Neuroendocrine System Regulatory Mechanisms: Acute Coronary Syndrome and Stress Hyperglycaemia

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Abstract

Neurohormonal systems are activated in the early phase of acute coronary syndromes to preserve circulatory homeostasis, but prolonged action of these stress hormones might be deleterious. Cortisol reaches its peak at 8 hours after the onset of symptoms, and individuals who have continued elevated levels present a worse prognosis. Catecholamines reach 100–1,000-fold their normal plasma concentration within 30 minutes of ischaemia, therefore inducing the propagation of myocardial damage. Stress hyperglycaemia induces inflammation and endothelial dysfunction, and also has procoagulant and prothrombotic effects. Patients with hyperglycaemia and no diabetes elevated in-hospital and 12-month mortality rates. Hyperglycaemia in patients without diabetes has been shown to be an appropriate independent mortality prognostic factor in this type of patient.

Keywords

Acute coronary syndrome, prognosis, hyperglycaemia, catecholamines, cortisol, insulin, neurosecretory systems, coronary thrombosis

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The aim of reviewing the neuroendocrine–humoral response in acute coronary syndrome (ACS) is based on the fact that beyond the distinctive thrombotic event that defines acute occlusion of a coronary artery, generically referred to as a plaque accident, it is not an isolated event.

It is clear that a series of physiological and physiopathological mechanisms related to stress – before, during and after the thrombotic occlusion of a coronary artery – mediate together with the plaque accident both in the genesis of the same and in its consequences.

Stress is, according to Walter Cannon, a physiological reaction provoked by the perception of situations or stimuli – aversive or pleasurable – and should be the first concept to bring us closer to evaluating the physiological response.[1]

Recently, publications focusing on neuroendocrine system regulatory mechanisms have increased, in an attempt to determine the importance of psychological and physical stress,[2] as well as determining what kind of influence catecholamines, cortisol, growth hormone, and thyroid hormones have on the pathophysiology of plaque. How do lipids interact in these events? How are inflammation mediators related to these effects? What is the role of all these circumstances regarding the activation of the thrombotic mechanism? How should we interpret elements called "acute phase reactants", such as leukocytosis, hyperglycaemia, or increased erythrocyte sedimentation rate? Are they causes or consequences? Should they be considered prognostic measures or just temporary situational phenomena?

Hans Seyle proposed the general adaptive syndrome, and defined it as the body's stereotyped physiological response to a stressful stimulus, which helps an organism to adapt, independent of the type of stimulus involved – either aversive or pleasurable.[3]

Physical stressors are stimuli that alter the physiological state affecting homeostatic mechanisms, and initiate a rapid adaptive response that is necessary to survive. Psychological stressors are stimuli that threaten the current state of an individual and provoke a state of anticipation – even if they do not represent an immediate threat to physiological conditions, being that these stimuli largely depend on previous experiences.

Role of Cortisol in Acute Coronary Syndrome

Cortisol is the final product of the hypothalamic–pituitary–adrenal axis, and acts as a ligand of both intracellular receptors – present in almost all tissues – and mineralocorticoid receptors in sodium transporter epithelia (for example, nephrons, colon, sweat glands, and salivary glands), vascular endothelium, and non-epithelial cells, such as vascular smooth muscle, myocardium, and the brain.[4]

ACS triggers a stress response that involves activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis, which causes cortisol and catecholamines release, with cardiovascular, metabolic, cerebral, and immunomodulatory effects tending to maintain homeostasis.[5–7] Cortisol may exert negative effects on the cardiovascular system – for example, increasing sensitivity to catecholamines and stimulating mineralocorticoid receptors present in the myocardium.[6,8]

In patients with ACS, cortisol increases at an early stage, reaches a peak around 8 hours after the onset of symptoms, and then progressively decreases to reach normal or almost normal levels within 30–72 hours.[6,9,10] Half of the patients hospitalised for MI show total cortisol levels above the maximum normal range (25 mg/dl) on the first day of admission, and the duration of cortisol increase is higher in patients with poor evolution, as well as those with left ventricle ejection fraction <50 %.[10]

