The stress response to trauma and surgery

J. P. Desborough

Department of Anaesthesia, Epsom General Hospital, Dorking Road, Epsom KT18 7EG, UK

Br J Anaesth 2000; **85**: 109–17

Keywords: surgery; hormones, cortisol; sympathetic nervous system, catecholamines; anaesthetic techniques, epidural

The stress response is the name given to the hormonal and metabolic changes which follow injury or trauma. This is part of the systemic reaction to injury which encompasses a wide range of endocrinological, immunological and haematological effects (Table 1). The responses to surgery have been of interest to scientists for many years. In 1932, Cuthbertson described in detail the metabolic responses of four patients with lower limb injuries.[10] He documented and quantified the time course of the changes. The terms 'ebb' and 'flow' were introduced to describe an initial decrease and subsequent increase in metabolic activity. The description of the 'ebb' phase was based partly on work in experimental animals and the estimations of increases in metabolic rate in the 'flow' phase were exaggerated. These descriptions have been perpetuated and are still quoted, but have been redefined[29] and are perhaps not critical to an understanding of the actual changes which occur.

After the early work on the stress response to accidental injury, attention turned to surgical trauma, and responses to most types of surgery were reported. Following on from this, the ability of anaesthetic agents and neural blockade to modify the endocrine and metabolic responses has been studied enthusiastically. Although it seems that the stress response developed to allow injured animals to survive by catabolizing their own stored body fuels, it has been argued that the response is unnecessary in current surgical practice. Strenuous efforts have been made to inhibit the stress responses to surgery and evaluate the outcome. In particular, the potential benefits of regional anaesthesia on surgical outcome are still under scrutiny. Over the past 10 yr, the role of cytokines in the response to surgery, and the interaction between the immunological and neuroendocrine systems, has furthered interest in the subject. This review describes the endocrine and metabolic changes which occur during surgery, and the effects of anaesthetic and analgesic regimens upon the responses.

Table 1 Systemic responses to surgery

Sympathetic nervous system activation
Endocrine 'stress response'
pituitary hormone secretion
insulin resistance
Immunological and haematological changes
cytokine production
acute phase reaction
neutrophil leucocytosis
lymphocyte proliferation

The endocrine response to surgery

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system.[13] The changes in pituitary secretion have secondary effects on hormone secretion from target organs (Table 2). For example, release of corticotrophin from the pituitary stimulates cortisol secretion from the adrenal cortex. Arginine vasopressin is secreted from the posterior pituitary and has effects on the kidney. In the pancreas, glucagon is released and insulin secretion may be diminished. The overall metabolic effect of the hormonal changes is increased catabolism which mobilizes substrates to provide energy sources, and a mechanism to retain salt and water and maintain fluid volume and cardiovascular homeostasis.

Table 2 Principal hormonal responses to surgery. ACTH, adrenocorticotrophic hormone (corticotrophin); AVP, arginine vasopressin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone. Based on Desborough and Hall[13]

Endocrine gland	Hormones	Change in secretion
Anterior pituitary	ACTH	Increases
	Growth hormone	Increases
	TSH	May increase or decrease
	FSH and LH	May increase or decrease
Posterior pituitary	AVP	Increases
Adrenal cortex	Cortisol	Increases
	Aldosterone	Increases
Pancreas	Insulin	Often decreases
	Glucagon	Usually small increases
Thyroid	Thyroxine, tri-iodothyronine	Decrease

Sympathoadrenal response

Hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from presynaptic nerve terminals. Norepinephrine is primarily a neurotransmitter, but there is some spillover of norepinephrine released from nerve terminals into the circulation. The increased sympathetic activity results in the well recognized cardiovascular effects of tachycardia and hypertension. In addition, the function of certain visceral organs, including the liver, pancreas and kidney, is modified directly by efferent sympathetic stimulation and/or circulating catecholamines.

The hypothalamic–pituitary–adrenal axis

Anterior pituitary

Anterior pituitary hormone secretion is stimulated by hypothalamic releasing factors.[32] The pituitary synthesizes corticotrophin or adrenocorticotrophic hormone (ACTH) as part of a larger precursor molecule, pro-opiomelanocortin. The precursor is metabolized within the pituitary into ACTH, β-endorphin and an N-terminal precursor. Growth hormone and prolactin are also secreted in increased amounts from the pituitary in response to a surgical stimulus. Concentrations of the other anterior pituitary hormones, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) do not change markedly during surgery.

Posterior pituitary

The posterior pituitary produces arginine vasopressin which has a major role as an antidiuretic hormone. It also has an endocrine function, acting with corticotrophin-releasing factor in stimulating the secretion of pro-opiomelanocortin from the anterior pituitary.

Corticotrophin

Corticotrophin (ACTH) is a 39 amino acid peptide, produced in the pituitary from the larger molecule, pro-opiomelanocortin. ACTH stimulates the adrenal cortical secretion of glucocorticoids so that circulating concentrations of cortisol are increased. Surgery is one of the most potent activators of ACTH and cortisol secretion, and increased plasma concentrations of both hormones can be measured within minutes of the start of surgery.

