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Yearbook

Indian College of Anaesthesiologists
Whole Constituent of
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(Member of the World Federation of
Societies of Anaesthesiologists)

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CHAPTER

4

The Stress Response to Surgery and the Effect of Anesthesia

Munisha Agarwal

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INTRODUCTION

Stress response to surgery is the body's response to surgical trauma characterized by the activation of sympathoadrenal system and increased secretions of pituitary hormones as well as immunological and hematological changes. Following surgical trauma, the stress response is activated via the afferent impulses from the injured site to the hypothalamus which in turn stimulates the pituitary to secrete hormones such as adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), etc. These hormones then act on respective target organs to release various hormones and mediators like cortisol, glucagon, catecholamines, and inflammatory cytokines. The overall effect of these hormones is increased catabolism, which mobilizes substrate to provide energy sources and retention of water and salt to maintain fluid volume and cardiovascular homeostasis. Different surgical techniques as well as different anesthetic techniques for the same surgical procedure can trigger variable stress response. Surgery, which is more extensive and has a longer duration elicits a more extensive stress response.[1]

In 1932, Cuthbertson studied the metabolic responses of four patients who sustained lower limb fractures.[2] The term "ebb" and "flow" was coined to describe an initial decrease followed later by an increase in metabolic activity. Presumably the stress response developed to allow a wounded animal to survive by catabolizing their own stored energy reserves. However, the stress response to surgery seems unnecessary and rather detrimental to the surgical outcome and has prompted wide range of research for methods to obtund or abolish the stress response.

THE ENDOCRINE RESPONSE TO SURGERY

Sympathoadrenal Response

Surgical trauma activates the sympathetic autonomic nervous system which stimulates the hypothalamus leading to rise in levels of both catecholamines secreted from the adrenal medulla and norepinephrine from presynaptic nerve terminals. These transmitters then lead to increased sympathetic activity

expressed as tachycardia, hypertension, raised cardiac output, increased myocardial contractility. There is peripheral and splanchnic vasoconstriction, coronary and cerebral vasodilation. Also stimulation of efferent sympathetic fibers and/or circulating catecholamines modifies function of organs like liver, pancreas, and kidney.

Hypothalamic-Pituitary-Adrenal Axis

Cortisol

Corticotropin-releasing hormone (CRH) secreted from the hypothalamus stimulates anterior pituitary to release ACTH into the circulation. ACTH stimulates the adrenal glands to produce the stress hormone, i.e. cortisol. Surgical trauma is one of the most-potent stimulus for ACTH and cortisol secretion. ACTH stimulates the adrenal glands to secrete cortisol as soon as the surgery begins and levels of cortisol rise rapidly thereafter. Cortisol concentration may increase to as high as greater than 1,500 nmol/L from baseline levels of about 400 nmol/L in about 4–6 hours from start of surgery, depending on the magnitude of surgical trauma. Raised concentration of cortisol inhibits further release of ACTH through a negative feedback mechanism. However, this mechanism becomes ineffective after surgery leading to high concentration of both ACTH as well as cortisol.[1]

Cortisol is a glucocorticoid hormone, mainly catabolic in nature and it mobilizes energy stores to prepare the body for an appropriate response to various stressors. It facilitates breakdown of proteins and gluconeogenesis in liver. Utilization of glucose by the cells is also inhibited which leads to increased blood glucose levels. Lipolysis promoted by cortisol increases production of precursors of gluconeogenesis from the breakdown of triglycerides into glycerol and fatty acids. Cortisol also has other important anti-inflammatory glucocorticoid actions due to which accumulation of macrophages and neutrophils into the inflammatory areas is inhibited and synthesis of various inflammatory mediators like prostaglandins is also hampered.[1]

Other Pituitary Hormones

Surgical trauma also stimulates the anterior pituitary to secrete GH and prolactin in increased amount. GH besides regulating growth, stimulates protein synthesis and inhibits protein breakdown, promotes lipolysis and has anti-insulin effect. The uptake and utilization of glucose by cells is inhibited by GH, which spares glucose to be used by the neurons whenever any scarcity occurs. Glycogenolysis is also stimulated by GH in the liver. Therefore, increased levels of GH in response to surgical stimulus leads to raised blood glucose levels.[1]

There is no significant change in the levels of other pituitary hormones like follicle stimulating-hormone (FSH), TSH, luteinizing hormone (LH) during surgery. Beta-endorphins secretion though increases following surgery, but has negligible metabolic effect. Arginine vasopressin is produced by the posterior pituitary and it has significant antidiuretic action. It also stimulates secretion of proopiomelanocortin from the anterior pituitary along with CRH.

