The metabolic and endocrine response to trauma

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Abstract

Metabolic and endocrine pathways are central to the body's compensatory response to trauma. They drive mobilization of energy substrates, volume conservation and haemostasis via activation of the hypothalamic pituitary adrenal axis, the sympathetic nervous system and an inflammatory response. As clinicians, we can intervene in these pathways, however optimal management of anaesthesia, fluids, transfusion, nutrition and the use of steroids remain controversial and to be determined.

Introduction

In order to survive traumatic insults, prior to the modern era of intravenous fluid resuscitation, humans have developed a crucial physiological response. The priority is to maintain perfusion and energy supplies to vital organs. Hence the response focuses on mobilizing fuel sources, conserving volume and minimizing blood loss. This is achieved through a complex interaction between the metabolic, endocrine and immunological pathways.

The endocrine and metabolic pathways

The hypothalamus is central in coordinating these endocrine and metabolic responses. It receives multiple inputs including from baroreceptors, volureceptors and pain fibres stimulated during trauma. In response, a number of vital pathways are activated via the pituitary and adrenal gland, and sympathetic nervous system.

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The anterior pituitary gland increases secretion of three key hormones: growth hormone, prolactin and adrenocorticotrophic hormone (ACTH), the latter stimulating the adrenal cortex to release cortisol. From the posterior pituitary gland there is increased secretion of antidiuretic hormone (ADH). Thyroxine-stimulating hormone secretion, from the anterior pituitary, is unchanged but there is an overall decrease in T3 and T4.

Hypothalamic stimulation results in increased sympathetic outflow leading to two important effector responses. Firstly, the preganglionic fibres synapsing with the adrenal medulla cause an increase in the release of catecholamines into the circulation. Secondly, there is an increase in output down all postganglionic sympathetic fibres. The most important during trauma are the cardio-acceleratory fibres and those to the smooth muscle of the vasculature. These postganglionic fibre outputs, together with increased circulating catecholamines, mediate their effects via the α and β adrenoreceptors of the end organs leading to the essential 'flight or fight responses'.

Physiological effects of the metabolic and endocrine responses to trauma

Increased energy substrates

Increased circulating levels of cortisol and growth hormone, together with catecholamines, result in mobilization of energy stores. This is an attempt to meet the increased energy demands of the body's vital organs during stress. The pancreas also plays a role by decreasing the secretion of insulin while increasing the secretion of glucagon. These pathways all result in an increase in gluconeogenesis via glycogenolysis, lipolysis and proteolysis. There is also a state of relative insulin resistance, which when combined with decreased insulin secretion, leads to decreased glucose uptake by cells and increased circulating blood glucose levels.

Overall this increase in circulating glucose attempts to ensure an increased supply at cellular level to generate ATP via aerobic respiration in the processes of glycolysis, the Krebs cycle and ultimately oxidative phosphorylation to support the body post-trauma.

As with all hormonal pathways, there is tight regulation with positive and negative feedback loops ensuring homeostasis so that, for example, the cortisol feeds back into the hypothalamus decreasing release of further corticotrophin releasing hormone.

Volume conservation and redistribution

Trauma can result in a shocked state with hypoperfusion of vital organs. In an attempt to maintain organ perfusion several

physiological responses occur, with the overall aim of ensuring redistribution of blood flow to vital organs, volume conservation and optimal haemostasis.

Increased sympathetic outflow leads to positive ionotropy and chronotropy. Sympathetically mediated peripheral venoconstriction mobilises blood from reservoirs, such as muscle, to increase venous return. Arteriolar vasoconstriction redistributes blood flow from peripheral to central structures.

In an attempt to correct volume loss various compensatory processes are activated, namely the renin—angiotensin—aldosterone system (RAAS) and ADH release from the posterior pituitary.

Renin is secreted from juxtaglomerular cells in the kidney as a result of increased sympathetic activity, renal hypoperfusion and reduced sodium delivery to the macula densa. Renin converts angiotensinogen to angiotensin I, which is further cleaved via angiotensin-converting enzyme (ACE), to angiotensin II (AT II). AT II has multiple effects. Primarily, it stimulates the release of aldosterone from the zona glomerulosa of the adrenal cortex and via its actions on the hypothalamus results in thirst and additional ADH secretion. It is also a potent peripheral vasoconstrictor. At the glomerulus, it causes preferential efferent arteriole constriction in an attempt to conserve glomerular filtration rate (GFR). ACTH and hyperkalaemia stimulate aldosterone release to a lesser extent.

