

Stress or metabolic response to surgery and anaesthesia

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Abstract

The stress response to surgery, trauma, burns, and critical illness is a well-known entity and encompasses derangements in metabolic and physiological pathways which leads to inflammatory, acute phase, hormonal and genomic responses. There is a state of hyper catabolism and hyper metabolism, which results in impaired wound healing, impaired immune functions and muscle wasting. The stress response to surgery is similar to that induced as a result of traumatic injuries, however it depends on the duration and severity of surgical or traumatic injury. Body responds to such stimuli which may range from minor to massive insults and response is characterized by local or generalized responses. The generalized responses vary from endocrinal, metabolic and biochemical changes in the body and magnitude of the same vary depending on the intensity, severity and duration of stimuli. Stress responses are known to be well tolerated in normal healthy adults, however in patients with known ailments and co-morbidities such as coronary heart disease, hypertension, diabetes, liver diseases, renal insufficiency, old age, changes may be detrimental and life threatening.

Keywords: Stress, Metabolic Response, Surgery, Anesthesia.

Introduction

Surgical Stress Response

Surgery and trauma induce a complex hematological, hormonal, metabolic and immunological responses in the body. Initial stimulus arises from cytokines which include interleukins 1, 6 and tumor necrosis factor which are released from leucocytes and endothelial cells, which leads to local and systemic manifestations.

Sympathetic Response

There is activation of sympathetic nervous system, which is activated via hypotension and hypoxemia leading to activation of alpha and beta receptors. Alpha 1 receptor activation leads to peripheral and splanchnic vasoconstriction, pupillary dilatation, intestinal muscle relaxation and glycogenolysis. Beta receptor activation leads to increase in cardiac contractility, heart rate, peripheral vasodilation, and bronchodilation, resulting in tachycardia, hypertension and sodium and water retention due to release of renin.^{1,2}

Hematological and Immunological Response

There is a state of fibrinolysis and hypercoagulability because of effects of acute phase proteins and cytokines on coagulation pathway. There is relative leukocytosis and lymphocytosis. There is a state of immunosuppression occurs due to direct cortisol secretion.^{1,2}

Metabolic Response

There is release of glucagon from alpha islet of Langerhans which result in glycogenolysis in liver and muscle, leading to increase in glucose, lactate and mobilization of free fatty acids. There is hyper catabolism from proteins and fat to provide energy substrates. Protein from skeletal muscle and glycerol produced from breakdown of fat are utilized in gluconeogenesis in liver. Fatty acids are metabolized into ketones which are utilized as energy sources in many organs.³

There is generation of multiple mediators as a result of cellular injury, which exert paracrine, autocrine and endocrine effects, even in low concentration. The various mediators are summarized in table 1.

Table 1: Summary of various mediators responsible for metabolic response to stress

Cytokines mediators	Effects
1. Interleukins (IL 1, 2 and 6)	They act on CNS inducing fever by stimulating local release of prostaglandins causing increase in oxygen consumption, basal metabolic rate. They promote the synthesis of acute phase proteins in liver and causing breakdown of muscle proteins into amino acids for energy production. These may be responsible for marginal increase in catecholamine's in blood
2. Tumor necrosis factor (TNF)	TNF cause release of prostaglandins E2, thromboxane synthesis which promotes platelet aggregation, and vasoconstriction, and platelet activating factor They may also be implicated in reduction of transmembrane potential in skeletal muscle owing to decrease in lipoprotein lipase activity
3. Eicosanoids	These are derivatives of arachidonic acid in cell membrane phospholipids of nucleated cells and are synthesized in response to hypoxia, tissue injury, angiotensin etc. These include prostaglandins, thromboxanes and leukotrienes.

	These have widespread effects on systemic, regional, pulmonary, central and peripheral neurotransmission. They are one of the powerful vasoconstrictors, vasodilators and pro aggregator substances
4. Serotonin	It is synthesized from entero-chromaffin cells of intestines and platelets during tissue insults and injury. Serotonin stimulates vaso-constriction, platelet aggregation, bronchospasm, increase in heart rate and myocardial contractility.
5. Histamine	It causes severe vasodilatation, which results in hypotension, increase capillary permeability, peripheral pooling and ultimately heart failure
6. Kallikreins-Kinins	The kinins are potent vasodilators, cause tissue edema, increases hepatic prostaglandin synthesis, evokes pain and cause reduction in renal blood flow.
7. Heat shock proteins	They are a group of intracellular proteins induced by hypoxia, anesthesia with ether, trauma and hemorrhage. They are named after heat stimulation.