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Insulin and Glucagon

Insulin is synthesized and secreted by β-cells of the pancreas and has dominant anabolic action. It facilitates uptake of glucose into the adipose tissue and the muscles and conversion of glucose into triglycerides and glycogen. It promotes glycogenesis in the liver. Insulin also inhibits breakdown of proteins and lipolysis. Thus, insulin plays a key role in controlling the glycemic levels in the blood. Following induction of anesthesia, insulin levels may decrease and they are unable to match the hyperglycemic response consequent to release of catabolic hormones. This may be caused due to alpha-adrenergic inhibition of β-cell secretion. Also insulin resistance, i.e. failure of the usual cellular response to insulin occurs during the perioperative period.[1]

Glucagon, which is produced by the α-cells of pancreas, stimulates glycogenolysis in the liver. It also promotes production of glucose from amino acids in the liver and has lipolytic action. There is slight increase in plasma glucagon levels after major surgery but this does not significantly contribute to the hyperglycemic response.[1]

Thyroid Hormones

Concentration of TSH decreases during first-two hours of surgery and return to baseline thereafter. Total and free T3 levels decrease after surgery and normalize after several days. These changes in thyroid hormone levels may be because of the close relationship between thyroid hormones, cortisol and catecholamines.[1] Exogenous steroids suppress T3 and therefore hypercortisolemia following surgery may also decrease T3 concentration.[3]

METABOLIC EFFECTS OF THE ENDOCRINE RESPONSE

The cumulative effect of the stress response to surgery is an excessive secretion of catabolic hormones. The classical "stress response" is characterized by increased levels of catecholamines, cortisol and glucose. These hormones in turn promote breakdown of carbohydrates, proteins and fat to provide food substrates. This kind of stress response perhaps evolved as a protective and a healing process following an injury. However, in modern day anesthetic and surgical practice, it is debatable whether such endocrinal stress response to surgery is useful for the patient or needs to be modulated or abolished by various interventions.

Carbohydrate Metabolism

Concentration of blood glucose rises after surgery begins. Cortisol and catecholamines facilitate production of glucose because of increase in gluconeogenesis and glycogenolysis in the liver. Also utilization of glucose in peripheral tissues is impaired in the perioperative period. Relative lack of insulin along with peripheral insulin resistance also contributes to raised blood glucose levels. Levels of circulating cortisol hormone are very significant predictor of increase in degree of insulin resistance consequent to postsurgical stress response. Blood glucose levels are related to the magnitude of the surgical insult and the surge in catecholamines.[4] During cardiac surgery, blood glucose concentration

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can rise as high as 10–12 mmol/L and remain elevated for more than 24 hours postoperatively. These changes are less significant after minor surgery.[1] Healing of the surgical wounds is significantly affected by hyperglycemia, which in turn leads to increased morbidity and mortality in surgical patients. In patients undergoing cardiac surgery, a higher incidence of wound infection and mediastinitis was found in diabetics and nondiabetic patients in which blood glucose levels were greater than 200 mg/dL.[5]

Protein Metabolism

Breakdown of proteins is stimulated by increased cortisol concentration as seen during surgery. Skeletal muscle and visceral muscle protein is catabolized to amino acids which may be broken down as substrates in the liver to provide energy or used to produce new acute phase proteins in the liver. Amino acids are also converted to glucose, fatty acids and ketones in liver. Protein catabolism results in increased muscle wasting weight loss in patients after major surgery and traumatic injury, which can lead to prolonged recovery time and hospital stay.[1]

Fat Metabolism

Increased levels of cortisol, catecholamines and GH following surgery stimulate conversion of triglycerides to glycerol and fatty acids. Fatty acids can get converted into ketone bodies or may get re-esterified while glycerol acts as a substrate for gluconeogenesis in liver.

