REVIEW

Psychosocial stress and cardiovascular diseases

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Fifty five years after the first finding relating mood disturbances and cardiovascular diseases, there is still debate on the formation of a cogent conception embracing all the fragments of insight within the various aspects relating psychosocial stress to cardiovascular diseases. The clinical comorbidity is empirically evident, but there are ambiguous research results limiting the value of the proposed pathophysiological mechanisms. Psychosocial stress represents here any event that relates psychological phenomena to the social environment and to the associated pathophysiological changes. Stress denotes the external or environmental factors to which people are exposed, as well as the behavioural or biological reaction to it (response that some authors call “distress”). Cardiovascular diseases will be considered here only when being the consequence of chronic inflammatory disease of arteries (atherosclerosis). The question is: Are there pathophysiological reliable mechanisms relating psychosocial stress to the development of cardiovascular diseases?

ACUTE PSYCHOSOCIAL STRESS AND CARDIOVASCULAR DISEASES

The consensus view is that high intensity mental stress may be a trigger of transient myocardial ischaemia, myocardial infarction, ventricular arrhythmia, and sudden cardiac death.^{1,2} For example, after an earthquake, the number of hospital admissions for acute myocardial infarction increases by about 35%.³ Anger and hostility can also contribute to atrial fibrillation.⁴ Recent researches show that the association sustains only for anger, but not for hostility, and only in men.^{4,5} This effect occurs in patients with previous ischaemic heart disease.^{6,7} Type A personality is not related to ventricular fibrillation or atherosclerosis.⁴ On the one hand, reacting with anger can also detonate stroke⁸ although the association is only true for young men with increased cholesterol concentrations. On the other hand, hostility associated to depression can also be related to stroke.⁹

A neural net participates in the regulation of the somatic responses to emotion. The ventral striatum, dorsomedial nucleus of the thalamus, amygdale, and anterior insula seem to be important for the identification of emotionally salient stimuli. However, the ventromedial and

ventrolateral prefrontal cortical regions are of particular importance for the generation of emotional experiences and behaviour in response to these stimuli and they probably congregate the neural efferent activation that links the perceived psychosocial problem with the “stress response” that will finally cause, among other somatic responses, the cardiovascular disease (CVD).¹⁰

Peripheral pathophysiological mechanisms

The main mechanisms linking the acute and intense mental stress to CVD consist in a rapid increase in arterial pressure and heart rate by means of increased sympathetic activity and vagal withdrawal coupled with transitory endothelial dysfunction, and atherothrombotic activation.¹¹ In addition, there is also a brief activation of the hypothalamus-pituitary-adrenal (HPA) axis with modifications in the immune state (reviewed below, in the section of chronic stress). A brief description of the central pathophysiological changes during acute stress will be explained:

(1) Sympathetic activation mediates the increase in arterial pressure and heart rate causing a higher demand of oxygen in the myocardium.¹² The endothelium dependent vasodilatation secondary to increased shear stress (resulting from the augmented blood flow) is reduced in atherosclerosis, an effect that may underlie the susceptibility of people with psychosocial stress (PSS) to the augmented sympathetic tone.¹³ Moreover, it has been shown that impaired vascular endothelium responses may predispose blood vessels to spasm.¹⁴ Hence, the paradoxical vasodilatation response to norepinephrine (NE) in coronary arteries, which is mediated by the endothelium (by nitric oxide overriding the NE vasoconstriction),¹⁵ does not occur in patients with atherosclerotic endothelial damaged responses.

(2) Short term sympathetic activation by mental stress, physical exercise, or catecholamine infusions induces activity of blood clotting factors and platelets. β_2 adrenergic receptor sensitivity secondary to increased plasma catecholamine activity may mediate this pro-coagulant response to acute stressors.¹⁶ Thereby, the platelet aggregability occurring during emotional stress may generate micro-circulatory occlusive effects.¹⁷ This clustering of thrombotic risk factors goes from an increase of plasminogen

Abbreviations: CVD, cardiovascular disease; PSS, psychosocial stress; SNS, sympathetic nervous system; HPA, hypothalamo-pituitary-adrenal; CRF, corticotrophin releasing factor; GR, glucocorticoid receptor; IL, interleukin; TNF α , tumour necrosis factor α ; VCAM, vascular cell adhesion molecule; COX 2, cyclooxygenase 2

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activator inhibitor preventing fibrinolysis to an increased fibrinogen activity, providing a plausible link between bio-behavioural factors and coronary artery disease.¹⁸

