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Review Article

CLINICAL PRACTICE

Redefining the perioperative stress response: a narrative review

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Summary

The systemic stress response triggered by surgical trauma is characterised by sterile inflammation preceding metabolic and neuroendocrine dysregulation. However, the relevance of the classically described 'stress response' is now highly questionable in an era where profound physiological deconditioning is common in older, frail surgical patients. Commonly used assessment techniques do not accurately reflect hypothalamic–pituitary–adrenal axis integrity after major surgery. Clinical interpretation of plasma concentrations of cortisol, the prototypical stress hormone, is rarely accurate, because of study heterogeneity, the inherently dynamic characteristics of cortisol production, and assay variability. Before surgery, chronic psychosocial stress and common cardiorespiratory co-morbidities are clinically relevant modifiers of neuroendocrine activation to acute stress/inflammation. The frequent development of multimorbidity after major surgery further clouds the compartmentalised, discrete model of neuroendocrine activation after initial tissue injury. Starvation, impaired mobility, and sepsis after surgery generate distinct neuroendocrine profiles that challenge the conventional model of neuroendocrine activation. Basic science studies suggest that high circulating levels of cortisol may directly cause organ injury. Conversely, randomised controlled clinical trials investigating glucocorticoid supplementation have delivered contrasting results, with some suggesting a protective effect in the perioperative period. Here, we consider many of the confounding factors that have emerged to challenge the conventional model of the surgical stress response, and suggest that a more nuanced understanding of changes in hypothalamic–pituitary–adrenal axis physiology is warranted to advance perioperative medicine. Re-examining the perioperative stress response presents opportunities for improving outcomes through enhancing the understanding of the neuroendocrine aspects of preparation for and recovery from surgery.

Keywords: cardiovascular deconditioning; hypothalamic–pituitary–adrenal axis; inflammation; stress response; surgery; trauma

Activation of the hypothalamic–pituitary–adrenal (HPA) axis is a critical feature of the coordinated physiological response to surgical trauma.[1,2] The perioperative focus on this neuroendocrine response has largely been restricted to glucocorticoid physiology during the intraoperative period, despite accumulating evidence that each stage of the perioperative journey may be profoundly influenced by dysregulation of the HPA axis. Acute and chronic disruption of the HPA axis impairs the ability to rapidly respond to initial and sequential perioperative stressors. Several clinically underappreciated factors can profoundly modulate the perioperative stress response, as characterised by changes in cortisol physiology. Randomised, placebo-controlled trials in cardiac[3] and pancreatic surgery,[4] and experimental medicine studies in critical illness[5] suggest strongly that there is a need to re-examine whether distinct endotypes are associated with benefit, or injury, from perioperative manipulation of the HPA axis. Here, we consider recent developments in basic, translational, and clinical neuroendocrinology showing several overlooked

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aspects of glucocorticoid physiology relevant to surgery that necessitate a substantial re-evaluation of this fundamental physiological response to injury.

Molecular mechanisms of glucocorticoid action

Glucocorticoids act via two distinct intracellular receptors: mineralocorticoid receptors (MRs)[6] and glucocorticoid receptors (GRs),[7] with tissue-specific expression of MRs and wide expression of GRs (Fig. 1).[11] Both receptors translocate into the nucleus after ligand activation, where they induce or repress gene transcription through three mechanisms: direct binding to DNA via glucocorticoid response elements, protein–protein interactions with other transcription factors, and binding to both DNA and other transcription factors. The GR selectively engages with several thousand chromatin binding sites,[12] depending, in part, on corticosteroid concentration.[13] The accessibility of chromatin determines the pattern of GR binding.[14] The GR also has non-genomic, rapid effects contributing to neuronal signalling via ion channel, endogenous cannabinoid, and G-protein coupled second messenger system signalling (Fig. 1).[15]

Cortisol has a higher affinity for the MR than the GR, while the MR has equal affinity for cortisol and aldosterone.[16] The action of cortisol on GRs and MRs is determined by the density of these receptors in tissue and by specific pre-receptor cellular mechanisms that facilitate aldosterone actions on MRs in certain tissues despite the higher endogenous concentrations of cortisol. Each of these mechanisms is likely to contribute to glucocorticoid sensitivity and resistance.

Biologically active cortisol is converted to inactive cortisone (and *vice versa*) by 11β-hydroxysteroid dehydrogenase (11β-HSD), which consists of two isoforms (Fig. 1). The two isoforms are differentially expressed within, and between, tissues. The isoform 11β-HSD2 converts cortisol to cortisone, thereby preventing cortisol from occupying most of the MR binding sites in tissues where it is expressed, such as the kidney and colon.[16] Modification of tissue-specific GR, MR, and 11β-HSD expression is likely to be pivotal in pathology driven by raised endogenous and exogenous glucocorticoid concentrations in acute and chronic illness.[16]

The GR and MR expression is controlled by gene transcription and post-translational mechanisms, including by their own substrate.[7] Oxidative stress down-regulates GR expression,[17] but up-regulates MR expression.[16,18] Increased cyclic adenosine monophosphate (e.g. by catecholamines), which is common in many chronic diseases, up-regulates GR[7] and MR expression.[19] Variable and dynamic changes in GR and MR expression in different tissues illustrate the likely complexity of the physiological response to acute increase in cortisol after surgery, and may contribute to temporal and spatial patterns of postoperative organ dysfunction.

Regulation of cortisol release

The basic peripheral and neurophysiological pathways underpinning the neuroendocrine response to surgical tissue trauma are shown in Figure 2. The central regulator of this axis, the paraventricular nucleus (PVN) of the hypothalamus, is a major relay for afferent information from limbic areas of the CNS that can detect cognitive and emotional stressors, and also from brainstem structures that can detect inflammation

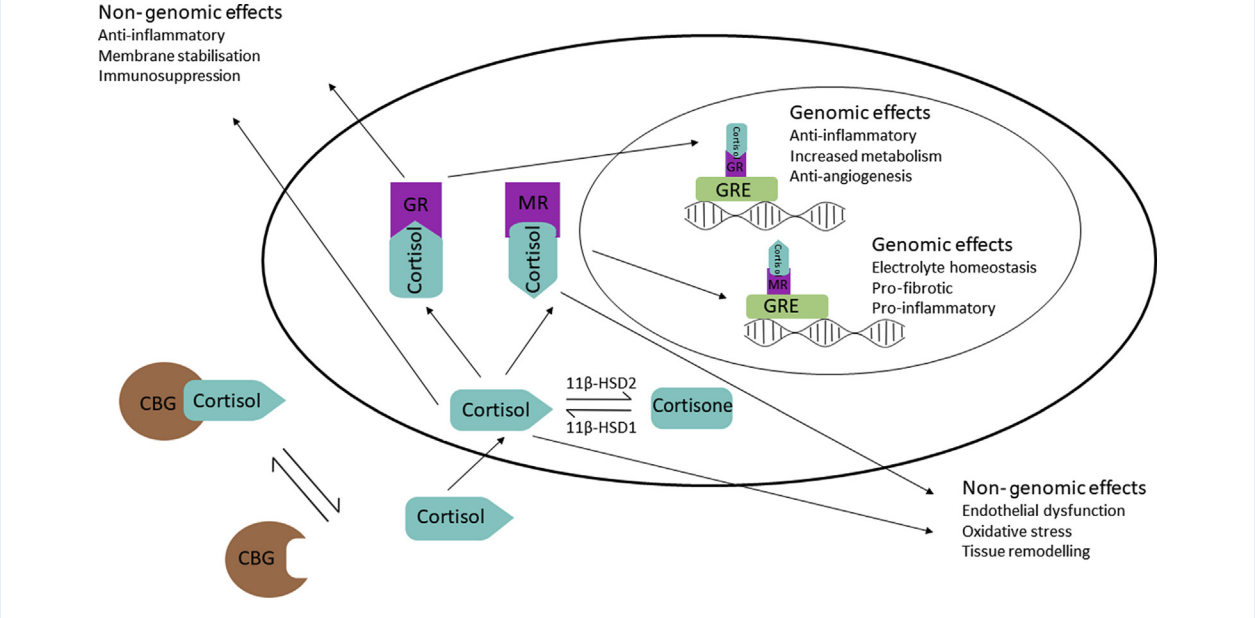

Fig 1. Genomic and non-genomic mechanisms of glucocorticoid action.[6,8–10] The classical genomic mechanism of action of glucocorticoids is mediated by the cytosolic GR, resulting in trans-repression (associated with desirable anti-inflammatory immunomodulatory actions) and trans-activation (associated with pro-inflammatory and pro-fibrotic downstream effects). Non-classical mechanisms of glucocorticoid action include both genomic effects driven by MR activation, and non-genomic effects driven by the activation of GR and MR. CBG, cortisol-binding globulin; GR, glucocorticoid receptor; GRE, glucocorticoid response element; MR, mineralocorticoid receptor; 11β-HSD, 11β-hydroxysteroid dehydrogenase.