Several authors have observed an association between disease severity and cortisol levels. Patients with ST segment elevation MI have higher cortisol levels than those without ST elevation, and there is a positive correlation between cortisol and peak creatine phosphokinase muscle/brain (CPK-MB) levels.[5,9,11] Morbidity and mortality of ST segment elevation MI increase with higher cortisol levels on admission.[4–6,9] Stress hyperglycaemia in patients with ACS is associated with increased morbidity and mortality. In agreement with other authors, we have reported that cortisol is one of the main determinants of hyperglycaemia in these patients and correlates independently with glycaemia.[5,11–13]

Catecholamine in Neuroendocrine Activity in Acute Coronary Syndrome

Neurohormonal systems are activated at early stages of ACS to preserve circulatory homeostasis.

The sympathetic nervous system is mainly an efferent system whose neurotransmitters are norepinephrine (NE) and epinephrine (EPI). The main site of synthesis of NE is the locus coeruleus, located on the floor of the fourth ventricle, and receives afferents from the hypothalamus, the cingulate cortex, and the amygdala. Nerve impulses descend along the neuroaxis to the preganglionic neurons located at T1 to L2–L3 levels and activate the postganglionic neurons. The axon travels with epicardial vascular structures to the myocardium, where NE is released and acts directly on the post-synaptic alpha and beta receptors.

NE also stimulates the hypothalamic–pituitary–adrenal axis, which is involved in the release of EPI from the adrenal medulla.[14] There is also a local release of catecholamines in various blood vessels of the peripheral sympathetic nervous system, and in cardiac myocytes that can synthesise and release NE and EPI in an autocrine/paracrine manner.[15] In the early stages of acute MI (AMI), the concentrations of NE and EPI are only fivefold the normal levels at rest, and these mildly increased levels of catecholamines do not induce a major deterioration of myocardial function during ischaemia.

Accumulation of neurotransmitter is prevented by three mechanisms: NE exocytosis is an active adenosine triphosphate-dependent process, and during ischaemia adenosine triphosphate levels are not sufficient; NE-specific uptake-1 transporter that reuptakes NE from the synaptic cleft; and adenosine accumulating in the ischaemic myocardium stimulates presynaptic A1-adenosine receptors and suppresses NE exocytosis. If ischaemia progresses for >10 minutes, the myocardium loses the protection against the excessive adrenergic stimulation. The catecholamines are released from the storage vesicles of the neuronal cytoplasm and normal transportation from the cytoplasm to the synaptic cleft through the axolemma is reversed. This results in extracellular levels that reach 100–1,000-fold the normal plasma concentrations within 30 minutes of ischaemia.[16] There is also a 20–30 % increase of the adrenergic receptors secondary to adenylyl cyclase sensitisation spreading the myocardial damage.[17]

Ischaemia sets up a context of excessive increase of catecholamines with sensitised adrenergic receptors that lead to intracellular calcium overload, formation of free radicals, functional hypoxia, decoupling of oxidative phosphorylation, electrolytic disorders, cell membrane increased permeability, and formation of aminolutins (that are the product of the pathological auto-oxidation of catecholamine catabolism), finally leading to irreversible myocardial injury.[18,19] Catecholaminergic activation is reduced during the first post-infarction days, mainly NE, as levels of EPI only remain high during the first 24 hours of hospitalization. However, in patients with anterior localization or stable coronary artery disease associated with various dysrhythmias, high levels of plasma NE at admission and during follow up were observed.[20] In addition, patients who develop heart failure (HF) with reduced ejection fraction after AMI have elevated levels of NE for 1 month.[21]

In conclusion, catecholamines in myocardial ischaemia are involved at different levels and its genesis has different origins. This determines a complex approach due to the multiple factors to consider and also that catecholamines play a physiological role in the response to ischaemia. In addition, the evaluation of neurohormonal activity can be difficult because of the overlap with other systems (such as the cortical adrenal system) and the multiple mechanisms of catecholamine's reuptake and metabolism. This could be the reason that neither plasmatic nor urinary concentration of catecholamines could precisely reflect the neuroendocrine activity in post-infarction patients.