(3) Endothelial dysfunction reduces nitric oxide (NO) in the vascular wall.^{19–21} The reduced endothelial NO may also cause the production of the “tissue factor”, a molecule that in the disrupted atherosclerotic plaques induces prothrombotic changes.²² Moreover, circulating endothelin 1 concentrations are raised in hypertensive patients with a high risk profile for CVD, and might favour the development of acute vascular damage. This phenomenon can be prevented by selective endothelin A receptor antagonism.²³

CARDIOVASCULAR DISEASES WHEN THE PSS PERSISTS

Many everyday adverse life situations have been taken into consideration as possible precursors of CVD. In this way, hopelessness and pessimism (being the expression of a depressive disease or as the consequence of any life condition) are associated with an increased risk of mortality related to arteriosclerosis. Severe hopelessness increases the risk of having a fatal ischaemic heart disease.²⁴ In the case of cerebrovascular disease, (although with different risk factors when compared with CVD, derived from different haemodynamical conditions) self reported high stress intensity was associated with the risk of stroke, even though the statistical results do not provide strong evidence of independent risk factors for fatal stroke. Because of the space limitation, a brief outline of reports on depression, anxiety, some personality traits, absence of social support, etc, in relation to the development of CVD, is presented in table 1.²⁵

Peripheral pathophysiological mechanisms

During the acute PSS reactions, patients should have previous atherosclerotic vascular damage because of their vulnerability. During chronic PSS, the CVD appears as a consequence of the psychosocial insult (sometimes concurring with other somatic risk factors). Commonly, PSS presents itself in clusters. Poverty, a known risk factor for stress, is an example of the cumulative burden that may overcome human capacity of tolerance. It may exert its effects by creating not only non-satisfactory conditions for living, family disruption, unemployment, and bad/hostile neighbourhoods, but by promoting unhealthy activities like misuse of alcohol or recreational drugs use, proneness to crime, and other risky behaviours. On the biological side, malnutrition during poverty can produce depression,^{37–38} with a synergistic effect for stress responses.

The mental suffering experienced during chronic PSS (irrespective of their objective or subjective sources and their

proportionality) generates several molecular cascades modifying the immune state of the organism. PSS reactions start in the brain and their consequences are labelled “stress response”. Here, brain controlled centrifugal pathways such as the HPA axis and the sympathetic nervous system (SNS) are activated. These sub-systems discharge glucocorticoids and catecholamines respectively. The HPA and SNS pathways are interconnected and the activation of one of them modifies the other (fig 1).

However, downstream signals (the triggers) converting PSS into cellular dysfunction and finally into vascular disease are still largely unknown. Nevertheless, recent data have showed interplay among stress released corticotrophin releasing factor (CRF) and sympathetic nerve responses to stress. The finding that there is an adrenergic signalling pathway that explains the rapid increase in activation of the nuclear factor κ B (NF κ B) in peripheral blood mononuclear cells shortly after exposure to PSS (see below), may be the link among PSS to mononuclear cell activation, the subsequent changes in the immune system, and the final cardiovascular damage.

HPA AXIS IN THE STRESS RESPONSE^{39–44}

Overview

Centrally, mental stress causes cognitive and emotional modifications. Centrifugally, as the hypothalamus is an efferent branch of the visceral brain, it is sensitive to information from the periphery and it integrates this information with the internal environment. The main component and the coordinator of the HPA system is the CRF. The hypothalamus influences the pituitary gland through several polypeptides, called group releasing factors. Among them, the CRF controls the release of corticotropin (ACTH) from the anterior pituitary gland, which acts systemically. The final result of HPA axis activation is the release to circulation of glucocorticoids from the adrenal cortex.

Cortisol and glucocorticoid receptors

During stress, the increased concentrations of glucocorticoids (cortisol in humans) have important immunosuppressive effects on the lymphoreticular system and antiallergic and anti-inflammatory effects as well. In leucocytes, macrophages, lymphocytes, and in various target tissues, glucocorticoids decrease cytokines and other molecules that mediate the inflammatory reactions. Raised cortisol concentrations are down regulated through the hypothalamic glucocorticoid receptors (GR α), which when activated, suppress CRF, ACTH, and cortisol. There are, at least, two GR subtypes: the high affinity GR α receptors, and the very low affinity GR β