Hormonal Responses

Following surgical or accidental trauma, there is activation of stress response which leads to activation of impulses from surgical site or injured site to hypothalamus. Hypothalamus stimulates the release of pituitary hormones such as adrenocorticotrophic hormone (ACTH) which leads to secretion of cortisol from adrenal cortex at the start of surgery. There is inhibition of negative feedback of ACTH and cortisol pathway which results in peripheral insulin resistance and hyperglycemia. It also cause stimulation of glucagon synthesis and has immunomodulatory effects. Also in the presence of excessive cortisol production, there is increase in catabolism of protein as compared to protein synthesis resulting in gluconeogenesis in liver from net catabolism of muscle proteins and also through breakdown of adipose tissues.^{4,5} Also there is sodium and water retention owing to mineralocorticoid action of cortisol and secretion of antidiuretic hormone.

Other anterior pituitary hormones which are secreted include thyrotrophin (TSH) and gonadotropins (which include follicle stimulating and luteinizing hormones), although they are not significantly altered. Growth hormone releasing hormone (GHRH) stimulates anterior pituitary to release growth hormone, which cause increase signaling via insulin like growth factors which regulate growth. Signaling via these regulators leads to increase in protein synthesis, lipolysis and reduced protein catabolism. Growth hormone increases overall blood glucose level by causing glycogenolysis, and direct anti-insulin action.⁶

There is increase in secretion of vasopressin from posterior pituitary after surgery owing to pain and other factors. It acts on arginine vasopressin (V2) receptors in kidneys resulting in aquaporin's insertion in renal wall, which allow the movement of water from the renal tubules back into circulation. Prolactin and beta endorphins are also produced from pituitary but their role in stress is not completely clear. There is also increase in acute phase proteins from liver which are involved in tissue repair, free radical scavenging and modification of immune responses.

Renin Angiotensin Pathway Regulation

Decrease in circulatory volume, ACTH, AVP, glucagon, potassium, magnesium and calcium are responsible for

secretion of renin from juxtaglomerular apparatus and macula densa in kidney. Angiotensin II acts on cardiovascular system leading to increase in heart rate, myocardial contractility and vascular permeability. It also maintain fluid electrolyte balance by causing sodium and water retention.⁷

Neuro-Endocrine Response

Reduction in effective circulating blood volume due to any reason (such as trauma, hemorrhage, burns, cardiac failure, sepsis etc) is sensed by baroreceptors in aorta, carotid and renal arterioles which is proportionate to magnitude of volume loss. The pathway is mediated via central autonomic pathway which cause a release of ACTH, AVP, GH and beta endorphins, which in turn leads to increase in heart rate, stroke volume, sodium and water retention, and blood sugar.

Decrease in renal blood flow due to splanchnic vasoconstriction is sensed by stretch receptors in juxta glomerular apparatus which results in synthesis of renin angiotensin leading to rise in blood pressure and reduction in urine output.

Ion concentration- there is activation of peripheral chemoreceptors which include carotid and aortic bodies as a result of hypoxia or hypercarbia or increase in hydrogen ion concentration. 9th and 10th cranial nerve carry the sensation to hypothalamus resulting in activation of cardiac sympathetic outflow which leads to increase in heart rate, cardiac contractility and increase in respiratory arte.

Emotions- Fear, anxiety, tension and emotions lowers the tolerance of a person to pain. These stimuli are known to pass through limbic region, especially amygdala and hippocampus which then passes the signals through posterior pituitary leading to release of AVP, ACTH, cortisol, aldosterone and catecholamines.

Temperature-Preoptic area of hippocampus sense the change in core temperature of the body which induces the secretion of stress hormone. The stress hormones cause an increase in heat production, but clinical conditions like starvation, induced hypothermia, cardiopulmonary bypass, neurosurgery, sepsis are known to influence neuroendocrine responses.