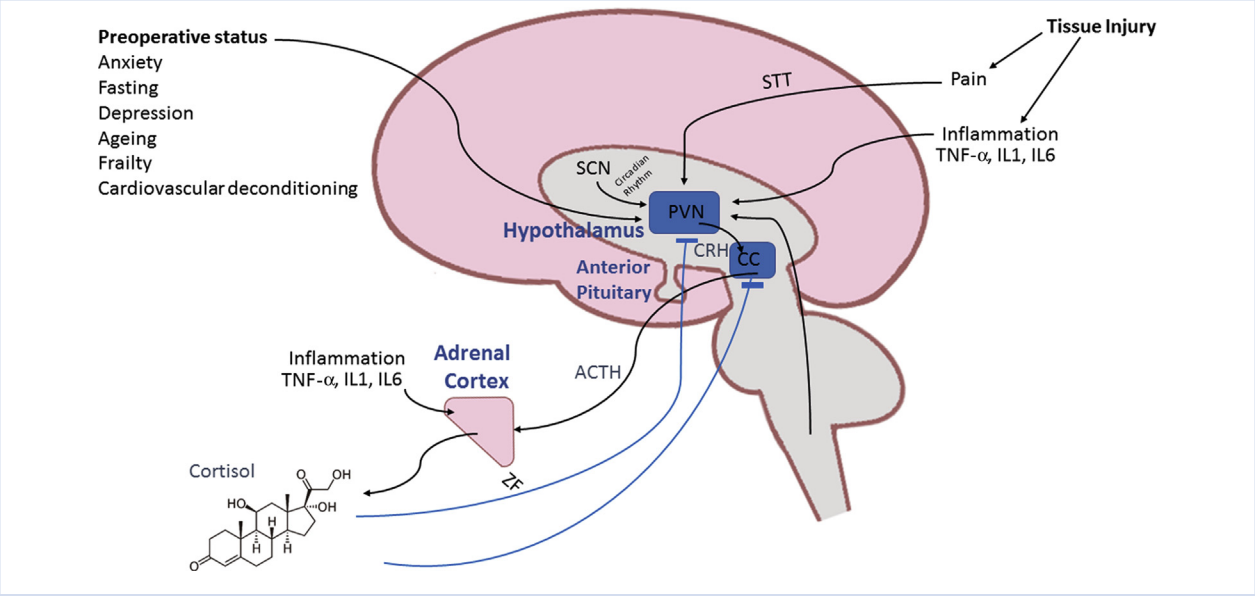

Fig 2. Regulation of the hypothalamic–pituitary–adrenal (HPA) axis during surgery. Established preoperative co-morbidities chronically alter the HPA axis in higher-risk patients. ACTH, adrenocorticotropic hormone; CC, corticotrophic cell; CRH, corticotrophin-releasing hormone; IL, interleukin; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; STT, spinothalamic tract; TNF-α, tumour necrosis factor-α; ZF, zona fasciculata.

and physiological changes.[1] Corticotrophin-releasing hormone (CRH) is then released into the hypophyseal portal plexus and binds to CRH receptors on corticotropes in the anterior pituitary gland to release the adrenocorticotropic hormone (ACTH). Vasopressin, released from the hypothalamus and reaching the corticotroph cells in the anterior pituitary via the short portal vessels, is a key component of the stress response to acute stimuli and stimulates the release of ACTH via the vasopressin-3 receptor. ACTH is released via exocytosis into the systemic circulation where it primarily acts on the melanocortin-2 receptors in the *zona fasciculata* of the adrenal cortex to synthesise glucocorticoids that are then released into the circulation, the most significant of which is cortisol.[20]

Carrier proteins, primarily cortisol-binding globulin (CBG) and, to a lesser extent, albumin, prevent cortisol from diffusing into cells in target tissues, with only ~5% of the circulating cortisol in its active form.[21] Increased free cortisol levels are paralleled by reductions in carrier proteins, and at sites of inflammation, activated neutrophils cleave CBG, which further increases the local active cortisol concentrations.[22]

Rhythms in cortisol regulation

The acute perioperative period disrupts the circadian cycles that regulate the cortisol levels. Ultradian pulsatile signalling is superimposed on the circadian pattern of cortisol release, a process controlled by the suprachiasmatic nucleus and by the hypothalamic parvocellular neurones of the PVN (Fig. 3).[26] The ultradian, pulsatile pattern of cortisol release is regulated by the feedback between the anterior pituitary and adrenal glands.[27] Cortisol replacement therapy fails to reproduce glucocorticoid pulsatility.

Under normal, 'unstressed' conditions, circulating free cortisol reduces ACTH secretion and inhibits CRH release through negative feedback at the hypothalamic PVN and anterior pituitary.[1] However, immediately after surgery, ultradian pulses in ACTH and cortisol increase substantially.[28] ACTH concentrations then return to normal within 24 h in the face of persistently elevated, but less frequent, pulses of cortisol (Fig. 3).[28] The mechanisms underlying this disconnection are unclear, but potential mechanisms are considered in the following discussion.

Perioperative cortisol studies

Analytical issues

Central to understanding the perioperative 'stress response' is the need for certainty that cortisol measurements are based on robust assay techniques that represent biologically relevant cortisol levels. By definition, single rather than repeated measurements of cortisol cannot capture the inherently variable cortisol levels driven by ultradian rhythms. Strikingly, the gold-standard technique for measurement of free cortisol, liquid chromatography/tandem mass spectrometry (LC/MS),[29] has been used in only 2/71 perioperative studies comprising 28 cardiac surgical patients (representing 0.95% of 2953 patients studied). The vast majority of the perioperative literature is based on measurements using immunoassays from highly heterogeneous studies.[24] No cortisol measurements made using LC/MS have been undertaken during or immediately after surgery. It is during this perioperative period when the discrepancy between values recorded by LC/MS or immunoassay is likely to be most pronounced,[30] as albumin and CBG decline substantially after commonly undertaken elective surgery.[31] Higher levels of biologically free cortisol will, therefore,

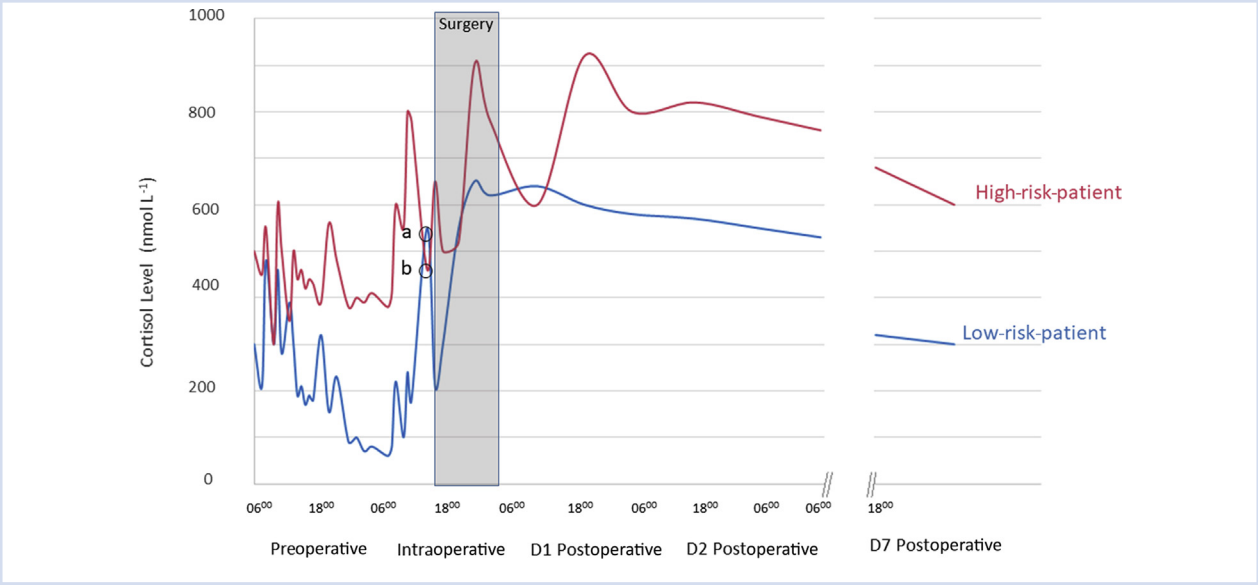

Fig 3. Stylised ultradian and circadian rhythms of cortisol before and after surgery. Throughout the perioperative period, hypothesised cortisol levels are shown for low-risk compared with high-risk patients undergoing surgery. Points a and b show cortisol levels taken on the day of surgery for the two different patients; this highlights that one time-point capture does not reflect the disruption of the hypothalamic–pituitary–adrenal axis, because at this point, the high-risk patient actually has a lower cortisol level compared with the low-risk patient despite the overall pattern of high-risk patients having higher cortisol levels before operation, with a reduction in circadian variation. Preoperative rhythms are adapted from Miller and colleagues (2017)[1] and van den Beld and colleagues (2018).[23] Intraoperative and postoperative rhythms are adapted from Prete and colleagues (2018)[24] and Chan and colleagues (2012).[25]

not be accurately quantified by immunoassays that measure total serum cortisol levels.[24] As a result of non-specific immune cross-reactivity, immunoassays overestimate cortisol levels as they also measure cortisol precursors.[32] Furthermore, various common pathologies, including critical illness, also increase the inter-assay variability.[33]

Patterns of perioperative plasma cortisol

Bearing in mind these analytical issues, plasma concentrations of total cortisol have been reported to increase by up to four-fold compared with healthy controls,[24] peaking within a few hours after surgery.[24] In minimally invasive procedures, the cortisol peak is delayed, but the total cortisol output still increases over 24 h compared with healthy controls.[24] Plasma concentrations of cortisol can remain elevated for at least 7 days after major surgery; this is accompanied by perturbations of the circadian and ultradian cortisol rhythm after surgery or trauma,[34] with decreased amplitude of circadian variation progressing to complete flattening in critical illness.[25] The severity of critical illness is associated with the degree of circadian disruption.[35]

Complications after surgery disrupt cortisol regulatory mechanisms

Until the landmark experimental medicine studies by Van den Berghe and colleagues, elevated cortisol after major surgery and critical illness was largely attributed to ongoing central activation by the inflammatory response.[36] However, the finding that ACTH concentrations return to normal within 24 h of surgery[28] and that ACTH concentrations in critically ill patients are low rather than high[36] strongly suggests that higher circulating cortisol levels occur independently of ACTH stimulation.