Glucose, Insulin and Fatty Acids in Acute Coronary Syndrome

In response to the stress that represents ACS, cortisol, catecholamines, glucagon, growth hormone, and some cytokines (tumour necrosis factor-alpha; TNF-alpha), which stimulate glycogenolysis and hepatic glyconeogenesis, are released. In addition, insulin resistance is generated due to defects at the glucose transporter type 4 and post-receptor signalling pathways. This configures 'stress hyperglycaemia'.[22,23] In this context, hyperglycaemia induces glycotoxicity at the systemic and cardiac levels, as it is able to prolong and generate dispersion of the QTc interval, which may predispose to arrhythmias,[24] generates oxidative stress that stimulates inflammation (interleukin-6, TNF and interleukin-18), and alters endothelium-dependent vasodilatation.[25–28] It also decreases the collateral coronary flow dependent on nitric oxide and may increase infarction size.[29,30] Hyperglycaemia attenuates the protective effect of ischaemic preconditioning and perconditioning, and exacerbates the non-reflow phenomenon.[30–34]

Hyperglycaemia has procoagulant and prothrombotic effects by stimulating thrombin formation, increasing factor VIII levels and procoagulant activity of tissue factor.[35,36] It induces adenosine diphosphate-mediated platelet activation and attenuates the inhibitory effect of aspirin on glycoprotein IIb–IIIa and P-selectin expression, and may attenuate the anti-aggregant response to nitric oxide, which reverts with glycaemic control.[37–39]

Hypoglycaemia also has deleterious effects, as it prolongs the QTc interval, stimulates inflammation, and favours platelet aggregation and coagulation. It has also been shown that insulin-induced hypoglycaemia decreases coronary flow reserve in healthy individuals and patients with diabetes.[40,41]

Fatty acids, together with glucose, are one of the major energy sources of the myocardium, but during ACS, catecholamines generate an excessive increase in the concentration of free fatty acids that are

capable of generating lipotoxicity on the myocardium, as they induce membrane peroxidation, inhibition of mitochondrial beta-oxidation, inhibition of the Na+, K+-adenosine triphosphatase pump with Ca++ and Na+ intracellular accumulation, and favour the occurrence of ventricular arrhythmias.[42]

As identified by other authors, it is important to remember that insulin has other important effects for the ischaemic myocardium besides metabolic modulation.[43]

Insulin is a vasodilator at the systemic and coronary level, and this effect seems to be largely dependent on the endothelium and on the action of nitric oxide. Improvement in coronary blood flow (in a dose-dependent manner) has been seen in healthy people, and in patients with diabetes, in ischaemic and non-ischaemic areas.[44,45] It also has proangiogenic effects mediated by vascular endothelial growth factor that could be involved in vascular regeneration at the peri-infarct areas.[46]

Therefore, it appears that beyond its determinant condition on the evolution of patients with myocardial ischaemia, hyperglycaemia should not be the only factor to be considered when an analysis focusing on the metabolic control of patients with ACS is posed.

Other Serum Markers in Neuroendocrine Activity in Acute Coronary Syndrome

Regarding ACS, parallel with the advancement of medical treatment, attention has focused on early patient stratification and, particularly, on the prognostic potential of serum markers.

(In the following section, some of these are listed together with the implications of their dosage for ACS prognosis).

B-type natriuretic peptide is the part of the natriuretic peptide family that is released by the ventricle in response to increased parietal stress; it exerts its biological effect by acting on the receptor of the guanylate cyclase system, increasing the concentration of cyclic guanosine monophosphate, generating vasodilatation and natriuresis, and inhibiting the renin–angiotensin–aldosterone system, decreasing the sympathetic activity and the synthesis of endothelin 1. Therefore, it has emerged as a serum marker that assists in the diagnosis of HF.

