenocorticotrophic hormone, thereby forming a negative-feedback control mechanism. This control mechanism is disrupted in the stress response. Cortisol promotes gluconeogenesis in the liver, lipolysis and protein breakdown. In addition it inhibits the uptake of glucose by cells, leading to an overall increase in plasma glucose levels. Cortisol also inhibits the inflammatory response to trauma (O'Connor et al, 2000).

In addition to adrenocorticotrophic hormone, the anterior pituitary secretes increased amounts of two other hormones during the stress response – growth hormone and prolactin.

Growth hormone is important in the regulation of growth, especially in childhood. It stimulates the production of peptide hormones, termed insulin-like growth factors, from the liver and skeletal muscle (Desborough and Hall, 1993). The metabolic effects of growth hormone are to increase lipolysis and glycogenolysis and inhibit glucose uptake into cells, thereby increasing the amount available for use by neurones.

Prolactin stimulates milk production from the breast following pregnancy. Secretion of prolactin is increased as part of the stress response but it has little metabolic activity and its role is unclear (Desborough, 2000).

The posterior pituitary also plays a role in the stress response, secreting increased amounts of arginine vasopressin (antidiuretic hormone).

The metabolic consequences

The overall metabolic effect of the endocrine changes outlined is to produce a 'catabolic state' post surgery.

Catecholamines and cortisol stimulate both hepatic glycogenolysis and gluconeogenesis. In addition insulin secretion is decreased and there is an increase in peripheral insulin resistance. The increase in carbohydrate catabolism coupled with the decrease in glucose uptake into cells produces a marked rise in plasma glucose concentration post surgery. The degree of plasma glucose concentration increase is related to the severity of the surgery, being less marked following minor surgery (Desborough, 2000).

Cortisol also stimulates the catabolism of protein – principally skeletal muscle. The amino acids produced can then be used in the liver to produce acute phase proteins, glucose, fatty acids and ketone bodies. The increased catabolism of protein leads to an increased urinary nitrogen concentration, as demonstrated by Cuthbertson (1932).

There is also an increase in the catabolism of stored fat. Under the influence of cortisol, catecholamines and growth hormone, triglycerides are converted to glycerol and fatty acids. Glycerol is a substrate for gluconeogenesis in the liver. Fatty acids may undergo β-oxidation to produce acetyl-coenzyme A which can then be used in the Krebs cycle to produce energy. Alternatively they may be converted to ketone bodies or re-esterified.

Finally, water and electrolyte metabolism is affected, principally under the influence of arginine vasopressin released from the posterior pituitary which acts directly on the kidney to promote water retention and concentrate the urine. In addition the renin–angiotensin–aldosterone system is activated, partly as a result of increased sympathetic activity, leading to further sodium and water reabsorption from the distal tubules of the nephrons (Desborough, 1999).

Inflammation, cytokines and the acute phase response

The inflammatory response to injury produces the well-recognized clinical findings of swelling, erythema and pain. But how is this mediated at a molecular level? Activated leucocytes, fibroblasts and endothelial cells from the damaged tissues produce a number of low molecular weight proteins termed 'cytokines' (Sheeran and Hall, 1997). In addition to stimulating the hypothalamic–pituitary–adrenal axis, they play a major role in mediating inflammation and immunity.

Cytokines are small protein molecules that are used for cell signalling. They act on surface receptors located on specific target cells to produce their effects. In the surgical stress response the principal cytokines secreted are interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), although many other cytokines are subsequently released (Sheeran and Hall, 1997).

IL-1β and TNF-α are among the earliest mediators of inflammation. They are released from activated macrophages and monocytes in the damaged tissues. Their main actions are to induce cell proliferation, differentiation and apoptosis, stimulating the production and release of further cytokines.

One of the most important of these cytokines is IL-6. Often undetectable preoperatively, it rises quickly reaching a peak plasma concentration at 24 hours postoperatively (Desborough, 2000). The production of IL-6 is proportional to the degree of tissue trauma, with the highest rises in plasma concentration coming after major procedures such as colorectal or vascular surgery. Laparoscopic colorectal surgery has been shown to stimulate significantly lower production of IL-6 than the equivalent open procedure (Sammour et al, 2010). IL-6 is pro-inflammatory and it is involved in the final differentiation of B-cells into antibody-forming cells (plasma cells). It also acts in the liver to stimulate acute phase protein synthesis (acute phase response – see below). By stimulating the release of IL-10 (which inhibits the release of IL-1β and TNF-α)(Jerin et al, 2003), IL-6 also performs an anti-inflammatory function.