Potential mechanisms to account for persistently elevated cortisol if postoperative morbidity develops into critical illness include adrenal sensitisation, reduced carrier proteins, and reduced plasma clearance of cortisol. The adrenal release of cortisol may become sensitised during systemic inflammation, resulting in uncoupling from the HPA axis.[37] The systemic inflammatory response to surgery, involving neuropeptides, cytokines (interleukin-1β and interleukin-6), adipokines, and endothelium-derived factors, modulates the adrenal glucocorticoid release independently of pituitary ACTH.[38]

Plasma clearance of cortisol is suppressed by more than 50% in critical illness.[36] The reduced hepatic cortisol breakdown could further account for higher plasma free and total cortisol levels, as revealed by a stable isotope infusion technique.[37] Cortisol is broken down primarily by hepatic and adipose tissue reductases, plus renal 11β-HSD2. Moreover, 11β-HSD1 can reconvert cortisol from cortisone in many different tissues.[16] In critically ill patients, reductase and 11β-HSD2 expression in human liver and adipose biopsy samples was reduced, in part promoted by bile acids suppressing hepatic enzymatic function.[5] Translational murine studies also suggest that hepatic GR expression is reduced in sepsis, which reduces the cortisol-binding proteins and suppresses the α-ring reductases, resulting in increased free cortisol.[39]

Chronic preoperative HPA dysfunction

Established alterations in HPA function are well described with age, endocrine syndromes, and non-endocrine

pathology, but these latter have received little attention in the perioperative period. Many common preoperative phenotypes exhibit HPA dysfunction that frequently comprises the cohort of patients in whom perioperative complications are most frequent (Fig. 4).

Ageing

Ageing is associated with higher basal cortisol levels.[23] Age-related genomic instability and epigenetic changes result in progressive loss of hypothalamic sensitivity through loss of GRs in the CNS, decreased diurnal variation of cortisol, and a blunted negative feedback at the level of the HPA axis.[20,23] Increased expression of CRH and vasopressin occurs in the PVN of elderly humans, despite higher circulating cortisol, suggesting a disruption in feedback mechanisms of the HPA axis.[55] Age-related reductions in CBG and tissue-specific expression of 11β-HSD isoforms also contribute to higher free cortisol levels.[23] Consequently, older adults may have a higher perioperative cortisol response compared with younger patients.[24]

Frailty

Declining physical performance, including impaired balance, reduced walking speed, and grip strength, is associated with HPA axis dysregulation characterised by decreased diurnal variation of cortisol and higher cortisol levels.[56] Chronic exposure to higher cortisol levels suppresses muscle protein synthesis and increases protein catabolism, further promoting sarcopenia[57] that leads to functional decline and increased frailty burden.[58] Sarcopenia has a 15% prevalence in patients with stable chronic respiratory disease[59] and as high a prevalence as 78% in cancer patients.[60] Intercurrent illness accelerates deconditioning, sarcopenia, and frailty. Frailty is associated with increased mortality in many diseases, including chronic respiratory disease[61] and cancer,[62] which share the common characteristic of persistent inflammation that further drives frailty.[63,64] Chronic inflammation, driven by cellular senescence and oxidative stress,[65] leads to neuronal dysfunction and HPA axis dysfunction.[66] Increased cortisol levels further exacerbate this process by promoting neuronal degeneration and apoptosis.[67]

Cardiovascular deconditioning

Physical inactivity, as a consequence of either cardiac failure or other pathology (e.g. chemotherapy for cancer and chronic joint pain), leads to cardiovascular and autonomic deconditioning. The mechanisms contributing to deconditioning include endothelial dysfunction and neuroendocrine disruption.[68] Profound cardiovascular deconditioning in healthy

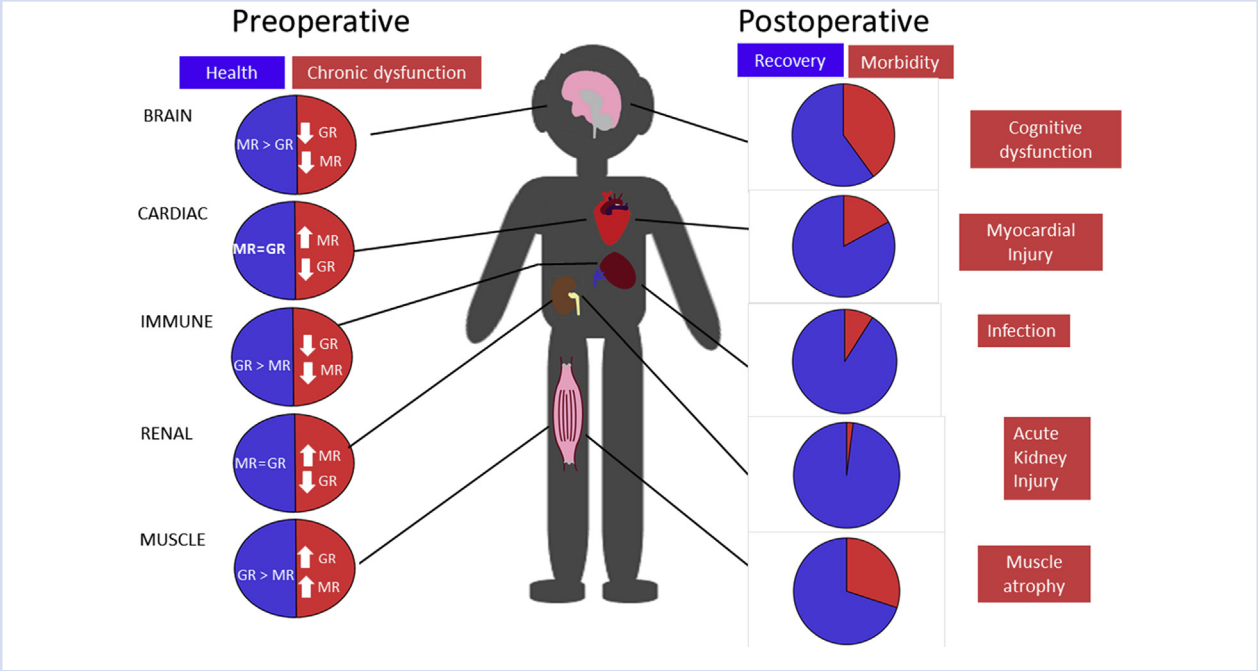

Fig 4. Schematic of distribution of corticosteroid receptors and changes in their expression in chronic disease. Relative expression of GR and MR in different tissues in health derived using the Genotype-Tissue Expression Project. Decreases in brain GR[40] and MR[11,41,42] and the ratio of MR:GR expression are implicated in anxiety and depression, and may result in postoperative cognitive decline, which can be as high as 40% in patients over 60 yr old after noncardiac surgery.[43] Increases in cardiac MR[44] and decreases in GR[44,45] are implicated in cardiac pathology, particularly heart failure and dysrhythmias, and may result in perioperative myocardial injury after noncardiac surgery, which can be as high as 20%.[46] Decreases in GR[47] and MR[48,49] in immune cells can result in immune suppression, and may account for a 9% incidence of postoperative infectious complications.[50] Increases in MR[44] and decreases in GR[51] in renal disease may contribute to the mechanisms resulting in postoperative acute kidney injury, which can have an incidence of up to 20%.[52] Increases in GR[53] and MR[53] in muscle resulting from deconditioning can precipitate muscle atrophy after operation, which can persist even after 1 yr after operation with an incidence of 30% and as high as 80%.[54] GR, glucocorticoid receptor; MR, mineralocorticoid receptor.

young volunteers develops rapidly during prolonged bed rest, leading to relative resting tachycardia,[69–71] cardiac atrophy,[72] increased sympathetic vasomotor tone,[73] decreased cardiac vagal activity,[74] and impaired arterial baroreflex control.[69] These alterations are associated with excess morbidity and mortality during critical illness,[75] and often persist beyond the period of immobilisation, leading to orthostatic intolerance,[69] reduced exercise performance,[76] and blunted cardiac responses to stress.[77,78] Just 3 days of head-down bed rest results in reduced exercise performance accompanied by exaggerated, exercise-evoked increases in total plasma cortisol.[76] Higher serum cortisol levels are independently associated with more cardiac events in established heart failure.[79] The cortisol response to standardised stressors or CRH in heart failure is unknown, despite overt and subclinical heart failure being strongly associated with increased morbidity and mortality after noncardiac surgery.[80–82]

Psychosocial reprogramming of HPA function

Anxiety and depression are common in surgical patients, and are associated with worse perioperative outcomes.[83,84] For example, before cardiac surgery, as many as 47% patients may be depressed. A key component of cardiac disease and depression is HPA dysfunction.[85] Although measurement of baseline cortisol rarely differs between different psychosocial disorders, tests challenging the HPA axis via the activation of GR or the Type 1 CRH receptor identify HPA axis dysfunction.[86] For example, in depression, the function of the GR at the limbic–hypothalamic level is impaired, resulting in reduced hypothalamic feedback and, consequently, increased production of glucocorticoids (termed 'glucocorticoid resistance').[87] Central CRH hyper-secretion may account for these neuroendocrine, autonomic, and behavioural changes.[88]

HPA axis dysregulation has been estimated to occur in up to 80% of depressed patients.[89] This may account for the increased susceptibility to upper respiratory tract infections and psychosocial stress,[90] mediated in part by lower absolute T-lymphocyte count, blunting the increase of T-cell numbers in response to viral infection and resulting in more frequent reactivation of latent viruses.[91] Recent bereavement is associated with risk of increased mortality, and correlates with elevation of plasma cortisol and altered immune function.[92] Human data show that cortisol contributes to an increased risk of wound sepsis. In high-school students, healing of skin punch biopsies is delayed by psychological stress induced by examinations, which correlates with higher morning levels of plasma cortisol.[93] Therefore, psychosocial disorders associated with HPA axis dysfunction are likely to have worse outcomes after operation, secondary to disruption in wound healing and immune function.