Growth hormone

Growth hormone is a protein of 191 amino acids secreted from the anterior pituitary.[13] Its release is stimulated by growth hormone releasing factor from the hypothalamus. Growth hormone, also known as somatotrophin, has a major role in growth regulation, particularly in the perinatal period and in childhood. Many of its actions are mediated through small protein hormones called insulin-like growth factors (IGFs), notably IGF-1, which is produced in liver, muscle and other tissues in response to stimulation by growth hormone. In addition to the regulation of growth, growth hormone has many effects on metabolism. It stimulates protein synthesis and inhibits protein breakdown, promotes lipolysis (the breakdown of triglycerides into fatty acids and glycerol) and has an anti-insulin effect. This means that growth hormone inhibits glucose uptake and use by cells, which spares glucose for use by neurones in situations of glucose scarcity. Growth hormone may also stimulate glycogenolysis in the liver. Growth hormone secretion from the pituitary increases in response to surgery and trauma, in relation to the severity of the injury.

β-Endorphin and prolactin

β-Endorphin is an opioid peptide of 31 amino acids produced from the precursor molecule proopiomelanocortin. Increased β-endorphin concentrations in the circulation after surgery reflect increased pituitary hormone secretion. The hormone has no major metabolic activity.

Prolactin is a protein hormone of 199 amino acids with a structure similar to that of growth hormone. Secretion of prolactin is increased as part of the stress reponse to surgery and also during exercise. It has little metabolic activity. Prolactin production increases during pregnancy and stimulates milk secretion from the breast.

Cortisol

Cortisol secretion from the adrenal cortex increases rapidly following the start of surgery, as a result of stimulation by ACTH. From baseline values of around 400 nmol litre^{-1}, cortisol concentrations increase to a maximum at about 4–6 h, and may reach >1500 nmol litre^{-1} depending on the severity of the surgical trauma.[38] The cortisol response can be modified by anaesthetic intervention (see below).

Usually, a feedback mechanism operates so that increased concentrations of circulating cortisol inhibit further secretion of ACTH. This control mechanism appears to be ineffective after surgery so that concentrations of both hormones remain high.

Cortisol has complex metabolic effects on carbohydrate, fat and protein. It promotes protein breakdown and gluconeogenesis in the liver. Glucose use by cells is inhibited, so that blood glucose concentrations are increased. Cortisol promotes lipolysis, which increases the production of gluconeogenic precursors from the breakdown of triglyceride into glycerol and fatty acids.

Cortisol has other glucocorticoid effects, notably those associated with anti-inflammatory activity. Corticosteroids inhibit the accumulation of macrophages and neutrophils into areas of inflammation and can interfere with the synthesis of inflammatory mediators, particularly prostaglandins.

Insulin and glucagon

Insulin is the key anabolic hormone.[13] It is a polypeptide with two chains (of 21 and 30 amino acids) linked by two disulphide bridges. Insulin is synthesized and secreted by the β cells of the pancreas. It is released after food intake, when blood glucose and amino acid concentrations increase. Insulin promotes the uptake of glucose into muscle and adipose tissue and the conversion of glucose into glycogen and triglycerides. It also stimulates the formation of glycogen from glucose in the liver. Protein catabolism and lipolysis are inhibited by insulin.

Insulin concentrations may decrease after the induction of anaesthesia, and during surgery there is a failure of insulin secretion to match the catabolic, hyperglycaemic response. This may be caused partly by α-adrenergic inhibition of β cell secretion. In addition, there is a failure of the usual cellular response to insulin, the so-called 'insulin resistance', which occurs in the perioperative period.

Glucagon is produced in the α cells of the pancreas. This hormone promotes hepatic glycogenolysis. It also increases gluconeogenesis from amino acids in the liver and has lipolytic activity. Although plasma glucagon concentrations increase transiently after major surgery, this does not make a major contribution to the hyperglycaemic response.

Thyroid hormones

Thyroxine (T_4) and tri-iodothyronine (T_3) are secreted into the circulation from the thyroid gland under the influence of thyroid-stimulating hormone (TSH). Small amounts of inactive, reverse T_3 (rT_3) are produced from the thyroid. T_3 is formed in the tissues by the monodeiodination of T_4. T_3 is three to five times more active metabolically than T_4. The hormones are bound extensively to their binding proteins, albumin, thyroxine-binding pre-albumin and thyroid-binding globulin (TBG). The free thyroid hormones in the plasma are metabolically active. Very low concentrations of free T_3 and T_4 are present in the circulation and are in equilibrium with bound hormone in the plasma and the tissues.[15]

Thyroid hormones stimulate the oxygen consumption of most of the metabolically active tissues of the body. Notable exceptions are the brain, spleen and the anterior part of the pituitary gland. As a result of thyroid hormone activity, metabolic rate and heat production is increased. The other principal actions of thyroid hormones are to increase carbohydrate absorption from the gut, to stimulate both the central and peripheral nervous systems and, in the longer term, to influence growth and development.

There is a close association between the activity of thyroid hormones and the catecholamines. In general terms, epinephrine and norepinephrine increase the metabolic rate and stimulate the nervous system. The thyroid hormones increase the number and affininty of β-adrenoceptors in the heart and, ultimately, increase the sensitivity of the heart to the actions of catecholamines.