Aldosterone acts predominantly on the distal convoluted tubule of the nephron resulting in reabsorption of sodium and loss of potassium and hydrogen ions. This increases water reabsorption and hence volume conservation. This is further accentuated by the aldosterone like effect of circulating cortisol and by ADH released from the posterior pituitary, which through its action on the collecting ducts leads to further water reabsorption.

Haemostasis

In an attempt to prevent ongoing blood loss and conserve volume, various haemostatic mechanisms are activated. These include vasoconstriction and platelet adhesion and aggregation, ultimately leading to clot formation. These processes are augmented by the inflammatory response to trauma, namely elevated arachidonic acid metabolites such as thromboxane A2, which acts as a potent vasoconstrictor and increases platelet activation and aggregation. Serum levels of acute phase proteins, such as the procoagulant fibrinogen, are also elevated whilst others such as the anti-coagulant protein C are decreased altering the balance between pro- and anti-coagulant factors. As a result of these pathways a hypercoagulable state occurs.

The immunological response

Trauma-induced tissue damage activates the complement pathway. This results in neutrophil and macrophage activation with subsequent release of inflammatory mediators including interleukin-1, tumour necrosis factor-α (TNF-α) and platelet-activating factor. Consequently, there is upregulation of other acute phase proteins including fibrinogen, oxygen free radicals and proteases as well as arachidonic acid metabolites including thromboxanes and prostaglandins. The end result of this earliest phase of tissue trauma is thrombus formation, accumulation of neutrophils at the site of injury and activation of cell-mediated and humoral immune pathways. These processes aim to limit further tissue damage and promote repair. There is a delicate balance between these pro- and anti-inflammatory pathways. Interfering with these in an attempt to optimise outcomes in trauma patients, for example by administration of steroids, is complex.

Management of the metabolic and endocrine pathways activated in trauma: current controversies

The metabolic and endocrine processes seek to preserve vital organ functions and allow survival following traumatic insult. If trauma is not managed appropriately these compensatory mechanisms can become overwhelmed and result in death.

The hypermetabolic state associated with trauma increases tissue oxygen demand. If cardiac output fails to increase sufficiently, inadequate oxygen delivery to the tissues occurs. This can be further compromised by peripheral vasoconstriction and anaemia. Overall this will result in cellular hypoxia, lactic acidosis and multiorgan failure. Equally, the compensatory mechanisms of the coagulation system can become overwhelmed resulting in disseminated intravascular coagulopathy (DIC) and uncontrolled haemorrhage.

There are numerous interventions utilised in the management of trauma patients, some augment the natural physiological responses but some interfere with these responses and can lead to poorer patient outcomes. It is important that we understand how our actions interfere with these processes so we can continue to optimise our management and improve patient outcomes.

Conduct of anaesthesia

Given its favourable haemodynamic profile, etomidate was traditionally used as an induction agent in haemodynamically unstable trauma patients. Despite studies failing to definitively link etomidate with negative outcomes[1] concerns have been raised regarding the resultant adrenal suppression and its potential impact on survival. Ketamine has a similar haemodynamic profile to etomidate and may be more appropriate in the cardiovascularly unstable trauma patient. The neuroprotective effects of thiopentone and propofol make them ideal induction agents in traumatic brain injury but they should be used in lower doses and with caution in unstable patients due to their vasodilatory and negative ionotropic effects. Midazolam and fentanyl are alternatives to the traditional induction agents.

Regional anaesthetic techniques have been used to improve analgesia and attenuate the sympathetic response to pain. There is increasing evidence to support the safety of regional anaesthesia in trauma[2] despite prior concerns regarding risks associated with coagulopathy and concealed compartment syndrome, but no clear evidence for improved patient outcomes exists.

Steroids

Steroid use in trauma remains controversial. The initial hyper-inflammatory response, aimed at limiting tissue damage, is followed by a hypoinflammatory phase. During this latter phase the body is susceptible to infection which can worsen tissue damage, the so-called 'two hit hypothesis'.[3] There is some evidence that administration of steroids to trauma patients may reduce their risk of pneumonia by interfering with the balance between this hyper- and hypo-immune response.[3] However there are concerns as etomidate was used in this trial and the results conflict with

those of a previous study which showed increased mortality with steroid use in traumatic brain injury (TBI).[4]

In hypotensive septic patients, it has been shown that the administration of steroids increases the rate of shock reversal but it is unclear if this can be translated to trauma patients.[5] Overall understanding of the hypothalamic–pituitary–adrenal (HPA) axis in critical illness remains limited with recent evidence suggesting that cortisol levels appear to be independent of ACTH.[6] This leads to further uncertainty regarding the role of steroids in critical care, including for trauma patients.