B-type natriuretic peptide has been evaluated in multiple trials as an independent predictor of prognosis in patients with ACS, showing that high concentrations of B-type natriuretic peptide, both within the first hours and at 7 days of evolution, are associated with higher mortality and worse prognosis. When compared with troponin I and C-reactive protein, it works as a stronger prognostic marker – predicting death at 30 days.[47,48]

Adrenomedullin (AM) is a 52-amino acid peptide related to the calcitonin gene. First isolated from pheochromocytoma cells, it could be detected in other tissues later, such as the adrenal medulla, heart, brain, lung, kidneys, and endothelial cells. It exerts a vasodilatatory action, increasing the levels of cyclic adenosine monophosphate, thus inducing diuresis and natriuresis. Increased levels in both HF and ACS predict an unfavourable evolution.

Preproadrenomedullin, a precursor of AM, was dosed in a clinical trial – secreted in equal proportion – revealing itself more stable than AM. Higher mortality and recurrent acute MI (AMI) at 30 days and 6 months have been shown in ACS patients with elevated levels within the first 36 hours of symptom onset and at 5 days after the event. This trial was compared with the Global Registry of Acute Coronary Events score, revealing that preproadrenomedullin is a better predictor of mortality at 6 months.[49,50]

Chromogranin A (CgA) is a 49-kDA polypeptide with 439 amino acids identified throughout the nervous and endocrine system. Significant high plasma levels are recorded in patients with neuroendocrine tumours. The increased concentration of CgA correlates with augmented sympathetic activity in both the adrenal medulla and nerve terminals, suggesting that CgA could involve neuroendocrine signals from several sources, thus representing an overall index of neuroendocrine activity.

The production of CgA was demonstrated among individuals with dilated and hypertrophic cardiomyopathy, and the plasma levels of CgA correlate with the disease severity. This association has a prognostic value in patients with HF and post-AMI HF.

Another study also revealed that CgA is independently associated with all-cause mortality, and through univariate analysis it was determined that basal CgA concentration was strongly associated with the incidence of hospitalization for HF and recurrent AMI.[51]

Osteoprotegerin – a member of the TNF receptor superfamily – is identified as a bone resorption regulator. Binding to the receptor activator of nuclear factor-kappa B ligand, it competitively inhibits the receptor activator of nuclear factor-kappa B ligand interaction with consequent inhibition of osteoclastogenesis. Osteoprotegerin is expressed in the vascular system, smooth muscle cells, atherosclerotic plaques, and early atherosclerotic lesions. In patients with ACS, early high dosage was associated with greater all-cause mortality and HF at 30 days and 1 year.[52]

All these serum markers have proven independent prognostic values. However, an integrated multivariate approach is required among patients with ACS within heterogeneous populations.

Neuroendocrine Activity and Thrombosis in Acute Coronary Syndrome

Progressive endothelial dysfunction is the initial event in the development of atheroma plaques within the coronary arteries, which can interrupt blood flow and cause ischaemic injury in the myocardium, triggering an ACS.

In response to an abnormal glycometabolic state, an oxidative stress and an inflammatory environment are generated; meanwhile, the endothelium acquires a prothrombotic phenotype.[53–56]

The acute inflammatory response is initiated by t-cells and mast cells, which synthesise pro-inflammatory cytokines and foster the expression of adhesion molecules, which ease the migration of monocytes and t-cells into the arterial intima. Interleukin-6 and TNF contribute to the local and systemic inflammatory process, and increase the expression of tissue factor in macrophages, endothelial cells, and smooth muscle vascular cells. The latter secrete collagen that expands the extracellular matrix and forms the atheromatous plaque surrounded by a covering of fibrous tissue and cellular infiltrates in the arterial intima, while a proliferation of smooth muscle cells occur.