Concentrations of total and free T_3 decrease after surgery and return to normal after several days. TSH concentrations decrease during the first 2 h and then return to preoperative levels. The reason for the changes remains unclear, but may be influenced by the close relationship between thyroid hormones, catecholamines and cortisol. Exogenous steroids suppress T_3, so hypercortisolaemia after surgery may also depress T_3 concentrations.[11]

Gonadotrophins

The gondotrophins, LH and FSH, are secreted from the anterior pituitary. FSH is responsible for the development of ovarian follicles in females. In males, FSH maintains the spermatic epithelium.

LH stimulates growth and development of the Leydig cells of the testis which produce testosterone. In females, LH promotes maturation of the ovarian follicles and the secretion of oestrogen. It also stimulates the formation of the corpus luteum from the follicles after ovulation.

Testosterone is a steroid manufactured from cholesterol in the Leydig cells of the testis. It has a negative feedback effect on LH secretion from the anterior pituitary. It has important effects on protein anabolism and on growth, in addition to its well known role in the development and maintainance of male secondary sexual characteristics.

The significance of changes in pituitary gonadotrophins following surgery requires further study. Testosterone concentrations are decreased for several days, while LH concentrations show variable changes.[51] In female subjects, oestradiol concentrations decrease for up to 5 days postoperatively.[50]

Metabolic sequelae of the endocrine response

The net effect of the endocrine response to surgery is an increased secretion of catabolic hormones. This promotes the provision of food substrates from the catabolism of carbohydrate, fat and protein. In evolutionary terms, it seems likely that the stress response developed as a survival mechanism which allowed injured animals to sustain themselves until their injuries were healed. By using stored body fuels and retaining salt and water, the animal had a chance to survive without food until healing and repair had taken place. In current surgical and anaesthetic practice, it is questionable whether the stress response is necessary.

Carbohydrate metabolism

Blood glucose concentrations increase after surgery begins. Cortisol and catecholamines facilitate glucose production as a result of increased hepatic glycogenolysis and gluconeogenesis. In addition, peripheral use of glucose is decreased.

Blood glucose concentrations are related to the intensity of the surgical injury; the changes follow closely the increases in catecholamines. In cardiac surgery, blood glucose concentrations can increase up to 10–12 mmol litre^{-1} and remain elevated for >24 h after surgery. The changes are less marked with minor surgery.

The usual mechanisms that maintain glucose homeostasis are ineffective in the perioperative period. Hyperglycaemia persists because catabolic hormones promote glucose production and there is a relative lack of insulin together with peripheral insulin resistance.

In diabetic subjects it is now established that poor glycaemic control is associated with an increase in diabetic complications, which can be avoided with tight control of blood glucose[47] (see paper by Halls). The risks of prolonged perioperative hyperglycaemia are less well established, although potential risks include wound infection and impaired wound healing. An increased incidence of wound infection and mediastinitis was found in diabetics and non-diabetics in whom blood glucose concentrations were >200 mg dl^{-1} after cardiac surgery.[49]

Protein metabolism

Protein catabolism is stimulated by increased cortisol concentrations. Predominantly skeletal muscle is broken down, but some visceral muscle protein is also catabolized to release the constituent amino acids. The amino acids may be further catabolized for energy or used in the liver to form new protein, particularly acute-phase proteins. The liver also converts amino acids into other substrates, glucose, fatty acids or ketone bodies. Protein catabolism results in marked weight loss and muscle wasting in patients after major surgical and traumatic injury. The loss of protein can be measured indirectly by increased nitrogen excretion in the urine.

There has been much interest in the provision of nutritional supplements for patients with critical illness and those undergoing major surgery. Certain nutrients may have a beneficial influence on the immune status of stressed patients. Glutamine, arginine, glycine, ω-3 polyunsaturated fatty acids and nucleotides have been studied most extensively.[44] Glutamine and arginine are semi-essential amino acids with multiplicity of functions including stimulation of immune activity. Studies of patients given enteral nutrition supplemented with arginine or glycine after major surgery benefited from a faster recovery of immunological parameters, fewer infectious complications and a shorter hospital stay.[44]

Fat metabolism

As a result of hormonal changes during surgery, fats stored as triglycerides are converted by lipolysis to glycerol and fatty acids. Lipolytic activity is stimulated by cortisol, catecholamines and growth hormone and is inhibited in the presence of insulin. The net result is increased mobilization of triglyceride, although plasma concentrations of glycerol and fatty acids may not change markedly. The glycerol produced by lipolysis is a substrate for gluconeogenesis in the liver. Fatty acids enter a 'pool' from which they may be oxidized in the liver and in muscle, converted to ketone bodies or re-esterified.

Water and electrolyte metabolism

A number of hormonal changes occur in response to surgery which influence salt and water metabolism. These changes support the preservation of adequate body fluid volumes. Arginine vasopressin, which is released from the posterior pituitary, promotes water retention and the production of concentrated urine by direct action on the kidney. Increased vasopressin secretion may continue for 3–5 days, depending on the severity of the surgical injury and the development of complications.

