STRESS HYPERGLYCEMIA IN NON DIABETIC CRITICALLY ILL PATIENTS

Essay
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INTRODUCTION

Stress hyperglycemia is a medical term referring to transient elevation of the blood glucose due to the stress of illness. It usually resolves spontaneously, but must be distinguished from various forms of diabetes mellitus. The stress response is the human body's reaction to anything that throws off the balance inside it, e.g. injury, infection, fear, exercise, or pain that cause changes in hormonal and mechanical balance.

Stress alters cortisol and lipid metabolism that appears in critical illness as diabetic ketoacidosis, hyperglycemic hyper-osmolar coma which require specific management by fluids, insulin and regulation of metabolic changes and also treatment of complications that may occur during stay in ICU.

Myocardial infarction is one of the most common causes of stress hyperglycemia which worsens the prognosis of the disease. In cerebral stroke, stress hyperglycemia increases ischemic area and affects the clinical progression of stroke which may change the treatment especially thrombolytic therapy. The stress in burns causes many hormonal changes which lead to hyperglycemia. This increases rate of infection, delays healing of wounds and prolongs hospital stay.

Surgery in traumatized patients changes blood glucose level and causes stress hyperglycemia. This is more likely in cases of undiagnosed diabetes or urgent surgery. Sepsis causes metabolic changes and increases morbidity and mortality. Stress hyperglycemia may also occur in other diseases such as acute pancreatitis and acute renal failure.

In pediatric critical illness, stress hyperglycemia may be transient or may develop into diabetes mellitus.

Chapter 1
BODY RESPONSE TO STRESS

Endocrine response to stress

The effect of severe trauma, disease, infection, and surgery can result in remarkable metabolic stress on the human body. Survival of such insults depends in great part upon a functioning neuro-endocrine system. The initial response to stress results in energy conservation toward vital organs, modulation of the immune system and a delay in anabolism. This acute response to critical illness is generally considered to be an appropriate one.

The body's response to protracted critical illness (weeks to months) also results in marked neuro-endocrine changes. Whereas many of the chronic endocrine responses are similar to the acute phase, research is revealing that the two entities do have distinct differences ***(Van den Berge, 2002a)*.**

The endocrine response to this prolonged critical illness can even be maladaptive. Protein breakdown and fat deposition often proceed unchecked, resulting in what has been described as a "wasting syndrome". In addition, a persistent hyperglycemic response and insulin resistance can ensue, and this is increasingly seen as potentially deleterious on the long run ***(Robinson and Van Soeren, 2004)*.**

Although the chronic endocrine response to critical illness is of less relevance to the emergency physician than the acute phase, a working understanding of such a continuum can prove useful in identifying potent points of intervention. There are also situations in which the patient's ability to respond appropriately to the acute critical illness has been compromised specifically in the situation of real or relative adrenal insufficiency. Such patients may require early exogenous steroid administration to survive the critical assault.

Last, the emergency physician should be aware that serologic hormonal levels can be affected differently by critical illness, depending on the phase of that illness.

An overview of the neuroendocrine response to critical illness

The somatotropic axis

Growth Hormone (GH) is secreted from the anterior pituitary gland under hypothalamic control. Its release is typically diurnal and pulsatile under healthy, nonstress situations ***(Van den Berge, 2002a)***. The hormonal effects of GH (and its interaction with other peptides) include lipolysis, amino acid muscle deposition, anti-insulin effects, linear growth (at puberty), and overall protein anabolism ***(Nylen and Muller, 2004).***

In acute critical illness, the mean levels of GH become elevated, usually within hours of onset ***(Van den Berge, 2002a)***.

There is a rise in both peak and thorough levels; however, the response may be variable. Growth hormone itself directly affects fat metabolism, and rising levels lead to lipolysis and inhibited lipid uptake. GH also has direct insulin antagonizing effects. During protein metabolism, GH normally exerts its influence through its interaction with other mediators. In a non- stress situation, this results in protein builds up. The acute response to critical illness, however, has been found to inhibit this indirect peripheral effect of GH, the result is acute protein degradation and liberalization of amino acids.

The combination of factors exerted by the somatotropic axis in acute critical illness is generally regarded as a survival mechanism. That is, the catabolic generation of substrates such as amino acids, glucose, and free fatty acids occurs instead of anabolism ***(Baxter, 1994)***.

The chronic critical illness is that phase occurring days to weeks into the insult, before recovery has begun. Growth hormone during this phase tends to show abnormal release patterns, and the total circulating GH levels are much lower than in acute illness ***(Van den Berge et al., 1999).*** The average GH levels in prolonged critical illness return

toward the normal seen in the absence of stress ***(Scott et al., 2005)***.

Although the peripheral resistance to GH seen during acute critical illness resolves during this phase, the net effect of prolonged critical illness on this axis is one of a relative GH deficiency. This net effect likely contributes to "the wasting syndrome". This is the syndrome noted during prolonged intensive care unit (ICU) stays in which fat deposition is prominent and protein is continually degraded. The syndrome persists until recovery from the critical illness, even when artificial nutrition is provided. The negative consequences of "the wasting syndrome" are obvious. In addition to the insult of the critical illness, patients fail to use fatty acids as substrates ***(Scott et al., 2005)***.