Eventually, interferon gamma released by t-cells and mast cell proteases induces an overexpression of metalloproteases that downgrade the components of the interstitial matrix and slim down the plaque, which becomes vulnerable and breakable at the most exposed areas to turbulent blood flow.[57]

The rupture of the plaque releases tissue factor that, in contact with blood, locally triggers the coagulation cascade that generates thrombin, which acts on protease-activated receptors (protease-activated receptor 1 and 4) of the platelet and cardiomyocyte.[58]

Collagen is exposed from the plaque and surrounding subendothelium, platelets attach to it, activate, and expose alpha IIb beta 3 integrin, which binds to fibrinogen and to von Willebrand Factor (VWF), and platelet aggregation occurs. Activated platelets also release VWF, thromboxane A2, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, fibronectin, and factor XIII, which stabilise the fibrin clot by cross-linking fibrin monomers and culminates with the formation of a thrombus within the vessel lumen, which may partially or totally obstruct the coronary artery.[59]

With this process in progress, tissue plasminogen activator and urokinase activator are released from the endothelium to digest the thrombus *in situ*, and at the same time the inhibitor PAI-1 is released, which forms an inactive complex with both activators. The increase of PAI-1 is related to adverse cardiovascular events; paradoxically, the same happens with tissue plasminogen activator increase, but this is due to the fact that tissue plasminogen activator antigen concentration mostly evaluates the inactive complex that it forms with PAI-1.

Local fibrinolytic capacity would depend on the balance between activators and inhibitors, which would determine a greater or lesser generation of plasmin. This enzyme downgrades the fibrin network – whose lysing product is D-dimer (DD) – plasmin also participates in plaque rupture, activating the metalloproteases.[60]

Meanwhile, factor XIII cross-links alpha 2 antiplasmin in the fibrin mesh to inactivate plasmin *in situ*. Fibrinolysis is a dynamic process; plasmin smoothes the fibrin mesh and increases DD, but if the fibrinolytic reserve is depleted, the possibility of thrombus lysis decreases, and DD does not increase.[61] Prospective studies show that the specificity of DD for the early detection and prognosis of ACS is questionable,[62] as it is a variable marker that depends on the moment when this system in continuous change is studied.[63,64]

In the early stages of plaque development, VWF and P-selectin are mediators of platelet–endothelial cell interactions. VWF is secreted from the endothelial cells as very high molecular weight multimers, and is highly adhesive.[65]

ADAMTS13 is the enzyme responsible for cleaving the multimers in smaller and less adhesive forms, but oxidative stress inhibits it, forming highly thrombogenic platelet aggregates that promote plaque progression.[66] Platelet thrombus is more resistant to lysis because of its high PAI-1 content and because platelet microparticles contribute to thrombin generation, which activates thrombin-activatable fibrinolysis inhibitor, a fibrinolytic inhibitor, which promotes thrombolysis resistance. Platelets – the source of growth factors and mitogens – play a major role in thrombus formation and propagation[67] and are the main target of antithrombotic therapy in arterial disease.

Prognosis Value of Hyperglycaemia According to Neuroendocrine Activity in Acute Coronary Syndrome

Hyperglycaemia is a common finding at admission in patients with MI in both people with and without diabetes.

This fact has been observed for several decades. In 1931, Cruikshank reported on the high prevalence of glycosuria in patients without diabetes with infarction.[68]

Numerous studies have been published confirming not only that hyperglycaemia is common in these patients, but also that it is an independent predictor of mortality in the short, medium, and long term.

In 2000, Capes published a meta-analysis of 15 studies focusing on the mortality or HF rate after MI in relation to blood glucose levels.[69] The proportion of patients with hyperglycaemia was 3–71 % in people without diabetes and 46–84 % in people with diabetes. Patients with no history of diabetes and with glycaemia ranging from 6.1 mmol/l to 8 mmol/l had a 3.9-fold (95 % CI [2.9–5.4]) higher mortality rate than patients without a history of diabetes and with lower blood glucose levels. Also, patients without diabetes with higher blood glucose levels of 8–10 mmol/l had an increased risk of HF or cardiogenic shock.