Renin is secreted from the juxtaglomerular cells of the kidney, partly as a result of increased sympathetic efferent activation. Renin stimulates the production of angiotensin II. This has a number of important effects; in particular, it stimulates the release of aldosterone from the adrenal cortex, which in turn leads to Na^+ and water reabsorption from the distal tubules in the kidney.[11]

Activation of the stress response

The endocrine response is activated by afferent neuronal impulses from the site of injury. These travel along sensory nerve roots through the dorsal root of the spinal cord, up the spinal cord to the medulla to activate the hypothalamus.

In the 1950s it was postulated that there might be 'wound hormones' produced in injured tissues which activated the pituitary–adrenal axis. In classical experiments, Egdahl demonstrated the role of the nervous system in the activation of the stress response.[16] He studied the adrenocortical responses to limb injury in dogs with innervated and denervated extremities. Blood samples were collected from the adrenal vein for assay of adrenal corticosteroid concentration. In animals with an intact sciatic nerve, operative injury and burns to the limb resulted in an immediate and sustained increase in adrenal hormone concentration in samples from the adrenal vein. If the nerve was cut after the injury, there was a rapid decline in the hormone response. In those animals in which the sciatic nerve was transected before operative or burn injury, there was no increase in adrenal hormone after the trauma. This work did not provide evidence that local substances were released after injury which stimulated the pituitary–adrenal axis. The idea that local substances might influence some of the changes associated with surgery was advanced by the discovery of the cytokines.

Cytokines

Cytokines are a group of low-molecular-weight proteins which include the interleukins and interferons. They are produced from activated leucocytes, fibroblasts and endothelial cells as an early response to tissue injury and have a major role in mediating immunity and inflammation.[42] The cytokines act on surface receptors on many different target cells and their effects are produced ultimately by influencing protein synthesis within these cells. Details of the cytokine network and the activation of cytokines in response to surgery have been reviewed recently.[19 42] The effects of chronic stimulation of the cytokine network, for example, in sepsis, has also been reviewed.[6]

The cytokines have a major role in the inflammatory response to surgery and trauma. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some of the systemic changes which occur. After major surgery, the main cytokines released are interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α) and IL-6. The initial reaction is the release of IL-1 and TNF-α from activated macrophages and monocytes in the damaged tissues. This stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response.[42]

Interleukin-6

This is a 26 kDa protein. Concentrations of circulating cytokines are normally low and may be undetectable. Within 30–60 min after the start of surgery, IL-6 concentration increases; the change in concentration becomes significant after 2–4 h. Cytokine production reflects the degree of tissue trauma, so cytokine release is lowest with the least invasive and traumatic procedures, for example, laparoscopic surgery. The largest increases in IL-6 occur after major procedures such as joint replacement, major vascular and colorectal surgery. After these operations, cytokine concentrations are maximal at about 24 h and remain elevated for 48–72 h postoperatively.

The acute phase response

A number of changes occur following tissue injury which are stimulated by cytokines, particularly IL-6. This is known as the 'acute phase response'; one of its features is the production in the liver of acute phase proteins (Table 3). These proteins act as inflammatory mediators, anti-proteinases and scavengers and in tissue repair. They include C-reactive protein (CRP), fibrinogen, α_2-macroglobulin and other anti-proteinases. The increase in serum concentrations of CRP follows the changes in IL-6. Production of other proteins in the liver, for example, albumin and transferrin, decreases during the acute phase response. Concentrations of circulating cations such as zinc and iron decrease, partly as a consequence of the changes in the production of the transport proteins.[42]

Table 3 Features of the acute phase response. C, C-reactive protein. Based on Sheeran and Hall[42]

Fever
Granulocytosis
Production of acute phase proteins in liver
CRP
fibrinogen
α_2-macroglobulin
Changes in serum concentrations of transport proteins
increase in ceruloplasmin
decrease in transferrin, albumin and α_2-macroglobulin
Changes in serum concentrations of divalent cations
copper increases
zinc and iron decrease

Interaction between the immune system and the neuroendocrine system

The cytokines IL-1and IL-6 can stimulate secretion of ACTH from isolated pituitary cells *in vitro*. In patients after surgery, cytokines may augment pituitary ACTH secretion and subsequently increase the release of cortisol. A negative feedback system exists, so that glucocorticoids inhibit cytokine production. The cortisol response to surgery is sufficient to depress IL-6 concentrations.[20]

Minimally invasive surgery

Laparoscopic surgery causes less tissue injury than conventional procedures, so the increase in concentrations of biochemical markers of inflammation, such as IL-6 and the acute phase protein, CRP, is not as great.[21] The classical stress responses (catecholamines, cortisol and glucose) to abdominal surgery such as cholecystectomy, are not changed greatly by reducing surgical trauma. This suggests that stimuli for the stress response arise from visceral and peritoneal afferent nerve fibres in addition to those from the abdominal wall. Anaesthesia has little effect on the cytokine response to surgery because it cannot influence tissue trauma. Although regional anaesthesia inhibits the stress response to surgery, it has no significant effect on cytokine production. Combined analgesic regimens which included high-dose steroids showed a small decline in IL-6 concentrations and the acute phase response because of the interaction of glucocorticoids and cytokines.[41] The technique was accompanied by unwanted side-effects, including wound breakdown.