Water and Electrolyte Metabolism

Endocrine response to surgery leads to secretion of various hormones leading to salt and water retention in an effort to maintain adequate body fluid volume. Arginine vasopressin facilitates water retention and stimulates the kidneys to produce concentrated urine. Concentration of vasopressin can remain high for 3–5 days postoperatively, depending on the magnitude of surgical trauma. Renin secretion due to increased sympathetic stimulation leads to increased production of angiotensin-II which in turn stimulates release of aldosterone from adrenal cortex leading to sodium and water reabsorption from the distal tubules of kidney.[3]

Temperature Alterations

Preoptic area of hippocampus senses the change in temperature of the body, which stimulates the release of stress hormones. The stress hormones cause an increase in heat production, but clinical conditions like starvation, induced hypothermia, cardiopulmonary bypass (CPB), neurosurgery, sepsis are known to influence neuroendocrine responses.[6,7]

HEMATOLOGICAL AND IMMUNOLOGICAL EFFECTS OF THE STRESS RESPONSE

Hypercoagulability and Fibrinolysis

Due to the effects of cytokines and acute phase proteins (discussed later) on the coagulation pathway, there is hypercoagulation and fibrinolysis.

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The surgical stress response also leads to relative leukocytosis and lymphocytosis. Immunosuppression occurs because of the direct effects of increased cortisol secretion.[8]

Cytokines

Discovery of cytokines led to the concept that besides endocrinal response to surgical stress, certain local substances are also released at the site of injury, which significantly contributes to surgical stress response.

Cytokines are heterogeneous group of low molecular weight proteins like interleukins, lymphokines and interferons. They are produced from activated leukocytes, especially monocytes, and from endothelial cells and fibroblasts in the initial stage of tissue injury and play a significant role in the inflammatory response to surgery and trauma. The main cytokines released after major surgery are interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and IL-6.[9] Activated macrophages and monocytes secrete IL-6 and TNF-α in the initial phase of tissue injury. This stimulates further release of cytokines in particular IL-6, which is the most significant cytokine responsible for producing the systemic changes, i.e. acute phase response.[9]

Interleukin-6

Normal concentration of cytokines in the blood is usually very low or undetectable. IL-6 concentration increases within 30–60 minutes of start of surgery and maximum changes in its levels are seen after 2–4 hours. The production of cytokine is proportional to the extent of surgical trauma. Therefore, release of cytokine is lowest following minimally-invasive surgery and highest after major surgical procedures like joint replacement, colorectal surgery, etc. Cytokine concentration reaches peak at about 24 hours after a major surgery and elevated levels are found even at 48–72 hours after surgery.[1]

Acute Phase Response

This phase is initiated by cytokines especially IL-6 following surgical trauma and mainly involves production of acute phase proteins by liver, i.e. C-reactive protein (CRP), fibrinogen, α-2 macroglobulin and antiproteinases. These act as inflammatory mediators, antiproteinases and scavengers in tissue repair. Following surgery, cytokines can increase the secretion of ACTH from pituitary, which then causes an increase in release of cortisol from adrenal glands. Glucocorticoids inhibit cytokine production through a negative feedback system. The cortisol response to surgery also decreases IL-6 concentration.[4,10]

STIMULI FOR THE STRESS RESPONSE

The stress response to surgery can be triggered by a variety of stimuli ranging from changes in metabolic and volume status of the body to the chemical mediators released in response to surgical trauma. They are as follows:

- Decrease in the effective circulating volume in the body due to any cause such as trauma, hemorrhage,[11] sepsis, cardiac failure, act via baroreceptors to stimulate release of ACTH, AVP, GH and β-endorphins which lead to increase

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in heart rate, blood pressure, stroke volume, sodium and water retention, hyperglycemia.[12,13]

- Hypoxia, hypercarbia, hypo or hyperthermia, changes in H^+ concentration in the blood activate peripheral chemoreceptors and cause hormonal reflex response.[12]
- Pain, anxiety and distress via the limbic system and cerebral cortex stimulate sympathetic nervous system. Light plane of anesthesia and intraoperative periods of intense stimulation (skin incision, tissue handling, peritoneal stretching) show exaggerated stress response.
- Surgical tissue trauma—activates the endocrinal stress response. Minimally-invasive surgery cause less tissue trauma and hence there is lesser rise of inflammatory mediators like IL-6, CRP, acute phase proteins. Stimuli from the surgical site, which elicit stress response and travel along peritoneal and visceral afferent nerve fibers along with those from the abdominal wall. Therefore, measures which decrease surgical trauma do not significantly reduce the classical stress response (raised levels of cortisol, glucose, catecholamines) to abdominal surgery like cholecystectomy.[1]
- Acute phase proteins—produced by the liver on stimulation by cytokines mainly IL-6.
- Interaction between the neuroendocrine and the immune system—cytokines augment ACTH secretion from pituitary after surgery and hence increase release of cortisol. Glucocorticoids via negative feedback mechanism inhibit cytokine production. Anesthesia cannot influence tissue trauma and therefore it cannot affect the cytokine response to surgery.[1] Regional anesthesia has no significant effect on cytokine production though it can reduce surgical stress response. Surgically induced stress response is less severe in magnitude as compared to that consequent to extensive trauma, burns, and sepsis.