Measuring preoperative HPA axis function

The peak cortisol response to insulin-induced hypoglycaemia can be used to confirm cortisol and ACTH reserve,[94] and is widely used in patients with hypothalamic–pituitary damage. The normal cut-off cortisol level in response to insulin-induced hypoglycaemia was established by comparing it to the cortisol levels reached in response to surgery. Understandably, surgery can demonstrate a higher and more sustained cortisol concentration compared with insulin-induced hypoglycaemia.[95] Nonetheless, insulin-induced hypoglycaemia was used to assess adrenal insufficiency in patients undergoing corticosteroid treatment and guide steroid replacement during surgery.[95]

Another test for assessment of adrenal function is the short Synacthen test, which is used routinely to assess adrenal reserve in hypocortisolaemic patients and the ability of glucocorticoid-treated patients to respond to surgical stress. However, there are significant concerns about sensitivity and lack of consensus regarding the protocol for post-surgical patients.[96] Stimulation with CRH is used in the diagnostic workup of Cushing's disease, while its role to assess the functional defect of ACTH secretion in patients with hypothalamic or pituitary lesions has not been established. There is no single test that can reliably predict adrenal insufficiency in response to surgical stress, although such tests have been used in studies to compare cortisol responses in disease states. For example, compared with controls, those with depression had a proportionally higher cortisol response to the amount of ACTH released during stimulation with CRH with blunted ACTH response,[97] suggesting desensitised pituitary CRH receptors as a result of down-regulation by higher basal cortisol levels. Therefore, patients with depression may have a disturbance in their hypothalamic regulation and may be unable to mount a significant response to surgical stress. Indeed, when depressed patients are stimulated with insulin-induced hypoglycaemia, their adrenal response is attenuated.

Clinical implications for perioperative medicine

HPA axis dysfunction is common across many chronic diseases present before operation in surgical patients. Established HPA axis dysfunction significantly impacts on the regulatory mechanisms governing cortisol release during stress. However, it is notable that no systematic exploration has been undertaken to determine whether this heterogeneous preoperative picture translates to different surgical stress responses between otherwise clinically indistinguishable individuals. With that in mind, translational studies provide several possible mechanisms of organ injury through which the perioperative release of cortisol may account for worse postoperative outcomes in susceptible individuals, as considered in the following section.

Glucocorticoid biology and perioperative morbidity

Myocardial injury

Cardiomyocytes express low levels of 11β-HSD2, resulting in cardiac MR being preferentially activated by cortisol.[16] MR is up-regulated in cardiac failure,[98] an established risk factor for perioperative myocardial injury. Landmark studies demonstrated a pivotal role for MR antagonists in reducing mortality in cardiac failure,[99] confirming robust basic science/translational data that over-activation of the MR signalling pathway is deleterious to the myocardium. Genetic deletion or inactivation of the MR gene (*NR3C2*) attenuates left ventricular dilatation, cardiac hypertrophy, and development of heart failure in murine models.[45] In contrast, genetic overexpression of cardiomyocyte MR causes ventricular remodelling, cardiac failure, and dysrhythmias.[45] Oxidative stress, driven by angiotensin II, up-regulates MR-dependent transcriptional activity.[18,100] These experimental data are consistent with the clinical observation that Cushing's disease is associated with a higher risk of cardiovascular events, which is not solely

explained by conventional cardiac risk factors.[101] Additionally, glucocorticoid modulation of immune cells infiltrating injured cardiac tissue may prevent the resolution of inflammation.[102]

A systematic review of RCTs in cardiac surgery demonstrated an increased risk of myocardial injury and increased plasma creatinine kinase-muscle/brain (CK-MB) concentrations, when exogenous high-dose methylprednisolone was administered before surgery.[3] An increase in CK-MB concentrations in patients randomised to the methylprednisolone group was associated with double the risk of death within 30 days of surgery. As methylprednisolone appears to have negligible affinity for the MR,[103] these data suggest that suppressing the inflammatory response required to resolve tissue injury after direct surgical cardiac tissue injury is deleterious. This contention is supported by both basic science and small clinical studies suggesting that methylprednisolone increases the infarct size after myocardial infarction.[104] On the other hand, a meta-analysis of glucocorticoid treatment after an acute myocardial infarction showed conflicting evidence on infarct size, suggesting a possible mortality benefit.[104]

Acute kidney injury

Up to 20% of patients sustain perioperative acute kidney injury (AKI), depending on the type of operation.[52] Chronic kidney disease is a key risk factor for perioperative AKI, which increases all-cause morbidity and accelerates mortality.[105] In health, renal 11β-HSD2 prevents the activation of renal MRs by cortisol by converting cortisol to its inactive metabolites.[16] However, impaired renal function is associated with a decrease in the expression of renal 11β-HSD2, leading to cortisol activation of renal MRs.[106] Furthermore, MR blockade limits the progression of AKI to chronic kidney disease.[107]

In addition to raised aldosterone concentrations within 24 h of surgery, experimental data support that glucocorticoids contribute to renal injury through an MR-dependent mechanism.[108] Daily subcutaneous administration of hydrocortisone to rats deficient in cortisol after bilateral adrenalectomy resulted in albuminuria; increased transcription of MR target genes; and histological changes, including glomerulosclerosis and podocyte depletion, consistent with renal injury.[108] This glucocorticoid-induced injury was reduced by MR antagonists.[108] Patients with Cushing's syndrome show similar histological changes after long-term exposure to endogenously high levels of cortisol.[109]

Renal vascular dysfunction has been suggested to contribute to glucocorticoid-induced renal injury, as genetic deletion of MR in vascular smooth muscle cells reduces AKI in a murine ischaemia–reperfusion injury model.[110] This is hypothesised to be mediated via Rac1-dependent promotion of reactive oxygen species generation, as also observed in cardiac myocytes.[110] MR antagonists prevent Rac1-mediated oxidative stress, which reduces endothelin B receptor expression through sulfenic acid modification.[111] Endothelin B maintains renal vasodilation in chronic kidney disease[112]; the protective effects of MR antagonism are lost when it is co-administered with an endothelin B receptor antagonist.[107] Taken together, these findings suggest that increases in cortisol perioperatively may contribute to renal injury through an MR-dependent mechanism, in part through compromising renal perfusion.

Postoperative neurological morbidity

Neurological morbidity after noncardiac and cardiac surgery frequently clusters with multi-organ dysfunction, impedes recovery, and increases mortality. Chronically elevated glucocorticoid concentrations cause memory decline and correlate with the development of hippocampus-dependent learning and memory deficits in humans.[113] Persistent flattening of circadian cortisol rhythms is associated with postoperative cognitive decline within a week of surgery.[114] Raised perioperative plasma cortisol concentrations are also associated with delirium,[115] which prolongs hospital stay and accelerates mortality in up to 60% of elderly patients after major surgery.[116]

Dynamic, ultradian patterns of glucocorticoid activity maintain synaptic activity and preserve cognitive and behavioural processing.[117] After blocking the adrenal steroid synthesis with the inhibitor metyrapone in healthy male volunteers, non-pulsatile cortisol dosing impaired the response to emotional stimulation, cognition, working memory performance, and quality of sleep, in contrast to pulsatile cortisol administration.[118] Clinically, these experimental data are reinforced by the finding that high-dose intraoperative methylprednisolone failed to reduce postoperative cognitive dysfunction or quality of recovery in high-risk cardiac surgical patients. Indeed, patients with postoperative cognitive dysfunction had a worse quality of recovery regardless of whether they received steroids.[119] These data support the possibility that postoperative neurological morbidity may, in part, be driven by continuous high cortisol levels.