The effect of anaesthesia on the stress response to surgery

General anaesthesia

Opioids

It has been known for many years that opioids suppress hypothalamic and pituitary hormone secretion. McDonald and colleagues demonstrated the suppressant effect of

therapeutic doses of morphine on the hypothalamic–pituitary–adrenal axis in humans.[33] Morphine suppressed the release of corticotrophin and, consequently, cortisol in normal and stress conditions, although the adrenals were found to respond to exogenous administration of ACTH. The inhibitory effects of morphine occur at the hypothalamic level.

In cardiac surgery, the effects of morphine and other opioids on the stress response to surgery have been well documented.[12] Large doses of morphine (4 mg kg^{-1}) block the secretion of growth hormone and inhibit cortisol release until the onset of cardiopulmonary bypass (CPB). Fentanyl (50–100 μg kg^{-1}), sufentanil (20 μg kg^{-1}) and alfentanil (1.4 mg kg^{-1}) suppress pituitary hormone secretion until CPB.[12] After the onset of CPB, the physiological changes are so profound that the hypothalamic and pituitary responses cannot be completely inhibited by opioids. A high-dose opioid technique leads inevitably to respiratory depression after surgery, which requires ventilatory support to be provided for the patient in the postoperative period.

In lower abdominal surgery, fentanyl 50 μg kg^{-1} will suppress the growth hormone, cortisol and glycaemic changes found during pelvic surgery.[18] In this study, the opioid was administered during induction of anaesthesia. When fentanyl 50 μg kg^{-1} was given 60 min after the start of pelvic surgery, there was no significant effect on the endocrine response which was already established.[5] It was subsequently established that fentanyl 15 μg kg^{-1} was sufficient to inhibit cortisol and glucose responses to lower abdominal surgery.[26]

In upper abdominal surgery, systemic opioids are relatively ineffective in preventing the stress response to upper abdominal surgery. Fentanyl 100 μg kg^{-1} abolished completely the hormonal changes after conventional cholecystectomy, but the technique resulted in respiratory depression requiring ventilatory support in the postoperative period.[24]

Etomidate and benzodiazepines

The anaesthetic induction agent etomidate is a carboxylated imidazole that interferes with the production of steroids in the adrenal cortex by reversible inhibition of the enzyme 11β-hydroxylase and cholesterol side-chain cleavage enzyme. The synthesis of both aldosterone and cortisol is blocked. A single induction dose of the drug will suppress hormone production for 6–12 h,[48] while infusion for 1–2 h blocks cortisol synthesis for up to 24 h.[37] In healthy patients, there were no adverse cardiovascular effects from such an infusion during pelvic surgery, and the only metabolic result of cortisol inhibition was a decrease in the expected glycaemic response.[25]

The use of etomidate by infusion as part of intravenous sedation for critically ill patients was found to be associated with increased mortality.[27] As a result, the drug is no longer licensed for use in long-term sedation. A recent study has examined adrenocortical function in critically ill patients after induction of anaesthesia with etomidate or thiopental.[3] Pre-induction cortisol concentrations were measured and a short ACTH stimulation test was performed at 24 h to assess adrenal function. Cortisol concentrations before induction of anaesthesia were high, in keeping with other studies of adrenal function in critically ill patients. Those patients who received etomidate tended to have a smaller cortisol response to stimulation by ACTH than the control thiopental group. Although assessment of adrenocortical function in critically ill patients using single cortisol concentrations and ACTH stimulation tests is the subject of great controversy,[34] this study suggests that etomidate may interfere with cortisol synthesis in these patients.[3]

The benzodiazepine, midazolam, which has an imidazole ring in addition to the basic benzodiazepine structure, attenuates the cortisol responses to both peripheral and upper abdominal surgery.[9 14] Midazolam and diazepam both inhibit cortisol production from isolated bovine adrenocortical cells *in vitro.* Although Crozier and colleagues showed that subjects produced cortisol in response to exogenous ACTH,[9] thus confirming that the site of action of the benzodiazepine is at the hypothalamic–pituitary level, a direct inhibitory effect on steroid production cannot be excluded.

Clonidine

Clonidine is a centrally acting antihypertensive drug which activates α_2-adrenergic receptors.[1] It provides haemodynamic stability through its sympatholytic activity, and can reduce anaesthetic and analgesic requirements and provide sedation. By reducing the sympathoadrenal and cardiovascular responses caused by noxious surgical stimuli, the α_2-agonists inhibit the stress responses mediated by the sympathetic nervous system.

Regional anaesthesia

Extensive epidural analgesia with local anaesthetic agents will prevent the endocrine and metabolic responses to surgery in the pelvis and on the lower limbs. Epidural blockade from dermatomal segment T4 to S5, established before the start of surgery, prevented increases in cortisol and glucose concentrations in response to hysterectomy.[17] Both afferent input from the operative site to the central nervous system and the hypothalamic–pituitary axis, and efferent autonomic neuronal pathways to the liver and adrenal medulla are blocked. Thus the adrenocortical and glycaemic responses to surgery are abolished. Less extensive neural blockade will not completely abolish the hormonal and metabolic changes.