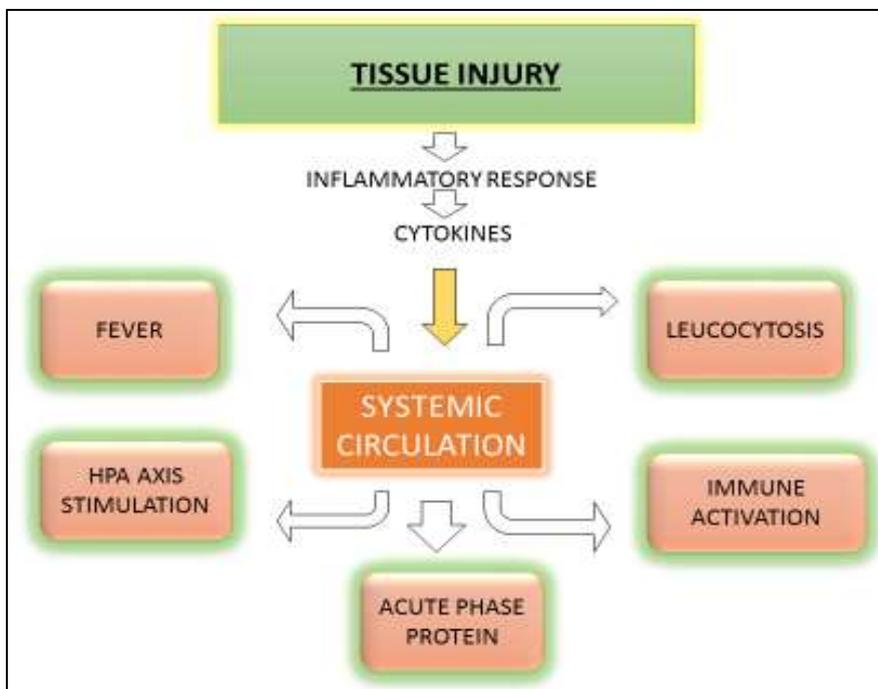


Fig. 1: Acute phase response to surgical stress

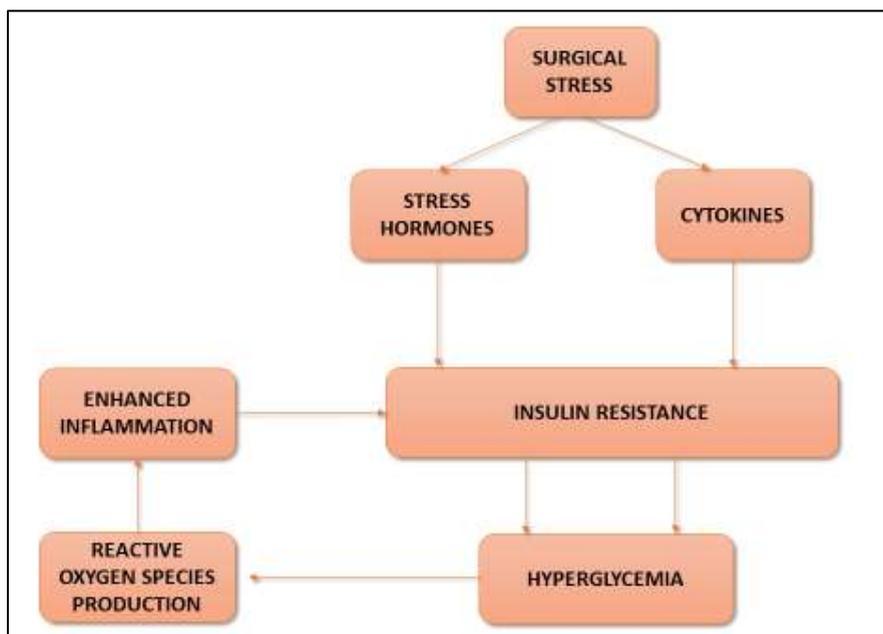


Fig. 2: Vicious cycle of stress of surgery

Detrimental Effects of the Stress Response

Overall, the multisystem effects of the stress response lead to many potentially harmful effects including:

1. Increased myocardial oxygen demand, increasing risk of ischemia
2. Hypoxemias
3. Splanchnic vasoconstriction which may impact on healing of anastomoses
4. Exhaustion of energy supplies and loss of lean muscle mass, leading to weakness of both peripheral and respiratory muscles
5. Impaired wound healing and increased risk of infections
6. Hypercoagulability
7. Sodium and water retention.