Infection and sepsis

Up to 10% of patients develop an infection after elective surgery.[120] Adrenal insufficiency is associated with increased mortality in sepsis,[121] but high cortisol levels are also associated with critical illness and increased mortality.[122] GR expression predominates in the immune system.[123] Cortisol exerts both pro-inflammatory effects and immunosuppressive effects in a complex cell-, time-, and concentration-specific manner (Fig. 5).[124] At low levels under physiological conditions, cortisol sensitises the innate immune response to enable the rapid detection of an insult, and hence, induction of an inflammatory response. This is achieved by upregulating the expression of Toll-like receptors, which recognise danger and pathogen-associated molecular patterns and the NLRP3 inflammasome.[125] However, sustained, higher 'stress' levels of cortisol suppress the adaptive immune response, in part through inducing metabolic dysfunction and death in lymphocytes after surgery.[126] Glucocorticoids help resolve inflammation by reducing neutrophil extravasation,[124] increasing apoptotic death of neutrophils,[127] and augmenting phagocytic activity in tissue-resident macrophages.[128] The potential effect of established preoperative disruption of normal glucocorticoid signalling on the orchestration of perioperative inflammation in patients with morbidity linked to HPA axis dysfunction is unclear.[129]

Insights from RCTs: a need for precision medicine

Experimental data demonstrate that high levels of cortisol released during systemic inflammation and acute oxidative stress can result in organ injury. Clinical trials exploring glucocorticoid supplementation have provided conflicting data, in part reflecting the lack of understanding in cortisol biology during the perioperative period. A meta-analysis of 56 trials of perioperative glucocorticoid administration showed no impact on length of stay or incidence of infection.[130]

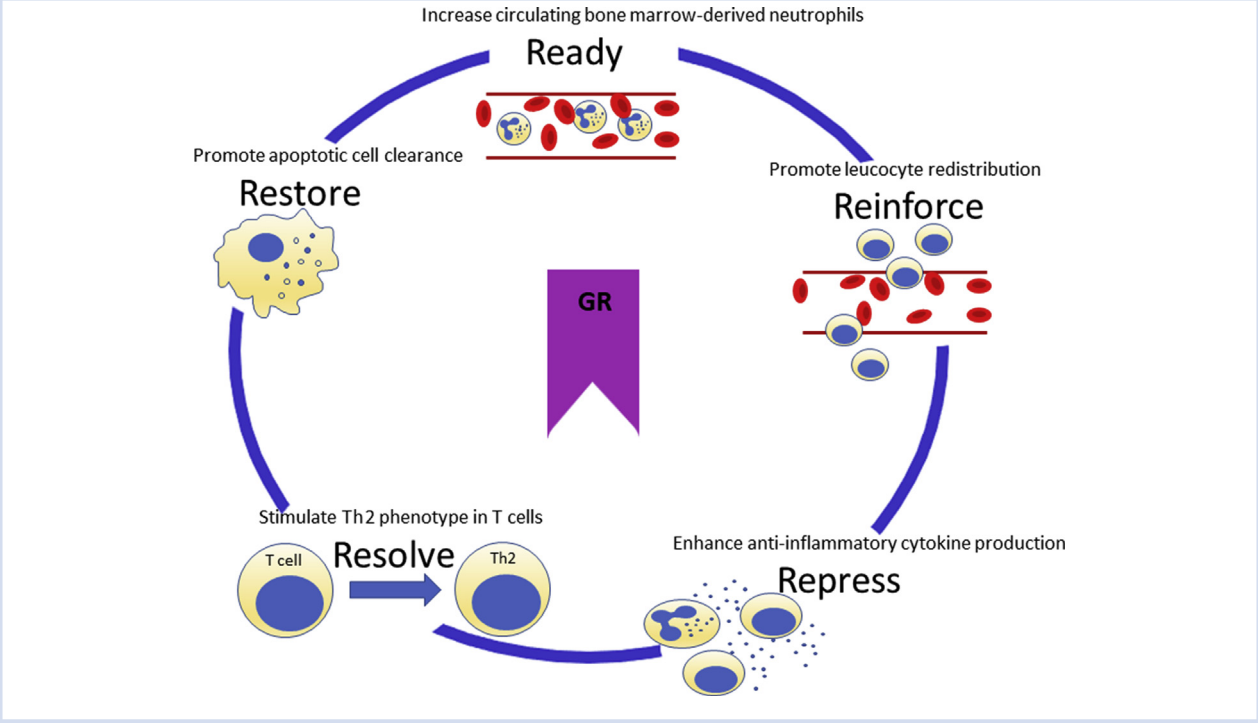

Fig 5. Regulation of inflammation by glucocorticoids. The GR pleiotropically fine-tunes the immune function at all stages of the inflammatory response to pathogens and tissue injury. Initial inhibition of pro-inflammatory cytokine production by the GR is followed by promotion of the resolution of inflammation. The GR-regulated mechanisms include stimulation of the secretion of pro-resolving molecules, such as annexin-1, driving a Th2 adaptive response, inducing programmed cell death in neutrophils and T cells, and promoting the removal of apoptotic cells. Adapted from Busillo and Cidlowski (2013).[124] GR, glucocorticoid receptor.

Similarly, low-quality trials precluded meta-analysis of trials examining the impact of systemic glucocorticoid administration in elective hip and knee surgery.[131] However, the heterogeneity amongst different patient groups in clinical trials suggests that the impact of glucocorticoid administration during a period of surgical stress is unlikely to neatly fit into a single approach.[132] For example, in the absence of systematic assessment of glucose levels after surgery, a negative impact of glucocorticoid-induced hyperglycaemia on morbidity and mortality cannot be ruled out.[133]

Heterogeneity in the timing, dose, and type of glucocorticoid administered adds further complexity. Cell-based work comparing glucocorticoid and mineralocorticoid properties suggests that inter-glucocorticoid drug therapy conversions are likely to be inaccurate.[103] A meta-analysis of trials where only high-dose methylprednisolone had been administered suggested that pulmonary complications were reduced, particularly in trauma patients.[134] This suggests that the dosing and type of glucocorticoid need to be taken into account. The timing of glucocorticoid administration may also be important. In laparoscopic cholecystectomy, a single dose of dexamethasone was administered 90 min before surgical incision, allowing sufficient time for pre-injury gene transcription (in contrast to other studies where administration was closer to surgery).[135]

Trials, in which a targeted, precision medicine approach to perioperative glucocorticoid therapy has been adopted, suggest that a rather more nuanced interpretation is warranted. Prolonged (72 h) i.v. treatment with hydrocortisone, stratified by intraoperative histological evidence for pancreatic inflammation, reduced major complications after pancreatic resection.[4] In an observational sub-study of the Measurement of Exercise Tolerance before Surgery study,[136] perioperative myocardial injury was associated with a relatively lower increase in plasma cortisol levels after surgery.[137] This suggests that, in patients with a blunted cortisol response to surgery, worse perioperative outcomes may be a feature if supplemental glucocorticoids are not provided.

Insights from trials in critically ill patients

Relative glucocorticoid insufficiency is a feature from the largest trial in critical illness (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock [ADRENAL]), where a pre-specified subgroup analysis revealed that supplemental hydrocortisone was associated with faster resolution of shock and extubation in 3800 critically ill patients with septic shock requiring mechanical ventilation randomised to receive hydrocortisone (200 mg day^{-1}) or placebo.[138] Although the primary outcome (death from any cause at 90 days) was similar in ADRENAL, cardiopulmonary benefits occurred without increasing the risk of new-onset bacteraemia or fungaemia. As the hydrocortisone doses used in this study were likely to saturate the MR, these data mirror sepsis studies, in which the potent mineralocorticoid agonist fludrocortisone was used in conjunction with hydrocortisone.[139] Either way, the clinical outcomes suggest glucocorticoids may have an effect on cardiovascular pathophysiology; volume