In upper abdominal or thoracic surgery, it is not possible to prevent pituitary hormone responses completely, even with extensive epidural local anaesthetic blockade. In a classical study by Bromage and colleagues, epidural block up to the C6 dermatome inhibited glycaemic changes but not the increases in cortisol concentrations in response to

upper abdominal and thoracic surgery.[7] Other studies confirm these findings. Many suggestions have been made to explain the failure to abolish completely the stress responses in these studies. Most of these centre around inadequate or incomplete afferent somatic and sympathetic neural blockade which allows pituitary activation and hence cortisol release from the adrenal cortex under the influence of ACTH, whilst efferent blockade of nerves to the adrenal medulla and the liver inhibits hyperglycaemic responses. Attempts were made subsequently to improve on the afferent blockade using vagal blockade, splanchnic nerve block or continuous intraperitoneal local anaesthetic, but no technique has abolished consistently the stress responses to upper abdominal or thoracic surgery.

Cardiac surgery

Perioperative thoracic epidural anaesthesia has been used successfully in the management of patients undergoing coronary artery bypass surgery.[28 46] Investigators have examined the effects of thoracic epidural analgesia on neuroendocrine secretion and on physiological variables. It is possible to prevent changes in catecholamine responses during CPB and up to 24 h after the start of cardiac surgery using thoracic epidural analgesia combined with general anaesthesia.[36] This cannot be achieved using opioid anaesthesia alone. The cortisol responses to CPB may also be attenuated using thoracic epidural analgesia, although studies show variable results.

Although there is no direct association between the attenuation of hormonal and metabolic responses and postoperative outcome, the use of thoracic epidural analgesia in cardiac surgery has many potential benefits in terms of improvements in organ function. Thoracic epidural anaesthesia provides intense analgesia, avoids the use of systemic opioids and improves postoperative pulmonary function.[28] It may reduce the incidence of thrombotic complications by decreasing the tendency towards hypercoagulability in the perioperative period.[45]

The myocardium-specific contractile protein, troponin T, is a highly specific biochemical marker of myocardial injury. Measurement of serum concentrations of the protein can be used to assess myocardial ischaemia. A recent study showed that thoracic epidural anaesthesia and general anaesthesia in cardiac surgery attenuated the myocardial sympathetic response and was associated with decreased myocardial damage as determined by less release of troponin T.[30] In medical patients, thoracic epidural analgesia has been used successfully to treat refractory angina. The sympatholytic effects of the blockade of cardiac sympathetic efferents and afferents may improve the balance of oxygen delivery and consumption. The use of thoracic epidural anaesthesia in patients with heart disease has been the subject of a recent review.[35]

Despite the potential benefits of thoracic epidural anaesthesia, there are specific cautions about the use of regional neural blockade in patients who are given anticoagulants because of the risk of epidural haematoma formation. Procedural guidelines may be used to minimize the risk of neurological complications.[3] Thoracic epidural anaesthesia is not without potential side-effects, which include possible cranial spread of the epidural block. This may lead to arm weakness, and apnoea may occur if the diaphragm is affected by blockade of nerve roots C3–C5. Testing of arm movements has been advocated to monitor cephalad spread of thoracic epidural anaesthesia.[2]

The stress response and surgical outcome

There has been a great deal of interest in the modification of the stress response with respect to the potential beneficial effects on surgical outcome. The extent to which the responses are modified depends on the choice of the analgesic techniques used. Inhibition of stress responses is greatest with neural blockade with local anaesthetics. Therefore attention has focused largely on the effects of regional anaesthetic and analgesic regimens, particularly epidural blockade with local anaesthetic agents. Individual studies show that provision of analgesia using neural blockade leads to improvements in physiological variables in specific organ systems. Single investigations often cannot show benefits in morbidity and mortality because the incidence of serious complications after surgery is generally low, and the numbers of patients studied is small. Meta-analysis is being used increasingly to demonstrate that regional analgesia has beneficial effects on surgical outcome.

Beneficial effects of regional analgesia

Thromboembolic complications

It is well established that regional analgesic techniques reduce the incidence of thromboembolic complications following surgery of the pelvis and lower limbs.[31] In upper abdominal procedures, there is not quite the same benefit in the incidence of thrombotic episodes.

Pulmonary function

Although it might be assumed that good analgesia with regional techniques should lead to decreased postoperative pulmonary complications, improvements in overall pulmonary outcome have not been demonstrated unequivocally. In single studies, pulmonary function has been shown to improve, and meta-analysis has found that continuous administration of epidural local anaesthetic decreases the incidence of pulmonary complications, whereas other techniques, including the use of systemic or epidural opioids, were less effective.[4]

Cardiac complications

Regional analgesia is very effective in tempering some of the cardiovascular responses to surgery which result from

sympathetic activation. Whether neural blockade techniques are more beneficial in terms of overall cardiac morbidity and outcome compared with other methods of pain relief has not been established.[22 31]

Gastrointestinal function

Continuous epidural analgesia at the thoracic level decreases paralytic ileus following abdominal procedures.[43] The use of local analgesia, or a combination of local and opioid analgesia, was more effective than either systemic or epidural opioids in preventing ileus. The elimination of ileus allows the early use of enteral nutrition which is an important factor in reducing the risk of infectious complications.[22]

Despite evidence that regional analgesia confers beneficial effects on organ function, improvements in overall postoperative morbidity and length of hospital stay have not been demonstrated conclusively. This is disappointing in view of the widespread introduction of acute pain services which consume time and resources. Of course, analgesia is provided for humanitarian reasons. Patient-controlled analgesia is popular and accepted by many patients, but has minimal effect on postoperative outcome.