They lose protein from muscle with resulting weakness and hindered recovery. This has led researchers to investigate intervening in this axis in an attempt to blunt the deleterious effects of "the wasting syndrome." Unfortunately, in an European study of patients with prolonged critical illness, increased mortality was found in those treated with high dose **GH** replacement therapy ***(Takala et al., 1999)***. Speculation as to this result is varied, and probably represents the incomplete knowledge of the whole somatotropic axis and its interplay with other endocrine axes ***(Nylen and Muller, 2004)***.

Some have suggested that the direct administration of GH does not allow for physiologic hypothalamic feedback inhibition loops or peripheral adjustments in responsiveness to the hormone. Such hypotheses have led to additional studies using GH-secretagogues (synthetically produced substances with hypothalamus-like GH-releasing capacities) infusions ***(Scott et al., 2005)***. Although preliminary, these studies suggest improvement in GH pulsatile release during chronic critical illness with maintenance of GH peripheral hormonal activity.

The thyrotropic axis

Thyroid releasing hormone (TRH) is secreted from the hypothalamus, which stimulates the anterior pituitary gland's release of thyroid stimulating hormone (TSH). TSH, in turn, controls the release of thyroxin (T4) from the thyroid gland. Peripherally, T4 is converted by de-iodination to T3, another active thyroid hormone. The active thyroid hormones (T3 and T4) are regulators of cellular metabolic activity and are essential for normal cardiac, pulmonary, and neurologic function. T4 is produced almost exclusively by the thyroid gland. The majority of T3 is produced by peripheral de-iodination of T4 to T3 (80%), and only 20% is produced by the thyroid gland itself. Most of the circulating T3 and T4 are bound to thyroxine-binding globulin.

In the acute phase of critical illness, changes in thyroid hormones begin to occur in as little as 30 to 120 minutes ***(Takala et al., 1999)***. There is an initial drop in T3 levels that has been attributed to decreased peripheral conversion of T4 to T3 .This drop in T3 levels tends to persist during critical illness; it is considered a hallmark response to a variety of critical illnesses ***(Fliers et al., 2001)***.

In fact, studies have suggested that the magnitude of the drop in T3 directly correlates with patient mortality. The lower the T3 level, the greater the mortality risk in ill patients. There is variability reported in the levels of T4 that occur acutely. This hormone may remain in the normal range, and there may be an early transient rise during the illness. However, in the most severely ill patients, the measured levels tend to decrease ***(Scott et al., 2005)***.

Despite this stress-induced drop in thyroid hormone levels, TSH tends to remain in the normal or low range during stress ***(Fliers et al., 2001)***. Under typical circumstances, a drop in T3/T4 levels would inhibit negative feedback loops, thus calling for an increase in TSH. The fact that this does not occur has been attributed to a change in the thyroid hormone set point ***(Fliers et al., 2001)***.

It has also been described as a homeostatic mechanism, whose purpose is to diminish the effects of T3

within the body ***(Nylen and Muller, 2004)***, perhaps to conserve energy expenditure .However, this teleologic view has been argued respective of these changes in thyroid hormone levels, such seriously ill patients generally do not acutely show evidence of thyroidal illness. This condition (low T3 and normal TSH levels in the face of critical illness with no clinical evidence of thyroid disease) has been termed "sick euthyroid syndrome "," low-T3 syndrome" or "non-thryroidal illness" ***(Wartofsky et al., 1999)***.

During chronic critical illness, T3 remains low, and TSH secretion, although typically measured in low-normal concentrations, loses its physiologic pulsatile pattern of secretion ***(Van den Berge et al., 1997)*****.** Because T3 contributes to the body's ability to synthesize protein, to use fats for fuel, and assists in GH functions, this chronic low T3 state has been theorized as contributing to the "wasting syndrome" of prolonged critical illness.

Early studies using thyroid hormone replacement, aimed at reversing this state, have failed to show benefit. However, some investigations using TRH infusions (combined with GH hormones) have suggested the ability to reactivate a physiologic thyroid axis during chronic critical illness, and may indicate a future treatment option ***(Scott et al., 2005)***.

The hypothalamus-pituitary-adrenal axis

Cortisol is the predominant glucocorticoid secreted from the adrenal cortex in humans. Stress-induced cortisol release is driven indirectly by corticotropin-releasing hormone (CRH) from the hypothalamus and directly via adrenocorticotropic hormone (ACTH), which responds to the CRH stimulus. In healthy individuals, this secretion occurs in a diurnal pattern that typically involves a low trough at approximately 2 a.m. and a peak at 8 a.m.

The accepted metabolic effects of cortisol include the maintenance of normal vascular tone, vascular permeability, and distribution of total body water. Cortisol also functions to potentiate the vasoconstrictor action of catecholamines. Acute critical illness such as trauma, burns, sepsis, anesthesia, and extensive surgery is known to induce a state of hypercortisolism.