Table 1 Chronic psychosocial stress associated with cardiovascular diseases

PSS associated to CVD	Mediator mechanisms proposed	References
Work stress		
High effort and few reward	Increased BMI and increased cholesterol concentration	26, 27
Exhaustive coping style (competitive)	Impaired fibrinolytic capacity	28
Home stress		
Marital dissolution in women	Mental stress no otherwise specified	29
Caregiving for a spouse with dementia	Mental stress no otherwise specified	30
Social isolation (and self neglect)	Hyperfibrinogenaemia and hypercortisolism	31–33
Low income (poverty)	Blunted serotonergic responsivity.	34, 35
Chronic emotional disorders		
Anxiety	Low grade inflammation and atherosclerosis	25
Hopelessness*	Autonomic dysfunction (vagal withdrawal)	36
Hopelessness plus depression	Low grade inflammation and atherosclerosis.	24
Depression	Low grade inflammation and atherosclerosis	25

*Hopelessness may reflect a current or past “life situation” or can be a symptom of depression. PSS, psychosocial stress; CVD, cardiovascular diseases; BMI, body mass index.

Figure 1 "The components of the "stress response". Both arms of the stress reaction may cause chronic diseases in which inflammatory components (like endothelial dysfunction and consequent atherosclerosis) are the pathophysiological core. Broken line in bold corresponds to inhibition; continuous lines represent activation. NFκB, nuclear factor κB; IL6, interleukin 6; TNFα, tumour necrosis factor α; CRP, C reactive protein.

receptors.⁴⁵ The GRβ can be up-regulated in some cases of peripheral HPA dysfunction leading to cortisol resistance. The consensus view is that this situation occurs in glucocorticoid resistant asthma, chronic sinusitis, ulcerative colitis, among other disorders.³⁹⁻⁴⁶ Sometimes, the depressive disease may present cortisol resistance as some previously depressed patients suffer with chronic amplification of their inflammatory responses thereafter.⁴⁷ Prolonged or repetitive exposure to proinflammatory cytokines also increases the activity of the low affinity GRβ, promoting glucocorticoid resistance.⁴⁶

Glucocorticoids and immune suppression

Glucocorticoids' effects are produced, in part, by controlling the expression of specific target genes. In this way, they down-regulate multiple inflammatory cytokines, some chemokines, and some adhesion molecules. Most of these effects are mediated by the inhibition of the transcription factor NFκB by several molecular mechanisms (reviewed below).³⁹⁻⁴⁶

Glucocorticoids excess in neural tissues

During chronic stress, the resultant hypercortisolaemia in addition to its effects on metabolic and anti-inflammatory processes have also extensive modulatory effects on neurotransmission and in neural cell survival. In this case, there is an association between the excess in glucocorticoids and hippocampal atrophy.⁴⁸ Memory and learning deficits that may appear late in depression, where hypercortisolaemia is frequently present, are related partially to it. Other cognition deficits are related to damage of the frontal lobe neurons, which are highly sensitive to the effects of glucocorticoid excess.⁴⁹ It is also important to mention that in some depressive patients the hippocampal atrophy do not regress completely after remission,⁵⁰ justifying the speculation that an early re-establishment of normal HPA activity in mood disorders, before permanent deficits in neural functions occur, may be an important therapeutic goal. Finally, as the

hippocampus also modifies the HPA reactivity, even its functional damages lead to an increased glucocorticoid release.⁴³

Cortisol, abdominal obesity, and atherogenesis

During acute PSS, a rapid feedback inhibition of ACTH occurs in the brain and pituitary. However, chronic cortisolaemia in the stress range redistributes stored energy toward an intra-abdominal distribution, not only by its hyperphagic and antithermogenic effects but also because visceral adipose tissue has more cells per mass units, higher blood flow, and more glucocorticoid receptors. Hence, glucocorticoids affect abdominal fat to a greater extent than subcutaneous adipose tissue. In turn, visceral obesity represents an important risk factor associated with atherosclerosis as the intra-abdominal adipose tissue is an important source of the pro-inflammatory cytokine interleukin 6 (IL6).⁵¹ However, specific genetic background may accentuate this visceral fat accumulation in some people exposed to stress. Additionally, released cortisol in the long term will cause: (a) salt retention, (b) insulin resistance, (c) visceral fat syndrome, and (d) higher concentrations of LDL cholesterol. Most of the effects of these changes are also atherogenic.⁵²

Cortisol, aging, and cytokines

Aging causes increased responses to stress, characterised by higher levels of glucocorticoids. One of the causes is the concurrently increased production of IL6, generated and sustained by many chronic life stressors as will be seen in the following section. This situation contributes in an important manner to the age related diseases.⁵³ Furthermore, under neuroendocrine stimulation, IL6 is released by activation of β₂ adrenergic receptors.⁵⁴ This cytokine is comparatively resistant to cortisol suppression, in contrast with other proinflammatory cytokines, such as TNFα and IL1, which are down-regulated by glucocorticoids.