Recovery from surgery

Many factors other than analgesic regimens influence recovery from major surgery and the ability of the patient to return home and resume work.[8] Surgical technique has an important role; laparoscopic procedures are associated with rapid recovery and early discharge from hospital. Other factors are also important, not least the expectations of patients and of the nursing and medical staff. Behavioural and subjective changes are part of the response to surgery. Feelings of malaise and postoperative fatigue have a strong influence on recovery from surgery and return to work. Salmon and Hall have developed a theory of postoperative fatigue which encompasses psychological and cultural mechanisms as well as physiological changes.[40] Postoperative fatigue is a complex multifactorial issue, and can be decreased in a number of ways including appropriate use of minimally invasive surgery and the avoidance of sleep disturbance. Such an 'intensive' approach is likely to be costly in terms of personnel but can be rewarded with early discharge from hospital.[22]

Kehlet advocates a 'multimodal' approach to accelerate postoperative recovery.[21] In addition to effective pain relief which allows normal function, other elements in patient management must be addressed. The use of minimally invasive surgical techniques, including laparoscopically assisted procedures, will reduce the effects of tissue injury. Postoperative nausea and vomiting and paralytic ileus should be avoided and enteral and oral feeding used. Early mobilization must be encouraged and is facilitated by good analgesia and the avoidance of tubes and drains. A rapid return to normal function has to be encouraged.

Conclusions

The stress response to surgery comprises a number of hormonal changes initiated by neuronal activation of the hypothalamic–pituitary–adrenal axis. The overall metabolic effect is one of catabolism of stored body fuels. In general, the magnitude and duration of the response are proportional to the surgical injury and the development of complications such as sepsis. Other changes also occur following surgery, notably an increase in cytokine production which is triggered locally as a tissue response to injury.

Regional anaesthesia with local anaesthetic agents inhibits the stress response to surgery and can also influence postoperative outcome by beneficial effects on organ function.

References

1 Aantaa R, Scheinin M. Alpha$_2$-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand* 1993; **37**: 1–16

2 Abd Elrazek E, Scott NB, Vohra A. An epidural scoring scale for arm movements [ESSAM] in patients receiving high thoracic epidural analgesia for coronary artery bypass grafting. *Anaesthesia* 1999; **54**: 1097–109

3 Absolom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia* 1999; **54**: 861–7

4 Ballantyne JC, Carr DB, deFerranti S. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* 1998; **86**: 598–612

5 Bent JM, Paterson JL, Mashiter K, Hall GM. Effects of high-dose fentanyl anaesthesia on the established metabolic and endocrine response to surgery. *Anaesthesia* 1978; **39**: 19–23

6 Blackwell TS, Christman JW. Sepsis and cytokines: current status. *Br J Anaesth* 1996; **77**: 110–17

7 Bromage PR, Shibata HR, Willoughby HW. Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon the upper part of the abdomen and thorax. *Surg Gynaecol Obstetr* 1971; **21**: 330–35

8 Chumbley GM, Hall GM. Recovery after major surgery: does the anaesthetic make any difference? *Br J Anaesth* 1997; **78**: 347–8

9 Crozier TA, Beck D, Schlager M, Wuttke W, Kettler D. Endocrinological changes following etomidate, midazolam or methohexital for minor surgery. *Anesthesiology* 1987; **66**: 628–35

10 Cuthbertson DP. Observations on the disturbance of metabolism produced by injury to the limbs. *Q J Med* 1932; **1**: 233–46

11 Desborough JP. Physiological responses to surgery and trauma. In: Hemmings HC Jr, Hopkins PM, eds. *Foundations of Anaesthesia*. London: Mosby, 1999: 713–20

12 Desborough JP, Hall GM. Modification of the hormonal and metabolic response to surgery by narcotics and general anaesthesia. *Clin Anaesthesiol* 1989; **3**: 317–34

13 Desborough JP, Hall GM. Endocrine response to surgery. In: Kaufman L. *Anaesthesia Review*, Vol. 10. Edinburgh: Churchill Livingstone, 1993; 131–48

14 Desborough JP, Hall GM, Hart GR, Burrin JM. Midazolam modifies pancreatic and anterior pituitary hormone secretion after upper abdominal surgery. *Br J Anaesth* 1991; **67**: 390–96

15 Edwards R. Thyroid and parathyroid disease. *Int Anesthesiol Clin* 1997; **35**: 63–83

16 Egdahl RH. Pituitary–adrenal response following trauma to the isolated leg. *Surgery* 1959; **6**: 9–21

17 Enquist A, Brandt MR, Fernandes A, Kehlet H. The blocking effect of epidural analgesia on the adrenocortcial and hyperglycaemic responses to surgery. *Acta Anaesthesiol Scand* 1977; **21**: 330–35

18 Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. A comparison with halothane anaesthesia. *Anaesthesia* 1978; **33**: 924–30