Hypercortisolism tends to be energy producing; that is, cortisol shifts energy production and substrates to vital organs and delays anabolic build up ***(Van den Berge, 2002a)*.** This creates immediate energy sources for the "fight or flight" stress response. Energy produced becomes selectively available to the vital organs of the body. Increased cortisol in acute illness has been speculated to help mute the body’s own inflammatory response to disease, protecting itself against over-reaction. Each of

these effects of cortisol appears to be augmented by a concomitant decrease in cortisol binding proteins (thus increasing the metabolically, protein-free hormone) during acute illness ***(Beishuizen et al., 2001)***.

Along with the rise in cortisol during critical illness, catecholamines are secreted. Epinephrine and norepinephrine have numerous essential functions in the body's stress response. The major homeostatic functions in critical illness include stimulation of heart rate, myocardial contractility, and vasoconstriction of some vascular beds (gut, skin, and skeletal muscles). These responses enable the body to maintain perfusion to vital organs in the setting of hypovolemia, sepsis, or cardiac failure. Catecholamine-mediated vasoconstriction is potentiated by cortisol, and cortisol may also be necessary for the production and secretion of the catecholamines themselves ***(Zaloga, 2001)*.**

In addition to the rise in cortisol and catecholamines during acute critical illness, the renin-angiotensin system is stimulated and aldosterone is produced. The net effect of these responses is fluid retention, vasoconstriction, and enhanced hemodynamics.

This overall hypothalamus-pituitary-adrenal axis (HPA) response to acute critical illness, lasting hours to days, is generally considered adaptive, evolutionary, and is

one of the most important coping mechanisms the body has to such stressors ***(Van den Berge, 2000)*.**

During chronic critical illness, cortisol levels remain elevated and may shift the immunologic balance further toward immuno-suppression. However, the normal diurnal variation is lost or blunted. As critical illness becomes prolonged, serum adrenocorticotrophic hormone (ACTH) levels drop, while cortisol concentrations remain elevated, if a properly functioning HPA axis exists.

Over time, the glucocorticoid effects of cortisol become increasingly prominent, and these effects are relied upon for ongoing hemodynamic stability. Such reliance has led to the description of a "relative adrenal insufficiency" state in some ICU patients (particularly those with septic shock) who may respond with improved outcomes when therapeutic doses of glucocorticoids are administered exogenously ***(Koo et al., 2001)***. Support for such treatment is not without conflicting data and continued debate ***(Ritacca et al., 2002)*.**

Other axes

Given the known anabolic properties of testosterone, it makes sense that alterations in gonadal hormones might occur during times when anabolism is being discouraged. Indeed, testosterone levels are acutely lowered during

stressful conditions. Such a decrease is hypothesized to be secondary to an immediate and direct Leydig cell suppression. As critical illness becomes prolonged, luteinizing hormone release is diminished in both men and women. Hypogonadism is frequently a result of these gonadal hormonal changes, albeit a transient effect ***(Van den Berge, 2002a).***

Prolactin levels also vary during critical insults, rising acutely and showing blunted pulsatile secretion in the chronic phase. Diminishing prolactin levels may play a role in the immuno-suppression associated with prolonged critical illness, particularly when combined with dopamine infusions ***(Van den Berge, 2003).*** A summary of the hormonal changes during critical illness for each axis is shown in Table (1).

Table (1): A summary of the hormonal changes during critical illness for each axis

Hormone	Change during acute critical illness	Physiological effects of the acute change	Change during chronic critical illness	Physiological effects of the chronic change
GH	• Increases • Resistance to GH effects develops at tissue level	• Lipolysis • Inhibited lipid uptake by cells • Effects of insulin are antagonized • Protein degradation	• Normalizes • Abnormal secretion Patterns • Relative GH deficiency	• Fat deposition in tissues • Continued protein degradation • Contributes to "wasting syndrome"
T3	• Decreases	• Minimal effects Possibly allows energy conservation	• Remains decreased	• Contributes to "wasting syndrome"
T4	• Variable, generally decreases	• Minimal effects Possibly allows energy conservation	• Remains decreased	• Contributes to "wasting syndrome"
TSH	• Normal or low normal	• Minimal effect • Change in thyroid "set point" (TSH normal despite drop in T3, T4)	• Normal or low normal	• Contributes to "wasting syndrome"
Cortisol	• Increases	• Energy production • Shifts energy to vital organs • Delays anabolism • Mutes inflammation "Fight or Flight"	• Remains elevated • Diurnal variation lost	• Additional immuno-suppression • Increased glucocorticoid effects
Testosterone	• Decreases	• Decreased anabolism	• Remains decreased	• Hypogonadism
Prolactin	• Increases	• Possibly stimulates inflammatory cascades	• Normalizes • Abnormal secretion patterns	• Possibly inhibits immune system

(Van den Berge, 2002a)

Metabolic response to stress

The net effect of the endocrine response to surgery is an increased secretion of catabolic hormones. This promotes the provision of food substrates from the catabolism of carbohydrate, fat and protein. In evolutionary