In contrast, among patients with diabetes, death risk was moderately augmented (RR 1.7 [1.2–2.4]) from glycaemia between 10 and 11 mmol/l. Similar findings were observed in Canada among 1,664 patients hospitalised for MI who were stratified according to the presence or absence of a history of diabetes and glycaemia at admission lower or higher than 11 mmol/l. The group with the worst prognosis in terms of in-hospital mortality and along 1 year (among the four groups analysed) was the patients without diabetes with hyperglycaemia on admission group.[70]

In a large cohort of elderly patients with MI (n=141,680), glycaemia on admission was analysed as a continuous and categorical variable (≤6.1, >6.1–7.8, >7.8 9.4, >9.4–13.3, >13.3 mmol/l), and its association with 30-day and annual mortality rates in patients with and without diabetes.[71] It was found that the 30-day mortality rate increased from 10 % in patients without diabetes with glycaemia at admission <6.1 mmol/l to 39 % in patients without diabetes with glycaemia >13.3 mmol/l, and from 22 % to 55 % in mortality per year. Among the patients with diabetes, 30-day mortality was 16 % in patients with glycaemia ≤6.1 mmol/l and 24 % in those with glycaemia >13.3 mmol/l. Mortality per year was 35–41 %. Higher blood glucose levels were associated with an increased risk of mortality in patients without a history of diabetes (p for interaction <0.001).

These findings imply that hyperglycaemia in patients with MI has a worse prognostic significance in patients without diabetes than in patients with diabetes. One possible explanation is that among patients considered to not have diabetes, one group would be undiagnosed diabetics who are often treated less with insulin. Only 26 % of patients without a history of diabetes and with glycaemia <13.3 mmol/l received insulin, whereas 73 % of patients with diabetes were treated with insulin.[71]

In both patients with or without diabetes, hyperglycaemia could reflect the seriousness of the disease as a result of increased catecholamines and other stress hormones, such as cortisol. Several studies have

shown the relationship. In 1986, Yudkin et al. showed a correlation between the EPI concentration at the early stages of infarct and the size of the infarct.[72] Also, hyperglycaemia on admission in people without diabetes was determined both by the extent of the MI, mainly through the secretion of EPI, and the secretion of other hormones that were independent of the extent of the infarct. Patients with a high glycaemic index on admission showed a high concentration of NE and cortisol, with no relationship between these hormones and the extent of MI.

A substudy of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) determined that NE is elevated in all patients and normalised within the first 2 days, remaining high in patients with HF during the first month after infarction.[21] This difference was not found in EPI, which also increased in the early stage of infarction. The authors concluded that sustained neurohormonal activation following infarction occurs primarily in patients with HF and at the same time is related to the size of the MI. This activation would initially be an early compensatory response mechanism to preserve circulatory homeostasis, but the extension of its activation could be deleterious. This activation, therefore, could be a marker of myocardial damage, but also a detrimental mechanism itself.

In this sense, several groups explored the value of persistent hyperglycaemia after MI. Aronson et al. studied fasting glucose after admission in 735 MI patients without diabetes.[73] Mortality in patients with blood glucose in a fasted state <5.6 mmol/l was 2 % at 30 days of MI, and 10 %, 13 %, and 29 % at the first, second, and third tertile of high fasting blood glucose was found. Fasting blood glucose was a better predictor than glycaemic control at admission. Greater risk was found in those who entered with hyperglycaemia and remained hyperglycaemic, followed by the group that entered without hyperglycaemia, but presented hyperglycaemia during the hospitalisation.

Likewise, with a larger number of patients (n=16,871), Kosiborod et al. observed that persistent hyperglycaemia is a better predictor of mortality than hyperglycaemia at admission.[74] They also showed that there is a gradual increase in the in-hospital mortality rate for every 0.6 mmol/l increase of glycaemia, when mean glucose is >6.7 mmol/l. In contrast, they observed a higher mortality at <3.9 mmol/l, determining a J-curve relationship between mortality and mean blood glucose during hospitalisation. The curves are different in people with diabetes than in people without diabetes, being more abrupt and with an increased rate of mortality in relation to blood glucose in people without diabetes.

Finally, and to emphasise the prognostic importance of the value of glycaemia in patients with MI, Timóteo et al. published a study where they proposed to include the glycaemia value at admission to the Global Registry of Acute Coronary Events score in patients with ACS. This incorporation increases the predictive value of the score, albeit with a modest magnitude.[75] ■

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