The 'acute phase response' describes the systemic changes that occur following tissue injury. A major element of this is the synthesis in the liver of acute phase proteins including C-reactive protein, α2-macroglobulin and α-1-antitrypsin. These proteins perform a number of different functions, for example C-reactive protein acts as an opsonin facilitating the identification and destruction of cells and/or microbes by the immune system, α2-macroglobulin inhibits thrombin thereby affecting coagulation, α-1-antitrypsin provides negative feedback for the inflammatory response (Sheeran and Hall, 1997).

The production of a number of other proteins is down-regulated in the acute phase response. Notable among these is albumin and transferrin. The decrease in production provides amino acids for the synthesis of the other acute phase proteins. These changes in production of important transport proteins bring about changes in the concentrations of cations such as zinc, iron and copper.

Cell-mediated immunity and the stress response

Cell-mediated immunity refers to the component of the immune system consisting of activated macrophages, T cells and natural killer cells. Their functions include both the phagocytosis and killing of intracellular pathogens and the direct killing of cells. These are particularly important for destroying intracellular bacteria, eliminating viral infections and destroying tumour cells (Snyder and Greenberg, 2010).

Following surgery there is significant suppression of cell-mediated immunity mediated in part by high circulating levels of plasma cortisol. Immunosuppression begins within hours of surgery and may last for several days. It is proportional to the extent of surgical trauma (Page, 2005).

The suppression of cell-mediated immunity during the stress response may have specific implications in the field of oncological surgery where it has been suggested that it may lead to an increased risk of metastasis and subsequent cancer recurrence. However, this theory remains controversial and much further research is required.

Although the primary role of the stress response following surgery is to promote healing and recovery, overactivity or underactivity of this response may lead to detrimental consequences for the individual. Variations in both surgical and anaesthetic technique can affect the magnitude of the stress response.

Modifying the stress response

The magnitude of the stress response following surgery is dependent on multiple factors including the type of surgery, type of anaesthetic, analgesia, the integrity of the patient's immune system and the presence of patient comorbidities. An exaggerated stress response following surgery has been associated with a worse prognosis and increased risk of postoperative complications (Kehlet, 1997). For this reason there has been a great deal of interest in the modification of the stress response with the hope of improving surgical outcome.

Modifying the neuroendocrine response

Opioid analgesics have long been known to suppress the hypothalamic–pituitary–adrenal axis and there has been work demonstrating this in both abdominal and cardiac surgery. However, the doses required to produce effective suppression are extremely high and produce undesirable side effects (e.g. prolonged respiratory depression). Even with high doses it is not possible to completely suppress the hormonal response in upper abdominal surgery (Desborough, 2000).

Clonidine is an α2-agonist which has sympatholytic activity. In this way it inhibits the stress response mediated by the sympathetic nervous system. It may also produce hypotension and prolonged sedation which is not always desirable.

Regional anaesthesia, particularly central neuraxial blockade (epidural or spinal anaesthetic), has been shown to prevent both the neuroendocrine and metabolic responses to lower abdominal or pelvic surgery. However, it is not possible to completely suppress these responses in upper abdominal or thoracic surgery in the same way (Desborough, 2000).

Modifying the inflammatory response

Laparoscopic or minimally invasive surgical techniques produce less tissue trauma and have been shown to significantly reduce the inflammatory response following surgery when compared with the equivalent open techniques (Sammour et al, 2010). In addition they are associated with less postoperative pain and earlier mobilization which may further reduce the magnitude of the inflammatory response. However, the neuroendocrine and metabolic responses in laparoscopic or minimally invasive abdominal surgery (catecholamines, cortisol) are not greatly reduced.

Perioperative high-dose steroids have been used to attenuate the stress response (Scmidt et al, 2007), producing reductions in TNF-α, IL-6, IL-8 and C-reactive protein. However, such regimens have been associated with increased wound breakdown.

In addition to these measures improved perioperative nutrition, in particular the administration of a carbohydrate-rich drink in the hours before surgery, has been shown to modify the stress response by reducing postoperative insulin resistance (Soop et al, 2001). Effective analgesia, especially with regional techniques which avoid the unwanted side effects of opioids such as nausea, vomiting and decreased gut motility, can reduce the stress response postoperatively (Kehlet, 1997; Desborough, 2000).

Other interventions that have been studied are perioperative counselling, acupuncture and music therapy although there is less firm evidence to support these.

'Enhanced recovery'

The realization that the stress response may be modified by various individual interventions has led to the development of the concept of 'enhanced recovery'. Enhanced recovery programmes bring together a number of evidence-based interventions throughout the perioperative period with the intention of modifying the stress response, decreasing morbidity and mortality, accelerating patient recovery and reducing length of hospital stay. They were originally developed for use in colorectal surgery where they have produced encouraging results and are now being implemented in a number of other surgical specialties nationwide. Some of the main elements necessary for an enhanced recovery programme are summarized in *Table 1*.