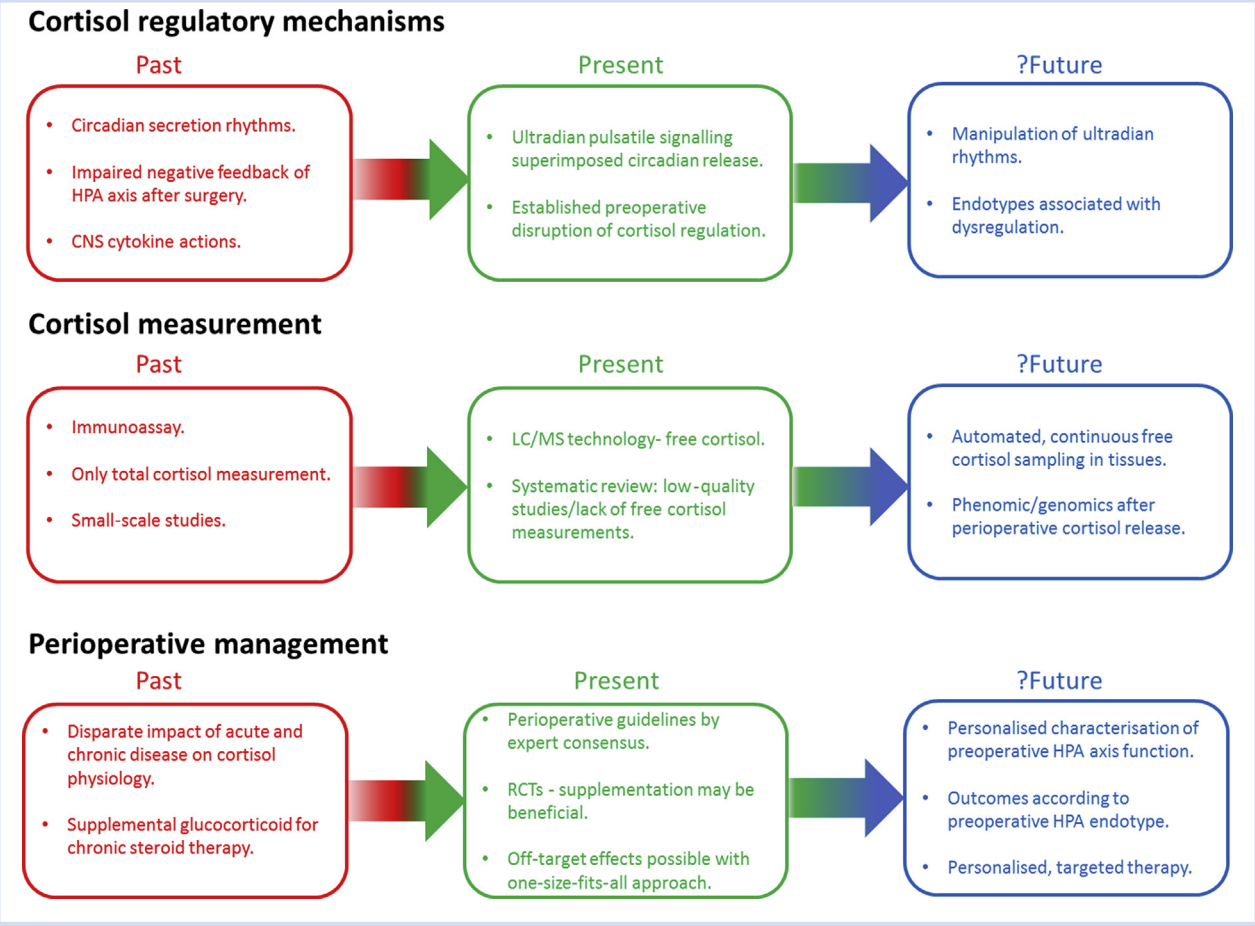

Fig 6. Current and future directions of cortisol physiology as applied to the perioperative setting. Summary of the key concepts discussed, highlighting key developments and changes in clinical management over the past 20 yr, and key areas requiring further exploration. HPA, hypothalamic–pituitary–adrenal; LC/MS, liquid chromatography/tandem mass spectrometry.

retention (MR effect) and restoration of vascular responsivity to catecholamines through inhibition of endothelial inducible nitric oxide synthesis (GR effect) may account for these findings.

On balance, critical care and perioperative trials suggest that glucocorticoid administration reduces inflammation, which is strongly implicated in promoting postoperative morbidity.[140] Moreover, they also highlight that timing, clinical context, and patient individualisation are likely key factors that require careful consideration. The Perioperative Administration of Dexamethasone and Infection RCT (the analysis of which was stratified by the presence/absence of controlled diabetes mellitus) may shed further light on some of these factors.[141]

Conclusions

Relative perioperative cortisol deficiency appears to be an under-recognised contributor to perioperative organ injury. Subclinical endotypes of HPA axis dysregulation are common in the surgical population before operation. A broad range of apparently disparate preoperative risk factors are associated with HPA axis dysfunction. In particular, glucocorticoid impairment may contribute to the poorer outcomes associated with preoperative cardiovascular deconditioning. There are clear indications that a refined, stratified approach to understanding the stress response to surgery at the molecular and organ levels is required (Fig. 6). A more detailed approach utilising omic technologies is likely to open up therapeutic opportunities that beneficially modify such a fundamental physiological response to tissue injury.

Authors' contributions

Literature search: VM, GLA
Literature review: VM, GLA, MK
Drafting of the manuscript: VM, GLA, MK

Declarations of interest

GLA is a member of the editorial advisory board for *Intensive Care Medicine Experimental* and an editor of the *British Journal of Anaesthesia*, and has undertaken consultancy work for GlaxoSmithKline. There are no other relationships or activities that could appear to have influenced the submitted work. MK and VM-S have no conflicts of interest to declare.

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References

1. Miller T, Gibbison B, Russell GM. Hypothalamic–pituitary–adrenal function during health, major surgery, and critical illness. *BJA Educ* 2017; **17**: 16–21
2. Gibbison B, Angelini GD, Lightman SL. Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery. *Br J Anaesth* 2013; **111**: 347–60
3. Whitlock RP, Devereaux PJ, Teoh KH, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; **386**: 1243–53
4. Laaninen M, Sand J, Nordback I, Vasama K, Laukkarinen J. Perioperative hydrocortisone reduces major complications after pancreaticoduodenectomy: a randomized controlled trial. *Ann Surg* 2016; **264**: 696–702
5. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *N Engl J Med* 2013; **368**: 1477–88
6. Ruhs S, Nolze A, Hubschmann R, Grossmann C. 30 Years of the mineralocorticoid receptor: nongenomic effects via the mineralocorticoid receptor. *J Endocrinol* 2017; **234**: T107–24
7. Vandevyver S, Dejager L, Libert C. Comprehensive overview of the structure and regulation of the glucocorticoid receptor. *Endocr Rev* 2014; **35**: 671–93
8. Fuller PJ, Young MJ. Mechanisms of mineralocorticoid action. *Hypertension* 2005; **46**: 1227–35
9. Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol Sci* 2013; **34**: 518–30
10. Rose AJ, Vegiopoulos A, Herzig S. Role of glucocorticoids and the glucocorticoid receptor in metabolism: insights from genetic manipulations. *J Steroid Biochem Mol Biol* 2010; **122**: 10–20
11. Gomez-Sanchez E, Gomez-Sanchez CE. *The multifaceted mineralocorticoid receptor*. Hoboken, NJ: John Wiley & Sons; 2014. p. 965–94
12. So AY, Chaivorapol C, Bolton EC, Li H, Yamamoto KR. Determinants of cell- and gene-specific transcriptional regulation by the glucocorticoid receptor. *PLoS Genet* 2007; **3**: e94
13. Reddy TE, Pauli F, Sprouse RO, et al. Genomic determination of the glucocorticoid response reveals unexpected mechanisms of gene regulation. *Genome Res* 2009; **19**: 2163–71
14. John S, Sabo PJ, Thurman RE, et al. Chromatin accessibility pre-determines glucocorticoid receptor binding patterns. *Nat Genet* 2011; **43**: 264–8
15. Tasker JG, Di S, Malcher-Lopes R. Minireview: rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology* 2006; **147**: 5549–56
16. Funder JW. Mineralocorticoid receptors: distribution and activation. *Heart Fail Rev* 2005; **10**: 15–22
17. Okamoto K, Tanaka H, Ogawa H, et al. Redox-dependent regulation of nuclear import of the glucocorticoid receptor. *J Biol Chem* 1999; **274**: 10363–71
18. Nagase M, Ayuzawa N, Kawarazaki W, et al. Oxidative stress causes mineralocorticoid receptor activation in rat cardiomyocytes: role of small GTPase Rac1. *Hypertension* 2012; **59**: 500–6
19. Wang J, Li X, Ke Y, et al. GPR48 increases mineralocorticoid receptor gene expression. *J Am Soc Nephrol* 2012; **23**: 281–93
20. Herman JP, McKlveen JM, Ghosal S, et al. *Regulation of the hypothalamic-pituitary-adrenocortical stress response*. Hoboken, NJ: John Wiley & Sons; 2016. p. 603–21
21. Lewis JG, Bagley CJ, Elder PA, Bachmann AW, Torpy DJ. Plasma free cortisol fraction reflects levels of functioning corticosteroid-binding globulin. *Clin Chim Acta* 2005; **359**: 189–94
22. Henley DE, Lightman SL. New insights into corticosteroid-binding globulin and glucocorticoid delivery. *Neuroscience* 2011; **180**: 1–8
23. van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. *Lancet Diabetes Endocrinol* 2018; **6**: 647–58
24. Prete A, Yan Q, Al-Tarrah K, et al. The cortisol stress response induced by surgery: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2018; **89**: 554–67
25. Chan MC, Spieth PM, Quinn K, Parotto M, Zhang H, Slutsky AS. Circadian rhythms: from basic mechanisms to the intensive care unit. *Crit Care Med* 2012; **40**: 246–53
26. Chung S, Son GH, Kim K. Circadian rhythm of adrenal glucocorticoid: its regulation and clinical implications. *Biochim Biophys Acta* 2011; **1812**: 581–91
27. Spiga F, Walker JJ, Terry JR, Lightman SL. *HPA axis-rhythms*. Hoboken, NJ: John Wiley & Sons; 2014. p. 1273–98
28. Gibbison B, Spiga F, Walker JJ, et al. Dynamic pituitary-adrenal interactions in response to cardiac surgery. *Crit Care Med* 2015; **43**: 791–800
29. Taylor AE, Keevil B, Huhtaniemi IT. Mass spectrometry and immunoassay: how to measure steroid hormones today and tomorrow. *Eur J Endocrinol* 2015; **173**: D1–12
30. Tractenberg RE, Jonklaas J, Soldin SJ. Agreement of immunoassay and tandem mass spectrometry in the analysis of cortisol and free t4: interpretation and implications for clinicians. *Int J Anal Chem* 2010; **2010**. https://doi.org/10.1155/2010/234808. pii: 234808
31. Roth-Isigkeit AK, Dibbelt L, Schmucker P. Blood levels of corticosteroid-binding globulin, total cortisol and unbound cortisol in patients undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass. *Steroids* 2000; **65**: 513–20
32. Monaghan PJ, Owen LJ, Trainer PJ, Brabant G, Keevil BG, Darby D. Comparison of serum cortisol measurement by immunoassay and liquid chromatography-tandem mass spectrometry in patients receiving the 11beta-hydroxylase inhibitor metyrapone. *Ann Clin Biochem* 2011; **48**: 441–6
33. Briegel J, Sprung CL, Annane D, et al. Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. *Intensive Care Med* 2009; **35**: 2151–6