EFFECT OF ANESTHESIA ON THE STRESS RESPONSE TO SURGERY

The most important factors determining the level of surgical stress response have been found to be the patient and the type of anesthesia and surgery. In addition, anesthesia may also modify the stress response via afferent blockage (local anesthesia), central modulation (general anesthesia) and peripheral interaction with the endocrine system (e.g. etomidate).[14]

General Anesthesia

General anesthesia (GA) can decrease the perception of sensations from the site of surgical trauma but cannot completely abolish the response because even in deeper planes of anesthesia, hypothalamus reacts to the noxious stimuli. Also, GA cannot influence the degree of surgical trauma and hence cannot significantly affect response of cytokines to surgery.[1] Intravenous (IV) or volatile anesthetic agents have only minor influence on endocrine metabolic response to surgery in usual clinical dosages. In patients undergoing cardiac surgery, large doses of opioids like morphine (4 mg/kg) inhibit cortisol and GH secretion until the

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cardiopulmonary bypass (CPB) is started. Short-acting opioids like fentanyl (50–100 μg/kg), sufentanil (20 μg/kg) and alfentanil (1.4 mg/kg) suppress pituitary hormone secretion until CPB. After the initiation of CPB, opioids were unable to abolish the stress response even at very high dosages.[15] For certain surgical procedures complete inhibition of stress response may be possible but at very high dosages of opioids at the cost of postoperative respiratory depression requiring ventilatory support. In patients undergoing pelvic surgery, fentanyl suppressed ACTH and cortisol secretion when administered before surgical incision but not when given after the start of surgery.[16]

Aldosterone and cortisol production is suppressed for 6–12 hours after the administration of a single induction dose of etomidate while cortisol synthesis is further inhibited for up to 24 hours following etomidate infusion for 1–2 hours.[17]

A single induction dose of propofol is known to influence sympathoadrenal axis and can suppress cortisol but does not block cortisol and aldosterone secretion in response to surgical stress.[18,19] However, propofol infusion at deep anesthetic dosage, abolished cortisol secretion during surgery.[18]

Sevoflurane in laparoscopic surgery decreased plasma concentration of ACTH, GH and cortisol when compared to isoflurane.[20] Perioperative use of dexmedetomidine reduces serum cortisol levels.[21]

Benzodiazepines may also inhibit steroid production but significance is not known. Midazolam obtunds the release of cortisol as a part of endocrinal stress response to both upper abdominal and peripheral surgery.[22,23] Hypothalamic-pituitary axis is not the site of action of benzodiazepines. However, they might exhibit a direct inhibitory action on steroid production. Clonidine, a centrally acting antihypertensive agent, reduces the sympathoadrenal and cardiovascular responses caused by noxious surgical stimuli by acting on α-2 adrenergic receptors.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) have no direct role in classical stress response, but metabolites of arachidonic acid cascade are involved in various steps of preventing stress response.

The normal communication between the hippocampus and the neocortex can get disturbed by increased levels of cortisol, seen as a part of stress response to surgery which in turn can disrupt the process of memory consolidation.[24,25] Prolactin, another stress hormone is also involved in modulating memory function.[26,27] The neuroendocrine stress response to surgery causes incomplete abolition of learning and memory during general anesthesia which can lead to awareness and subsequently posttraumatic stress disorder (PTSD).[25,28] Neuroinflammation due to metabolic stress response to major surgery was also found to be correlated with postoperative cognitive dysfunction (POCD).[29] Both PTSD and POCD can perhaps be prevented by neuromonitoring during various surgical procedures. However, the stress response to surgery must be abolished to inhibit the process of neuroinflammation and memory consolidation.[29,30,31]

Regional Anesthesia

Epidural block with local anesthetic agents involving majority of relevant dermatomes prevents a major part of metabolic endocrine response to surgery,