Conclusions

The surgical stress response comprises a network of interrelated hormonal, metabolic, inflammatory and immunological responses. Their relationship with one another is complex and still not completely understood, but the net effect of the stress response is to produce an increase in the catabolism of energy storage molecules. By producing an increase in available fuel it facilitates the subject's recovery at a molecular level.

However, an exaggerated stress response can lead to immunosuppression and the development of the systemic inflammatory response syndrome which may in fact be detrimental to the patient's recovery from surgery and lead to an increased risk of developing postoperative complications.

For this reason there has been a great deal of interest in developing ways of modifying the stress response via changing surgical techniques and anaesthetic and analgesic regimens. This led to the development of the 'multimodal surgical approach' which now forms the basis of today's enhanced recovery programmes. Enhanced recovery has shown significant clinical benefits in colorectal surgery, reducing postoperative complications and improving outcomes. Further work is needed to show whether this approach can be applied to other surgical specialties to produce the same results.

As our understanding of the immune system and its interactions grows so will our appreciation of the potential influence of perioperative events on its integrity – an area which is likely to be the focus of a great deal of research in the future. **BJHM**

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KEY POINTS

- The surgical stress response comprises characteristic hormonal, metabolic and immunological changes.
- An exaggerated stress response may be detrimental to the patient and increase the incidence of complications and poor outcome.
- Research has shown that the stress response may be modified by numerous different interventions across the perioperative period.
- Enhanced recovery programmes use a multidisciplinary approach to bring together many of these interventions and optimize patient care.

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Table 1. Elements of an enhanced recovery programme, the rationale for their use and how they modify the stress response

Enhanced recovery element	Rationale	Potential impact on stress response
Preoperative information and counselling	Giving patient a clear understanding of what to expect and outlining specific preset targets, giving them a more active role in their recovery, helps to reduce anxiety	Reduction in anxiety reduces circulating catecholamines
Preoperative nutritional support	Malnourishment is common in the hospital population and predisposes patients to develop postoperative complications	Improving patients' nutritional status may reduce the impact of postoperative catabolism and improve immune function
Minimize preoperative fasting	Fasting increases patient anxiety and discomfort and predisposes them to metabolic stress	Reduction in postoperative insulin resistance and metabolic disturbance
Carbohydrate preload	Preoperative carbohydrate load reduces the preoperative fasting time, improves patient wellbeing and promotes early return of gut function	Reduction in postoperative insulin resistance and metabolic disturbance
Avoid bowel preparation	Bowel preparation causes dehydration and electrolyte disturbance	Reduction in metabolic disturbance
Prophylactic antibiotics	Minimize the risk of infectious complications	Development of a postoperative infection may exacerbate the catabolic and inflammatory responses as well as impair immune function
Venous thromboembolism prophylaxis	Venous thromboembolism is associated with prolonged hospitalization and increased morbidity	Development of postoperative complications exacerbates the stress response
Regional anaesthetic techniques	Appropriate regional techniques provide effective anaesthesia and analgesia while avoiding the potential complications of opioids – nausea, vomiting, decreased gut motility, hallucination	Regional techniques (especially central neuraxial blockade) reduce the endocrine and metabolic response
Avoid hypothermia	Hypothermia increases the risk of wound infections, bleeding and cardiac complications	Hypothermia stimulates the release of catecholamines, stimulating the stress response
Targeted fluid therapy	Sodium and fluid overload delays the return of gut function, increases the incidence of complications	Reduction in metabolic disturbance. Avoiding complications reduces the subsequent exacerbation of the stress response
Minimally invasive surgery	Smaller incisions produce less tissue damage and pain facilitating early mobilization, early return of gut function and reduced complications	Decreased inflammatory response compared with open procedures
Opioid-sparing analgesic regimens	Postoperative pain is stressful and unpleasant for the patient. Analgesic regimens must be effective, but opioid analgesics are associated with a number of undesirable side effects. Regional anaesthetic techniques can produce effective analgesia while reducing opioid requirements	Reduction of endocrine and metabolic response through use of regional anaesthetic techniques and decreasing likelihood of postoperative ileus
Aggressive treatment of postoperative nausea and vomiting	Postoperative nausea and vomiting is stressful for the patient, decreases the ability to take oral nutrition and increases the risk of developing postoperative ileus	Reduction endocrine and metabolic response
Early oral nutrition	Promotes return of gut function and improves nutrition, decreasing the chance of complications	Reduction in metabolic response
Early mobilization	Decreases risk of venous thromboembolism and pulmonary dysfunction. Increases muscle strength	Decreases insulin resistance. Development of postoperative complications exacerbates the stress response

From Varadhan et al (2010b)