Table 2: Stress responses on various organ systems

Organ systems	Effects
1. Cardiovascular System	Increase in cardiac output, heart rate, blood pressure, myocardial demands, myocardial contractility
2. Blood Volume	There is peripheral and splanchnic vasoconstriction, cerebral and coronary vasodilation
3. Respiratory System	There is increased respiratory rate
4. Fluid and Electrolytes	Sodium and water retention
5. Coagulation	Hypercoagulability and fibrinolysis
6. Immuno-suppression	Wound infection
7. Metabolic Changes	Substrate mobilization-hyperglycemia
8. Renal	Reduced urine output

Effect of General Anesthesia on Stress of Surgery

General anesthesia does not abolish the stress response completely as hypothalamus and pituitary reacts to noxious stimuli even in deeper plane of anesthesia, and has little effect on cytokine response, however GA may limit the perception of sensations due to surgical steps. Anxiety is known to cause catecholamine's surge and can cause hemodynamic surges, and increase oxygen consumption, which can be detrimental in compromised cardio-respiratory patients. Preoperative verbal reassurance, use of anxiolytics at night time before surgery, cardiac drugs such as beta blockers can prevent anxiety and its ill effects.⁸

Preoperative Management

Appropriate use of pre-operative fluid, with sufficient dextrose especially in diabetics, avoiding prolonged starving hours, are known to maintain adequate nitrogen balance and avoid undue catabolic state. Administration of substrate in the form of glucose and amino acids during period of starvation and injury is known to reduce extent of stress, although catabolism is not abolished in the presence of substrate.

Providing oral glucose solution preoperatively can lower the increase in cortisol and blood glucose levels compared with patients who have fasted preoperatively. Administration of twice oral glucose solution (evening and morning) before surgery is more effective in lowering the increase of cortisol level but not significant lowering the increase of blood glucose level compared with patients who are given oral glucose solution just once time (only mornings).

Monitoring

Continuous automated measurement of vital parameters such as HR, BP, ECG, SPO₂, ETCO₂. Temp, blood sugar, BIS, and timely intervention plays an important role in patient's stabilization. The use of poly-pharmacy, such as sedatives, anxiolytics, narcotics, muscle relaxants of different onset, peak action and duration may result in fluctuation of the depth of anesthesia is assessed by PSRT scores (pressure,

sweating, rate, tear). Inadequate drug titration may result in light or deep anesthesia. During light planes of anesthesia feeling of pain, inadequate sleep, amnesia or muscle relaxation results in stress response.

Perioperative Management

Careful titration of anesthetic drugs and use of multi-modal analgesia and use of cardio stable agents are useful to prevent hemodynamic changes during induction, endotracheal intubation and maintenance of depth of anesthesia is required. Stressor responses at laryngoscopy and intubation is mediated via mechanical stimulation of upper respiratory tract, whose afferents are carried via glossopharyngeal nerve and from trachea-bronchial trees via vagus nerve which enhance the cervical sympathetic afferent fibers resulting in transient rise in heart rate and blood pressure. This stressor response can be prevented by adequate depth of anesthesia, opioids, beta blockers such as metoprolol, esmolol, or labetalol.

Role of Anesthetic Agents

Volatile agents and induction agents have only minor influence on endocrine and metabolic responses in usual clinical dosages. There have been various studies to measure response of stress by measuring blood levels of ACTH, cortisol, prolactin, nor-epinephrine etc. There have been periods of stimulation such as skin incision, tissue handling, stretching of peritoneum which have shown exaggerated sympathetic responses characterized by increase in heart rate and blood pressure. Many clinically used anesthetic drugs such as opioids, propofol, sevoflurane, thiopentone were found to stimulate prolactin release. According to few authors, opioids have abolished ACTH and cortisol response before initiation of cardiopulmonary bypass, but were unable to suppress the same after CPB initiated. Opioids and etomidate are known to suppress cortisol secretion only in higher dosages and that too before the start of surgery, and were unable to suppress it after surgery started. Complete inhibition of surgical stress responses is usually possible with high dose of opioids at the cost of post-operative respiratory depression. A single dose of etomidate is known to suppress corticosteroids synthesis by inhibiting 11 beta hydroxylase, and effect may last up to 8 hours. Single dose of propofol is also known to influence sympatho-adrenal axis but is not shown to block cortisol response to surgical stress. However propofol infusions at deep anesthesia dosage, abolished cortisol secretion during surgery. Benzodiazepines may also inhibit steroid production but significance is not established. Sevoflurane in laparoscopic surgery decreased plasma concentration of ACTH, GH and cortisol when compared to isoflurane. Use of cyclopropane and ether although not variedly used clinically now is known to cause release of catecholamine's.