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more consistently during lower abdominal and lower extremity surgeries. In patients undergoing hysterectomy, epidural block from T4 to S5 dermatomal level administered before the start of surgery prevented increase in glucose as well cortisol levels.[32] Afferent impulses from the site of surgery travel to the hypothalamic-pituitary axis and the efferent autonomic fibers to the liver and adrenal medulla get blocked. Therefore, the increase in glucose and cortisol levels is abolished. Neural blockade confined to fewer dermatomes does not completely obtund the metabolic and hormonal changes. However, in thoracic or upper abdominal surgery even an extensive epidural blockade cannot prevent the pituitary hormone responses completely though glycemic changes are inhibited.[1]

Till date, no anesthetic technique has been found to obtund completely the stress response to thoracic and upper abdominal surgery. GA combined with thoracic epidural analgesia has been shown to inhibit changes in catecholamine secretion during CPB for up to 24 hours after the beginning of the cardiac surgery. It may also attenuate the cortisol response to CPB.[33] Myocardial sympathetic response was attenuated by combined thoracic epidural block and GA and was associated with decreased myocardial damage as evident by decreased release of Troponin T.[34] The blockade of cardiac sympathetic fibers, both efferent and afferent can help in improving the balance between myocardial oxygen demand and supply.[35]

EVALUATION OF THE STRESS RESPONSE

Evaluation of the stress response to surgery under anesthesia remains difficult as no method can directly measure or quantify it. Clinical parameters like heart rate and blood pressure, which are signs of autonomic reactions, have been used for assessing the stress response, though with less specificity. Entropy and bispectral index used for monitoring depth of anesthesia are again indirect measures to evaluate this response. Blood levels of various stress hormones like ACTH, cortisol, prolactin and chemical mediators like epinephrine, norepinephrine have also been used for evaluating stress or nociception level in surgery.[1,36] Surgical stress index (SSI) is a recently developed tool to quantify intraoperative stress level during anesthesia and is derived from photoplethysmograph waveform amplitude (PPGA) and the heart beat to beat interval (HBI). SSI reflects nociception-antinociception balance and ranges from 0 to 100. A high value is indicative of high level of stress.[37]

MODULATORS OF THE SURGICAL STRESS RESPONSE

The continuous hypermetabolic state consequent to the stress response, may result in complete depletion of essential components of the body, e.g. glucose, proteins, fats, minerals which may lead to fatigue, weight loss, decrease in body resistance, delayed ambulation and increased morbidity and mortality. This knowledge about the detrimental effects of neuroendocrine stress response to surgery has led to increased interest in interventions, which can modulate the stress response to have a better surgical outcome.

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Regional Anesthesia

Regional anesthetic techniques involving neuraxial blockade with local anesthetic agents maximally inhibits the stress response to surgery and it improves the functioning of specific organ systems. In patients undergoing pelvic and lower limb surgery, analgesia with regional neuraxial blocks lowers the incidence of thromboembolic complications.[38] Continuous epidural infusions of local anesthetic agents decrease the incidence of pulmonary complications much more than that by epidural or systemic opioids. Continuous thoracic epidural analgesia decreases paralytic ileus following abdominal surgery.[39] Early enteral nutrition can thus be resumed which significantly reduces the risk of infectious complications.[40]

Oral Glucose

Preoperative administration of oral glucose has been found to reduce the rise in blood cortisol and glucose levels postoperatively compared with patients who were made to fast preoperatively.[41] Oral glucose loading done twice (evening and morning) before surgery was found to be more effective in reducing the rise of cortisol level but not significant in reducing the rise in blood glucose level compared with patients who were administered oral glucose solution only once (morning) before surgery. Preoperative glucose loading obtunds postoperative insulin resistance, reduces protein and nitrogen losses, preserves skeletal muscle mass and decreases preoperative hunger, thirst and anxiety. In also promotes rapid recovery through early return of bowel function and shorter hospital stay, finally leading to an improved perioperative well-being.[41,42]

Insulin and Glycemic Control

The degree of insulin suppression and resistance is proportional to the extent of surgical trauma. Intensive insulin therapy reduced insulin resistance along with reduction in the incidence of infections and sepsis significantly leading to improvement in organ function and also reversed the posttraumatic catabolic state. Maintenance of blood glucose levels within a reasonable range reduced morbidity and wound healing time in the postoperative patient.[42]