SNS AXIS IN THE STRESS RESPONSE^{39–44}

Overview

The second arm of the stress response is the “locus coeruleus/norepinephrine system” within the central nervous system. Its activation causes central sympathetic discharge and peripheral sympathetic outflow. During stress, the CRF stimulates the production of tyrosine hydroxylase, the rate limiting enzyme in the synthesis of norepinephrine, which is then synthesised centrally and secreted (while adrenaline (epinephrine) is secreted in the adrenal medulla). During stress, both molecules are invariably present in circulation. Moreover, the primary (bone marrow, thymus) and secondary (spleen, lymph nodes, etc) lymphoid tissues are innervated by SNS centrifugal pathways; hence, stress responses are transmitted to lymphoid tissue also by neurogenical channels.

Rapid translocation of the NFκB molecule

During stress, the cardiovascular and cerebrovascular systems are the immediate targets of catecholamines. However, among the plethora of the adrenergic biological effects, the SNS starts some proinflammatory molecular cascades, which are more evident during chronic stress. For example, in circulating monocytes starts the norepinephrine dependent adrenergic activation of the transcription factor NFκB³⁵ which, in turn, activates the nuclear transcription of several proinflammatory cytokines such as TNFα, IL1, IL6, among others (see the NFκB section, below). Finally, during chronic stress the proinflammatory reactivity from the SNS can surpass the immunosuppressant effects of the HPA axis activity.

Th2 subset activation and “natural killer” cells down-regulation

SNS activates immune responsive cells: (a) from the innate immune system such as monocytes/macrophages and dendritic cells, and (b) a T helper lymphocytes subset from the adaptive immune system. In this T helper compartment, there is a shift toward the T helper 2 (Th2) subclass derived from the inhibitory activity of catecholamines on the T helper 1 (Th1) cells (as β adrenoceptors are expressed on Th1 cells but not on Th2 cells). However, because the response to β adrenoceptors wanes during monocyte maturation, in some compartments of the body the α adrenoceptor mediated effect of catecholamines may become transiently dominant, increasing Th1 cellular immune responses.

In the short term, catecholamines mobilise the natural killer cells from storage areas, whereas in the long term they reduce their circulating amounts. As CRF also decreases the natural killer activity independently of the adrenocortical activation, the result is a drastic diminution of these cells responses.

Generation of the sickness syndrome and the acute phase reaction

Circulating TNFα, IL1, and IL6 (and the family of other proinflammatory cytokines such as interferon gamma, etc) also cause a systemic syndrome: anorexia, fatigue, asthenia, somnolence, and fever, collectively identified as the sickness syndrome. Moreover, these cytokines activate the synthesis (in the hepatic and other tissues) of the acute phase proteins (C reactive protein (CRP), cell adhesion molecules, fibrinogen, etc). These molecules will cause another adaptive phenomenon referred as the acute phase reaction. These biological responses are commonly seen when stress is the consequence of an inflammatory or an infectious disease, although also appear during PSS.

Increased CRP consequences

During the acute phase reaction, CRP is directly implicated in CVD risk: (a) promoting secretion of inflammatory mediators by vascular endothelium, (b) increasing the expression of cell adhesion molecules, (c) facilitating the uptake of low density lipids into macrophages, a situation that decreases the endothelial nitric oxide synthase expression, (d) inhibiting endothelial progenitor cells differentiation, survival, and function, and (e) activating vascular smooth cells. The acute phase reactants, because of the resultant low grade chronic inflammation increase the risk of atherosclerotic complications.^{56–58} Moreover, CRP can be produced locally by the damaged endothelium, promoting inflammatory changes in situ.^{57–59}

Inhibiting loop of the SNS activation

TNFα, IL1, and IL6, during its circulation and in a synergistic manner, activate the HPA axis (despite block from the blood-brain barrier).³⁹ Then, the HPA will generate signals toward the SNS, down-regulating it. Inflammatory molecules may also activate the HPA axis indirectly, by brain noradrenergic pathways.