Fluid management

Traditionally, trauma patients have received large-volume fluid resuscitation in an attempt to reverse their hypovolaemic state and improve organ perfusion. But, it has been increasingly suggested that large-volume resuscitation can lead to dilution of coagulation factors, hypothermia and increased blood pressure resulting in clot dislodgement, coagulopathy and poor organ perfusion. Evidence also suggests a link between increased volume of fluid resuscitation and mortality.[7] The principle of damage control resuscitation (DCR) is increasingly being used, with permissive hypovolaemia/hypotension, haemostatic transfusion and damage control surgery. Despite this, controversy remains over blood pressure targets in trauma resuscitation. There is some evidence that targeting a lower blood pressure in penetrating trauma has a survival benefit[8] but other studies, especially of blunt trauma, have failed to show such benefit.[9]

Current European guidelines recommend targeting a systolic blood pressure of 80–100 mmHg (Grade 1C evidence).[10] Hypotensive resuscitation should be avoided in TBI where there is evidence that even a single hypotensive episode is associated with increased mortality. Current recommendations from the Brain Trauma Foundation are to maintain systolic BP above 90 mmHg in this patient group.

Blood product management

Blood product administration is a controversial topic in trauma resuscitation. Initially, as a consequence of the stress response, acute phase proteins increase. These include fibrinogen, which, together with hypovolaemia, result in a hypercoaguable profile. Despite this, there is emerging evidence to suggest that an early coagulopathy occurs in trauma and this is associated with increased mortality.[11]

Traditionally, trauma resuscitation focused on administration of large volumes of packed red cells with a small volume of plasma. However there is some evidence from military trauma that increased plasma to red cell ratio might lead to an improved coagulation profile.[12] It is now generally accepted in civilian trauma, that after four units red blood cell transfusion, a combination of platelets and coagulation factors should be administered in high ratios to maintain supply of these substrates and avoid DIC.

Traditional laboratory tests often do not reflect the coagulation picture accurately. There is increasing interest in the use of point of care testing, for example thromboelastography, although unvalidated in the acute setting. This, together with a recent study, suggests that the coagulation picture in trauma might be more complicated than initially thought and has suggested, for example, that such patients might benefit from earlier fibrinogen replacement.[13] The consumptive coagulopathy often seen in trauma may be exacerbated by accelerated fibrinolysis. The early use of tranexamic acid, an antifibrinolytic agent, as described in the CRASH 2 (Clinical randomisation of an antifibrinolytic in significant haemorrhage) trial[14] may decrease morbidity and mortality by minimizing this.

Feeding

The hypercatabolic state associated with trauma can lead to muscle atrophy and a resultant negative nitrogen balance. If inadequate fuel sources are available, ketogenesis occurs which can exacerbate any existing acidaemia. The European Society of Enteral and Parenteral Nutrition (ESPEN) recommends early feeding in critically ill patients. Enteral nutrition should be used if possible but if abdominal injuries do not allow, parenteral nutrition should be used.

In this hypercatabolic state glutamine stores can become rapidly depleted and this has been associated with an increased incidence of nosocomial infections. The evidence is conflicting regarding glutamine supplementation and its potential benefits on infection and mortality rates. A recent meta-analysis indicated reduced infection rates and a trend towards reduced mortality in surgical patients receiving glutamine supplements.[15] Current recommendations from ESPEN are to supplement glutamine in trauma patients receiving parenteral nutrition.

It is clear that severe trauma results in immense physiological derangement with an impact on various pathways: metabolic, endocrine and immune.

Overall, in recent years survival has improved possibly reflecting improved understanding and management of these patients. Nonetheless, John Hunter, a military surgeon, as early as 1794, summed up the body's innate ability to survive trauma and reminds us of the need to manage trauma patients with caution, to support rather than hinder these metabolic and endocrine responses.

'There is a circumstance attending accidental injury which does not belong to disease — namely, that the injury done has in all cases a tendency to produce both the disposition and the means of cure'. ◆

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