Preemptive analgesia in the form of NSAIDs and epidural analgesia also provide excellent perioperative analgesia. NSAIDs have no direct role on the classical stress response, but metabolites of arachidonic acid cascade are involved in various steps of preventing stress response.⁹

High dose systemic opioids such as fentanyl (50 micrograms/kg) and etomidate are known to inhibit hypothalamus thus preventing endocrine and metabolic responses to stress but at the cost of post-operative respiratory depression.

Alpha 2 agonists- cause reduced pain sensation owing to stimulation of descending inhibitory pathway from brainstem. Hormone modulation by means of beta blockers, growth hormones, insulin etc are known to reduce protein breakdown and improving nitrogen balance.

DVT prophylaxis by means of Use of early ambulation, aspirin, and regional anesthesia reduces the hypercoagulable state in perioperative period.

Effect of Regional Anesthesia on Stress of Surgery

Regional nerve blockade by local anesthetics are known to influence metabolic and endocrine responses to stress. The underlying mechanism involves prevention of nociceptive signaling pathways to reach central nervous system by causing nerve blockade. Afferent pathway is involved in release of pituitary hormones and cortisol is released via efferent pathway to pituitary and neural efferent pathway to adrenal cortex by ACTH. Efferent pathway is also responsible for release of epinephrine, cortisol, and renin angiotensin. Extensive nerve blockade involving T4 to S5 is only inhibited by higher thoracic (T2-6) blockade and not by lower thoracic (T9-10) block.¹⁰⁻¹³

General Anesthesia and Neural Blockade

General anesthesia plus epidural analgesia is known to reduce circulatory, hyperglycemic response due to inhibition of endocrine response, by inhibiting cortisol and catecholamine release to stress. Adequate pain relief by means of epidural opioids and local anesthetics are known to prevent protein catabolism.

Local Wound Infiltration

Use of local anesthetics in infiltration of surgical wound is known to completely block pain transmission, local inflammation and pituitary hormonal response.

Peripheral Nerve Blockade

Peripheral nerve blockade are known to reduce stress responses better as compared to that prevented under general anesthesia.¹⁴⁻¹⁶

Enhanced Recovery after Anesthesia and Surgery

Enhanced recovery programs (ERP) involve changes in every step of the patient care process, starting from primary care to post-operative care and follow up. Although majority of evidence of ERP comes from colorectal surgeries but it equally applies for other surgeries such as orthopedic, urological and gynecological. Pre-operative optimization includes optimizing anemia, diabetes, blood pressure and other medical ailments. Smoking cessation and advice on alcohol consumption will also be helpful in many patients as both are associated with adverse outcomes. The purpose of pre-operative nutritional drinks and any new medication can

also be explained at this time. Key tasks of pre-operative planning includes admission on the day of surgery itself, avoiding bowel preparation, avoiding prolonged fasting hours, avoiding sedatives and carbohydrate drinks. Return of normal bowel function is desirable in colorectal surgeries, which is governed by preoperative fasting, bowel preparation, analgesia and anesthetic approaches.^{17,18} Preoperative carbohydrates are provided with the sole aim of minimizing stress response, avoiding catabolic state, negative nitrogen balance and insulin resistance, thereby minimizing loss of lean muscle mass.

Intraoperative Care

Minimally invasive procedure should be used wherever possible. Laparoscopic resection surgeries are associated with reduced length of hospital stay, return of gastrointestinal tract function and minimizing wound complications. In case open procedure is planned, transverse incision should be made to reduce pain in post-operative period. Wound drains should be avoided as they don't provide any beneficial advantage, similarly nasogastric tubes should be avoided in elective surgeries to reduce time to return bowel function. Over hydration should be avoided as comparison of liberal and restrictive fluid regimens have suggested detrimental effects of the same by causing delay in return of bowel functions, impaired healing process and length of hospital stay. Goal directed fluid therapy using cardiac output monitoring devices such as esophageal Doppler to avoid overloading and optimize cardiac output, especially in high risk patients with compromised cardio-pulmonary reserve. Use of thoracic epidural is preferred in abdominal surgeries especially colorectal. If hypotension is a concern because of the use of epidural, it should be treated with vasopressors rather than large quantity of intravenous fluids. Intravenous fluids should be stopped as soon as possible in post-operative period and early commencement of oral intake is desired. Specific attention is required for thrombo-prophylaxis, temperature control and post-operative nausea and vomiting risk stratification and management. High dose opioids are not desirable to avoid untoward side effects such as sedation, respiratory depression and to avoid suppression of hypothalamic and pituitary hormone secretions. Alpha 2 agonists reduce cortisol secretion and sedatives such as benzodiazepines have a modulatory effect on stress response by central effects, but they are not commonly used in ERP because of sedative actions. Short acting analgesics such as fentanyl and anesthetics are preferred wherever possible, long acting ones such as morphine are avoided as immediate post-operative goals are not met with them. Total intravenous anesthesia (TIVA) may be used using remifentanyl and short acting volatile anesthetic agents. Epidural anesthesia is commonly employed as they are known to reduce the dose of general anesthetics and stress response of surgery. They also provide post-operative pain relief and reduce ileus in post-operative period by blockade of sympathetic nervous system when compare to opioid based analgesic regimens. The use of low concentration local anesthetic mixtures (facilitate by opioids such as fentanyl) reduces motor block and therefore