34. Llompart-Pou JA, Perez G, Raurich JM, et al. Loss of cortisol circadian rhythm in patients with traumatic brain injury: a microdialysis evaluation. *Neurocrit Care* 2010; **13**: 211–6
35. Gazendam JAC, Van Dongen HPA, Grant DA, Freedman NS, Zwaveling JH, Schwab RJ. Altered circadian rhythmicity in patients in the ICU. *Chest* 2013; **144**: 483–9
36. Peeters B, Langouche L, Van den Berghe G. Adrenocortical stress response during the course of critical illness. *Compr. Physiol.* 2017; **8**: 283–98
37. Peeters B, Boonen E, Langouche L, Van den Berghe G. The HPA axis response to critical illness: new study results with diagnostic and therapeutic implications. *Mol Cell Endocrinol* 2015; **408**: 235–40
38. Bornstein SR, Engeland WC, Ehrhart-Bornstein M, Herman JP. Dissociation of ACTH and glucocorticoids. *Trends Endocrinol Metab* 2008; **19**: 175–80
39. Jenniskens M, Weckx R, Dufour T, et al. The hepatic glucocorticoid receptor is crucial for cortisol homeostasis and sepsis survival in humans and male mice. *Endocrinology* 2018; **159**: 2790–802
40. Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? *Psychoneuroendocrinology* 2011; **36**: 415–25
41. de Kloet ER, Otte C, Kumsta R, et al. Stress and depression: a crucial role of the mineralocorticoid receptor. *J Neuroendocrinol* 2016; **28**
42. Qi XR, Kamphuis W, Wang S, et al. Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients. *Psychoneuroendocrinology* 2013; **38**: 863–70
43. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008; **108**: 18–30
44. Bauersachs J, Fraccarollo D. Mineralocorticoid receptor-dependent adverse remodeling after myocardial infarction mediated by uNGALant activation of NFκB. *Hypertension* 2017; **70**: 1080–1
45. Oakley RH, Cidlowski JA. Glucocorticoid signaling in the heart: a cardiomyocyte perspective. *J Steroid Biochem Mol Biol* 2015; **153**: 27–34
46. Writing Committee for the VISION Study Investigators, Devereaux PJ, Biccard BM, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017; **317**: 1642–51
47. Baschant U, Tuckermann J. The role of the glucocorticoid receptor in inflammation and immunity. *J Steroid Biochem Mol Biol* 2010; **120**: 69–75
48. Haas JG, Weber J, Gonzalez O, Zimmer R, Griffiths SJ. Antiviral activity of the mineralocorticoid receptor NR3C2 against herpes simplex virus type 1 (HSV-1) infection. *Sci Rep* 2018; **8**: 15876
49. Munoz-Durango N, Vecchiola A, Gonzalez-Gomez LM, et al. Modulation of immunity and inflammation by the mineralocorticoid receptor and aldosterone. *Biomed Res Int* 2015; **2015**: 652738
50. International Surgical Outcomes Study Group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016; **117**: 601–9
51. Zhou H, Tian X, Tufro A, Moeckel G, Ishibe S, Goodwin J. Loss of the podocyte glucocorticoid receptor exacerbates proteinuria after injury. *Sci Rep* 2017; **7**: 9833
52. Vaara ST, Bellomo R. Postoperative renal dysfunction after noncardiac surgery. *Curr Opin Crit Care* 2017; **23**: 440–6
53. Chadwick JA, Hauck JS, Gomez-Sanchez CE, Gomez-Sanchez EP, Rafael-Fortney JA. Gene expression effects of glucocorticoid and mineralocorticoid receptor agonists and antagonists on normal human skeletal muscle. *Physiol Genomics* 2017; **49**: 277–86
54. Farhan H, Moreno-Duarte I, Latronico N, Zafonte R, Eikermann M. Acquired muscle weakness in the surgical intensive care unit: nosology, epidemiology, diagnosis, and prevention. *Anesthesiology* 2016; **124**: 207–34
55. Hibberd C, Yau JL, Seckl JR. Glucocorticoids and the ageing hippocampus. *J Anat* 2000; **197**: 553–62
56. Gardner MP, Lightman S, Sayer AA, et al. Dysregulation of the hypothalamic pituitary adrenal (HPA) axis and physical performance at older ages: an individual participant meta-analysis. *Psychoneuroendocrinology* 2013; **38**: 40–9
57. Sakuma K, Yamaguchi A. Sarcopenia and age-related endocrine function. *Int J Endocrinol* 2012; **2012**: 127362
58. Varadhan R, Walston J, Cappola AR, Carlson MC, Wand GS, Fried LP. Higher levels and blunted diurnal variation of cortisol in frail older women. *J Gerontol A Biol Sci Med Sci* 2008; **63**: 190–5
59. Jones SE, Maddocks M, Kon SS, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax* 2015; **70**: 213–8
60. Morishita S. Prevalence of sarcopenia in cancer patients: review and future directions. *Int J Phys Med Rehabil* 2016; **4**: 1–8
61. Galizia G, Cacciatore F, Testa G, et al. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Aging Clin Exp Res* 2011; **23**: 118–25
62. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 2015; **26**: 1091–101
63. Singer JP, Diamond JM, Gries CJ, et al. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. *Am J Respir Crit Care Med* 2015; **192**: 1325–34
64. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860–7
65. Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? *Aging Cell* 2017; **16**: 444–50
66. Cavadas C, Aveleira CA, Souza GF, Velloso LA. The pathophysiology of defective proteostasis in the hypothalamus—from obesity to ageing. *Nat Rev Endocrinol* 2016; **12**: 723–33
67. Ferrari E, Cravello L, Muzzoni B, et al. Age-related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates. *Eur J Endocrinol* 2001; **144**: 319–29
68. Coupe M, Fortrat JO, Larina I, Gauquelin-Koch G, Gharib C, Custaud MA. Cardiovascular deconditioning: from autonomic nervous system to microvascular dysfunctions. *Respir Physiol Neurobiol* 2009; **169**: S10–2
69. Liu J, Li Y, Verheyden B, et al. Orthostatic intolerance is independent of the degree of autonomic cardiovascular