Enhanced Recovery after Surgery

Despite several significant advances in surgical and anesthetic techniques aiming towards better patient care, major surgeries like radical cystectomy, colorectal surgery are still associated with morbidity and prolonged recovery periods. Enhanced recovery after surgery (ERAS) or fast-track programs are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the profound stress response following surgery. These programs have been shown to improve the cardiopulmonary functions and lead to earlier return of bowel function, reduction in complications and hospital stay along with early resumption of normal activities.[43]

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Preoperative planning in ERAS protocol includes preoperative optimization of nutrition and other medical ailments, avoiding prolonged fasting hours, carbohydrate loading up to 2 hours preoperatively, avoiding sedatives, and avoiding mechanical bowel preparation.[44] Intraoperatively, it is advocated to use laparoscopic and laparoscopic-assisted surgical techniques which are associated with reduced effects of tissue injury, reduced length of hospital stay, early return of bowel function and minimized wound complications. Wound drains and nasogastric tubes should be avoided. Detrimental effects of over hydration, i.e. delay in return of bowel function, impaired wound healing and increased length of hospital stay, mandates use of goal directed fluid therapy. Use of thoracic epidural analgesic technique for major abdominal surgeries should be preferred. This provides good intra and postoperative analgesia, which reduces ileus in postoperative period by blocking sympathetic nervous system. Hypotension following central neuraxial blockade should be treated with vasopressors rather than fluid overloading. Specific attention is required for thromboprophylaxis, temperature control and postoperative nausea and vomiting management. High-dose opioids are not advisable to avoid side effects like sedation, respiratory depression, nausea or vomiting. Shorter-acting analgesics (like fentanyl), and anesthetics are preferred wherever possible.[43,45]

Postoperatively, early commencement of oral intake, including carbohydrate drinks and discontinuation of IV fluids is desirable. Early oral intake is associated with lesser wound complications, reduced rates of ileus and shorter hospital stay. Thoracic epidural analgesia is strongly recommended in open abdominal surgery. Drains and urinary catheters should be removed as soon as possible. Multimodal analgesia is used with NSAIDs, paracetamol, gabapentin or pregabalin which has opioid sparing affect and facilitates early mobilization.[43]

CONCLUSION

Stress response to surgery encompasses complex metabolic and hormonal changes triggered by the stimulation of hypothalamus-pituitary-adrenal axis. The cumulative response is hypermetabolic and hypercatabolic, which leads to impaired wound healing and immune function, muscle wasting and organ failure. The magnitude and duration of the stress response is proportional to the surgical trauma. General anesthesia cannot abolish the metabolic hormonal responses completely. Epidural blockade using local anesthetic agents abolishes the stress response to a greater extent. Recently introduced ERAS programs aim to attenuate the body's response to surgery by multimodal perioperative pathways aimed at achieving early recovery after surgery. For how long does the stress response to surgery last postoperatively? Do patients exhibit genetic predisposition to this response? Specific long-term studies are needed to answer these queries. Till such time, the stress response to surgery should be recognized as a definitive clinical entity which needs to be aggressively managed to ensure better patient and surgical outcome.

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KEY POINTS

- Stress response to surgery is body's response to tissue trauma and is proportional to the extent and duration of surgery.
- There is activation of sympathetic system and hypothalamus-pituitary-adrenal axis leading to release of mediators and hormones like cortisol, catecholamines, glucagon, and inflammatory cytokines.
- Overall response of the body is hypermetabolic and hypercatabolic leading to muscle wasting, impaired wound healing, delayed recovery, morbidity and mortality.
- The stress response though evolved as a protective and healing process following an injury, needs to be attenuated or abolished for better surgical and patient outcome.
- General anesthesia in usual clinical dosages does not completely abolish the stress response.
- Epidural blockade with local anesthetic agents is effective in suppressing stress response to a large extent.
- Surgical Stress Index (SSI) is a new method of evaluation of surgical stress response besides clinical parameters like heart rate, blood pressure and measuring blood levels of stress hormones like cortisol ACTH, epinephrine, nor-epinephrine and prolactin.
- Interventions like use of newer shorter-acting anesthetic agents, minimally-invasive surgery, epidural analgesia with local anesthetic agents and multimodal perioperative ERAS protocols are effective in attenuating the surgical stress response.

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