19 Helmy SAK, Wahby MAM, El-Nawaway M. The effect of anaesthesia and surgery on plasma cytokine production. *Anaesthesia* 1999; **54**: 733–8

20 Jameson P, Desborough JP, Bryant AE, Hall GM. The effect of cortisol suppression on the interleukin-6 and white cell responses to surgery. *Acta Anaesthesiol Scand* 1997; **40**: 123–6

21 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17

22 Kehlet H. Acute pain control and accelerated postoperative surgical recovery. *Surg Clin N Am* 1999; **79**: 431–43

23 Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg* 1999; **86**: 227–30

24 Klingstedt C, Giesecke K, Hamberger B, Janberg P-O. High- and low-dose fentanyl anaesthesia, circulatory and catecholamine responses during cholecystectomy. *Br J Anaesth* 1987; **59**: 184–8

25 Lacoumenta S, Paterson JL, Myers MA, Hall GM. Effects of cortisol suppression by etomidate on changes in circulating metabolites associated with pelvic surgery. *Acta Anaesthesiol Scand* 1986; **30**: 101–4

26 Lacoumenta S, Yeo TH, Burrin JM, Bloom SR, Paterson JL, Hall GM. Fentanyl and the β-endorphin, ACTH and glycoregulatory hormonal responses to surgery. *Br J Anaesth* 1987; **59**: 713–20

27 Ledingham IMA, Watt I. Influence of sedation on mortality in critically ill patients. *Lancet* 1983; **i**: 1270

28 Liem TH, Hasenbos MAWM, Booij LHDJ, Gielen MJM. Coronary artery bypass grafting using two different anaesthetic effects: Part 2: Postoperative outcome. *J Cardithorac Vasc Anesth* 1992; **6**: 156–61

29 Little RA, Girolami A. Trauma metabolism—ebb and flow revisited. *Br J Intensive Care* 1999; **9**: 142–6

30 Loick HM, Schmidt C, van Aken H *et al*. High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. *Anesth Analg* 1999; **88**: 701–9

31 Lui S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995; **82**: 1474–506

32 Lyons FM and Meeran K. The physiology of the endocrine system. *Int Anesthesiol Clin* 1997; **35**: 1–21

33 McDonald RK, Evans FT, Weise VK *et al*. Effect of morphine and nalorphine on plasma hydrocortisone levels in man. *J Pharmacol Exp Ther* 1959; **125**: 241–7

34 Masterson GR, Mostafa SM. Adrenocortical function in critical illness. *Br J Anaesth* 1998; **81**: 308–10

35 Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks and controversies. *Anesth Analg* 1997; **85**: 598–612

36 Moore CM, Cross MH, Desborough JP, Burrin JM, Macdonald IA, Hall GM. Hormonal effects of thoracic extradural analgesia for cardiac surgery. *Br J Anaesth* 1995; **75**: 387–93

37 Moore RA, Allen MC, Wood PJ, Rees LH, Sear JW, Feldman D. Peroperative endocrine effects of etomidate. *Anaesthesia* 1985; **40**: 124–30

38 Nicholson G, Hall GM, Burrin JM. Peri-operative steroid supplementation. *Anaesthesia* 1998; **53**: 1091–4

39 Rolf N, Mollhoff T. Epidural anaesthesia for patients undergoing coronary artery bypass grafting. *Curr Opin Anesthesiol* 1997: **10**: 17–20

40 Salmon P, Hall GM. A theory of postoperative fatigue. *J R Soc Med* 1997; **90**: 661–4

41 Schulze S, Sommer P, Bigler D *et al*. Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response to surgery. *Arch Surg* 1992; **127**: 325–31

42 Sheeran P, Hall GM. Cytokines in anaesthesia. *Br J Anaesth* 1997; **78**: 201–19

43 Steinbrook RA. Epidural anesthesia and gastrointestinal motility. *Anesth Analg* 1998; **86**: 837–44

44 Tepaske R. Immunonutrition. *Curr Opin Anaesthesiol* 1997; **10**: 86–91

45 Tuman KJ, McCarthy RJ, March R. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* 1991; **73**: 696–704

46 Turfrey D, Ray D, Sutcliffe NP, Ramayya P, Kenny GNC, Scott NB. Thoracic epidural anaesthesia for coronary artery bypass grafting. Effects on postoperative complications. *Anaesthesia* 1997; **52**: 1090–13

47 UKPDS group. Effect of intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risks of complications in patients with type 2 diabetes. *Lancet* 1998; **352**: 837–53

48 Wagner RL, White PF. Etomidate inhibits adrenocortical function in surgical patients. *Anesthesiology* 1984; **61**: 647–51

49 Wallace LK, Starr NJ, Leventhal MJ, Estafanous FG. Hyperglycaemia on ICU admission after CABG is associated with increased risk of mediastinitis or wound infection. *Anesthesiology* 1996; **85** (Suppl): A286

50 Wang C, Chan V, Yeung RT. Effects of surgical stress on pituitary testicular function. *Clin Endocrinol* 1978; **9**: 255–66

51 Woolf PD, Hamill RW, McDonald JV *et al*. Transient hypogonadotrophic hypogonadism caused by ctitical illness. *J Clin Endocrinol Metab* 1985; **60**: 444–450