adaptation after 60 days of head-down bed rest. *Biomed Res Int* 2015; **2015**: 896372
70. Iwasaki KI, Zhang R, Zuckerman JH, Pawelczyk JA, Levine BD. Effect of head-down-tilt bed rest and hypovolemia on dynamic regulation of heart rate and blood pressure. *Am J Physiol Regul Integr Comp Physiol* 2000; **279**: R2189–99
71. Hirayanagi K, Kamiya A, Iwase S, et al. Autonomic cardiovascular changes during and after 14 days of head-down bed rest. *Auton Neurosci* 2004; **110**: 121–8
72. Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. *Circulation* 1997; **96**: 517–25
73. Kamiya A, Iwase S, Kitazawa H, Mano T. Muscle sympathetic nerve activity (MSNA) after 120 days of 6 degrees head-down bed rest (HDBR). *Environ Med* 1999; **43**: 150–2
74. Hughson RL, Yamamoto Y, Blaber AP, et al. Effect of 28-day head-down bed rest with countermeasures on heart rate variability during LBNP. *Aviat Space Environ Med* 1994; **65**: 293–300
75. Schmidt H, Muller-Werdan U, Hoffmann T, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. *Crit Care Med* 2005; **33**: 1994–2002
76. Smorawinski J, Nazar K, Kaciuba-Uscilko H, et al. Effects of 3-day bed rest on physiological responses to graded exercise in athletes and sedentary men. *J Appl Physiol* 2001; **91**: 249–57. 1985
77. Sundblad P, Spaak J, Linnarsson D. Cardiovascular responses to upright and supine exercise in humans after 6 weeks of head-down tilt (–6 degrees). *Eur J Appl Physiol* 2000; **83**: 303–9
78. Joyner MJ. Standing up for exercise: should deconditioning be medicalized? *J Physiol* 2012; **590**: 3413–4
79. Yamaji M, Tsutamoto T, Kawahara C, et al. Serum cortisol as a useful predictor of cardiac events in patients with chronic heart failure: the impact of oxidative stress. *Circ Heart Fail* 2009; **2**: 608–15
80. Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 2008; **108**: 559–67
81. Abbott TEF, Pearse RM, Archbold RA, et al. Association between preoperative pulse pressure and perioperative myocardial injury: an international observational cohort study of patients undergoing non-cardiac surgery. *Br J Anaesth* 2017; **119**: 78–86
82. Abbott TEF, Minto G, Lee AM, et al. Elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment in high-risk surgical patients. *Br J Anaesth* 2017; **119**: 87–94
83. Mavros MN, Athanasiou S, Gkegkes ID, Polyzos KA, Peppas G, Falagas ME. Do psychological variables affect early surgical recovery? *PLoS One* 2011; **6**, e20306
84. Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review. *J Geriatr Cardiol* 2012; **9**: 197–208
85. Miller R, Kirschbaum C. Cultures under stress: a cross-national meta-analysis of cortisol responses to the Trier social stress test and their association with anxiety-related value orientations and internalizing mental disorders. *Psychoneuroendocrinology* 2019; **105**: 147–54
86. Leistner C, Menke A. How to measure glucocorticoid receptor's sensitivity in patients with stress-related psychiatric disorders. *Psychoneuroendocrinology* 2018; **91**: 235–60
87. Rodriguez JM, Monsalves-Alvarez M, Henriquez S, Llanos MN, Troncoso R. Glucocorticoid resistance in chronic diseases. *Steroids* 2016; **115**: 182–92
88. Reul JM, Holsboer F. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. *Curr Opin Pharmacol* 2002; **2**: 23–33
89. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosom Med* 2011; **73**: 114–26
90. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection—a meta-analysis of prospective studies. *Psychosom Med* 2010; **72**: 823–32
91. Webster Marketon JI, Glaser R. Stress hormones and immune function. *Cell Immunol* 2008; **252**: 16–26
92. Gerra G, Monti D, Panerai AE, et al. Long-term immune-endocrine effects of bereavement: relationships with anxiety levels and mood. *Psychiatry Res* 2003; **121**: 145–58
93. Christian LM, Graham JE, Padgett DA, Glaser R, Kiecolt-Glaser JK. Stress and wound healing. *Neuroimmunomodulation* 2006; **13**: 337–46
94. Donald RA. Plasma immunoreactive corticotrophin and cortisol response to insulin hypoglycemia in normal subjects and patients with pituitary disease. *J Clin Endocrinol Metab* 1971; **32**: 225–31
95. Plumpton FS, Besser GM. The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects. *Br J Surg* 1969; **56**: 216–9
96. Barth JH, Seth J, Howlett TA, Freedman DB. A survey of endocrine function testing by clinical biochemistry laboratories in the UK. *Ann Clin Biochem* 1995; **32**: 442–9
97. Gold PW, Loriaux DL, Roy A, et al. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *N Engl J Med* 1986; **314**: 1329–35
98. Yoshida M, Ma J, Tomita T, et al. Mineralocorticoid receptor is overexpressed in cardiomyocytes of patients with congestive heart failure. *Congest Heart Fail* 2005; **11**: 12–6
99. Galuppo P, Bauersachs J. Mineralocorticoid receptor activation in myocardial infarction and failure: recent advances. *Eur J Clin Invest* 2012; **42**: 1112–20
100. Ayuzawa N, Nagase M, Ueda K, et al. Rac1-mediated activation of mineralocorticoid receptor in pressure overload-induced cardiac injury. *Hypertension* 2016; **67**: 99–106
101. De Leo M, Pivonello R, Auriemma RS, et al. Cardiovascular disease in Cushing's syndrome: heart versus vasculature. *Neuroendocrinology* 2010; **92**: 50–4
102. Huang WC, Yang CC, Chen IH, Liu YM, Chang SJ, Chuang YJ. Treatment of glucocorticoids inhibited early immune responses and impaired cardiac repair in adult zebrafish. *PLoS One* 2013; **8**, e66613
103. Grossmann C, Scholz T, Rochel M, et al. Transactivation via the human glucocorticoid and mineralocorticoid receptor by therapeutically used steroids in CV-1 cells: a comparison of their glucocorticoid and mineralocorticoid properties. *Eur J Endocrinol* 2004; **151**: 397–406

104. Giugliano GR, Giugliano RP, Gibson CM, Kuntz RE. Meta-analysis of corticosteroid treatment in acute myocardial infarction. *Am J Cardiol* 2003; **91**: 1055–9
105. O'Connor ME, Hewson RW, Kirwan CJ, Ackland GL, Pearse RM, Prowle JR. Acute kidney injury and mortality 1 year after major non-cardiac surgery. *Br J Surg* 2017; **104**: 868–76
106. Quinkler M, Zehnder D, Lepenies J, et al. Expression of renal 11beta-hydroxysteroid dehydrogenase type 2 is decreased in patients with impaired renal function. *Eur J Endocrinol* 2005; **153**: 291–9
107. Lattenist L, Lechner SM, Messaoudi S, et al. Nonsteroidal mineralocorticoid receptor antagonist finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. *Hypertension* 2017; **69**: 870–8
108. Rafiq K, Nakano D, Ihara G, et al. Effects of mineralocorticoid receptor blockade on glucocorticoid-induced renal injury in adrenalectomized rats. *J Hypertens* 2011; **29**: 290–8
109. Smets P, Meyer E, Maddens B, Daminet S. Cushing's syndrome, glucocorticoids and the kidney. *Gen Comp Endocrinol* 2010; **169**: 1–10
110. Barrera-Chimal J, Andre-Gregoire G, Nguyen Dinh Cat A, et al. Benefit of mineralocorticoid receptor antagonism in AKI: role of vascular smooth muscle Rac1. *J Am Soc Nephrol* 2017; **28**: 1216–26
111. Barrera-Chimal J, Prince S, Fadel F, et al. Sulfenic acid modification of endothelin B receptor is responsible for the benefit of a nonsteroidal mineralocorticoid receptor antagonist in renal ischemia. *J Am Soc Nephrol* 2016; **27**: 398–404
112. Dhaun N, Webb DJ, Kluth DC. Endothelin-1 and the kidney—beyond BP. *Br J Pharmacol* 2012; **167**: 720–31
113. Lupien SJ, de Leon M, de Santi S, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci* 1998; **1**: 69–73
114. Rasmussen LS, O'Brien JT, Silverstein JH, et al. Is perioperative cortisol secretion related to post-operative cognitive dysfunction? *Acta Anaesthesiol Scand* 2005; **49**: 1225–31
115. Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R. Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study. *Crit Care* 2013; **17**: R38
116. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *Br J Anaesth* 2009; **103**: i41–6
117. Liston C, Cichon JM, Jeanneteau F, Jia Z, Chao MV, Gan WB. Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. *Nat Neurosci* 2013; **16**: 698–705
118. Kalafatakis K, Russell GM, Harmer CJ, et al. Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man. *Proc Natl Acad Sci U S A* 2018; **115**: E4091–100
119. Royse CF, Saager L, Whitlock R, et al. Impact of methylprednisolone on postoperative quality of recovery and delirium in the steroids in cardiac surgery trial: a randomized, double-blind, placebo-controlled substudy. *Anesthesiology* 2017; **126**: 223–33
120. Torrance HD, Pearse RM, O'Dwyer MJ. Does major surgery induce immune suppression and increase the risk of postoperative infection? *Curr Opin Anaesthesiol* 2016; **29**: 376–83
121. Mesotten D, Vanhorebeek I, Van den Berghe G. The altered adrenal axis and treatment with glucocorticoids during critical illness. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 496–505
122. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. *Clin Endocrinol (Oxf)* 2004; **60**: 29–35
123. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* 2006; **126**: 789–99
124. Busillo JM, Cidlowski JA. The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore. *Trends Endocrinol Metab* 2013; **24**: 109–19
125. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol* 2017; **17**: 233–47
126. Edwards MR, Sultan P, del Arroyo AG, et al. Metabolic dysfunction in lymphocytes promotes postoperative morbidity. *Clin Sci (Lond)* 2015; **129**: 423–37
127. Perretti M, D'Acquisto F. Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. *Nat Rev Immunol* 2009; **9**: 62–70
128. Jurberg AD, Cotta-de-Almeida V, Temerozo JR, Savino W, Bou-Habib DC, Riederer I. Neuroendocrine control of macrophage development and function. *Front Immunol* 2018; **9**: 1440
129. Butcher SK, Lord JM. Stress responses and innate immunity: aging as a contributory factor. *Aging Cell* 2004; **3**: 151–60
130. Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB. Safety of perioperative glucocorticoids in elective noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology* 2017; **126**: 234–48
131. Lunn TH, Kehlet H. Perioperative glucocorticoids in hip and knee surgery—benefit vs. harm? A review of randomized clinical trials. *Acta Anaesthesiol Scand* 2013; **57**: 823–34
132. Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative steroid management: approaches based on current evidence. *Anesthesiology* 2017; **127**: 166–72
133. Tzimas P, Petrou A, Laou E, Milionis H, Mikhailidis DP, Papadopoulos G. Impact of metabolic syndrome in surgical patients: should we bother? *Br J Anaesth* 2015; **115**: 194–202
134. Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EA. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Saf* 2000; **23**: 449–61
135. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. *Ann Surg* 2003; **238**: 651–60
136. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391**: 2631–40

137. Manou-Stathopoulou V, Abbott TEF, May SM, et al. Perioperative plasma cortisol levels and myocardial injury after non-cardiac surgery. *Br J Anaesth* 2019; **122**: e45–6
138. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; **378**: 797–808
139. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; **378**: 809–18
140. Ackland GL, Abbott TEF, Cain D, et al. Preoperative systemic inflammation and perioperative myocardial injury: prospective observational multicentre cohort study of patients undergoing non-cardiac surgery. *Br J Anaesth* 2019; **122**: 180–7
141. Corcoran TB, Myles PS, Forbes AB, et al., Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA), Australian Society for Infectious Diseases (ASID) Clinical Research Network. The perioperative administration of dexamethasone and infection (PADDI) trial protocol: rationale and design of a pragmatic multicentre non-inferiority study. *BMJ Open* 2019; **9**, e030402

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