interference with mobilization. PONV avoidance is also very important, as it is one of the most feared complication, patients face, also it interferes with starting oral feeds and oral analgesics. The ERAS Group has recommended risk stratification of patients for PONV during surgery using Apfel scoring system with risk factors as female sex, motion sickness or previous PONV, non-smokers and administration of opioids post operatively. Two risk factors constitute moderate risk and three risk factors constitute high risk patients. PONV should be aggressively managed with the use of drugs according to availability and local practice of drugs. A Cochrane review of antiemetic prophylaxis has not shown any beneficial effects of one antiemetic over another, so it is mainly governed by patient factors, practical aspects and cost. The ERAS group has recommended use of dexamethasone at the time of induction and 5 HT3 antagonists at the end of surgery in moderate risk patients, and combination of 5ht 3 antagonist, droperidol or metoclopramide in addition to dexamethasone in high risk patients. Surgical site infections should be reduced with the use of antibiotics, avoidance of hypothermia, avoidance of hypo and hyperoxia and hand hygiene.

Postoperative

Early commencement of oral intake, including carbohydrate drinks and discontinuation of intravenous fluids is desired in post-operative period. These can be continued if pre-operative nutritional status was poor and continued beyond the return of normal intake. Post-operative fasting is detrimental similar to prolonged pre-operative fasting as early oral intake is associated with lesser wound complications, reduced rates of ileus and shorter hospital stay. Thoracic epidural analgesia is recommended strongly in open abdominal surgeries and weakly recommended in laparoscopic surgeries. Intravenous lidocaine is moderately recommended for both surgical techniques. Transversus abdominis plane block is strongly recommended in laparoscopic abdominal surgery. Continuous local wound infiltration is weekly recommended in open abdominal technique. Drains and urinary catheters are removed as soon as possible. Multimodal analgesia is used with non-steroidal anti-inflammatory drugs and oral paracetamol. Intravenous opioids especially long acting opioids are avoided to avoid undue sedation, ileus, and respiratory depression, however shorter ones are preferred for break through pain. The use of analgesic adjuncts such as gabapentin or pregabalin has been shown to have a beneficial opioid sparing effect post-operatively and facilitates early mobilization. Effectively modulating these responses to attenuate the impact of surgery may help promote an early recovery and has been associated with reduced length of stay, complication rates, and use of analgesia, costs for patients and increased patient comfort and satisfaction.^{19,20}

Conclusion

There are various stress responses of the body to surgical stimuli, which are less pronounced during minor procedure and in normal healthy male. They can be profound in patients

who suffer from multiple co-morbidities such as cardiac disease, hypertension, diabetes etc. The surgical stress responses are varied in pre, peri and post-operative period and are influenced by other factors such as hypoxemia, hypovolemia, hypercarbia, pain, sympathetic stimulus etc. General anesthesia do not abolish such responses completely, although can blunt many of them. Regional anesthesia in the form of local anesthetics in nerve block or epidural or intrathecal abolish such responses to a greater extent. Maintaining adequate hydration, anxiolytics, glucose, preventing stress responses such as laryngoscopy, intubation, surgical incision, adequate hemodynamics are all known to prevent and abolish stress responses. Adequate analgesia via epidural opioids and local anesthetics reduce catecholamine releases. Early recovery from surgery is a new norm to prevent post-operative complications.

Conflict of Interest: None.

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