DEREGULATION OF THE HPA AND SNS

The stress response is tightly autocontrolled for: (a) preserving the equilibrium between immunosuppression and inflammation, (b) obtaining the appropriate and opportune suppression of both arms after the tissular injury has been resolved, and (c) returning to the physiological levels from the previously increased concentrations of cortisol and catecholamines. However, during chronic PSS, the tissular damage required for the classic stress response does not exist and the reaction is orchestrated in the brain without physical injury. This situation results that the equilibrium of the response sometimes does not regress. Consequently, the immunosuppressant or the inflammatory sides of the response may dominate the scenery. How and when exactly this deregulation presents itself, is still a poorly understood matter.

On the one hand, an excessive HPA response during chronic PSS can imitate the hypercortisolaemic state, increasing the susceptibility to certain infectious agents, neoplasms, and increasing the resistance to autoimmune or inflammatory diseases. This HPA hyperreactivity can be present in: (a) the visceral obesity and the associated syndrome of insulin resistance, and (b) the response to HIV infection (during acute and subacute stages). The hippocampal atrophy occurring late in the depressive disease is also considered as a consequence of glucocorticoid excess.

On the other hand, the stress induced hypoactivity of the HPA (acquired glucocorticoid resistance) can be present as the resultant of the intense or repetitive action of the proinflammatory molecules, or during the severe activation of the innate and adaptive immunity surpassing the inhibitory loops, similar to that which occurs during the acute respiratory distress syndrome⁶⁰; only on rare occasions is it produced by glucocorticoid receptors that are genetically defective. Other stress independent human diseases are facilitated by a decreased HPA sensitivity: (a) rheumatoid arthritis, (b) corticosteroid resistant asthma, (c) acquired immunodeficiency syndrome in terminal stages, (d) degenerative osteoarthritis, (e) Crohn's disease, (f) systemic lupus erythematosus, among others.⁶¹ In all diseases mentioned above, a sustained PSS has severe deleterious effects.

Conversely, a hypernoradrenergic function (although coupled to hypercortisolism) has been described in the melancholic depression (also called atypical depression, with hypersomnia, hyperphagia, letargy, and fatigue).⁶² In the case of the metabolic syndrome, there is also hyperactivity in both

arms of the stress response, but with a clear (indirect) sympathetic predominance.⁶³ Specific pathological situations where the SNS response to PSS can be hypoactive have not been described; however, it is reasonable to speculate that patients with poor SNS sensitivity behave, under stress conditions, like HPA hyper-reactors.

NFKB SYSTEM IN PSS RESPONSE

Overview

During the past decade, the transcription factor NFκB has been shown crucial for the induction of genes involved in inflammation and in diseases originated from chronic activation of the immune system. Most immunoregulatory genes that code for proinflammatory molecules contain NFκB sites in their regulatory or promoter regions. Examples of some NFκB regulated genes are: vascular cell adhesion molecule (VCAM)1, E-selectin, tissue factor, plasminogen activator inhibitor (PAI)1, cyclooxygenase 2 (COX2), and inducible nitric oxide synthase (iNOS), plus several proinflammatory cytokines (such as interferon gamma, IL1α, IL1β, IL2, IL11, transforming growth factor β, and RANTES. Importantly, IL1, a master regulator cytokine, is often produced at the site of inflammation and then activates other cytokines including some chemokines).

In unstimulated cells, NFκB molecules are present in the cytoplasm in an inactive form, associated with members of other family of proteins called inhibitors of κB (IκB). Under stimulation, IκB is degraded and allows the NFκB to migrate to the nucleus to exert its effects on gene regulation. Activation of the NFκB is a transient phenomenon because it is up-regulated on demand for a limited period of time and then shut down. Prolonged activation may occur through persistence of their stimulator agents, or through impairment of the mechanisms for down-regulation.^{64 65}

NFκB activation and endothelial dysfunction

During mental stress, noradrenergic signalling on peripheral blood mononuclear cells (through the β₁ adrenergic receptors) begins a rapid but brief activation of the transcription factor NFκB (activation that terminates itself by inducing the inhibitory molecule IκBa by the β₂ receptors among other mechanisms), changing the immune state of monocytes towards activation.^{55 58} It is probable but not yet proved that endothelial cells also react rapidly with the NFκB activity during mental stress, as occurs with the NFκB system in the brain cortex as a result of acute and/or chronic stress.⁶⁶

NFκB autoregulatory loop

On the one hand, activation of NFκB occurs under the following circumstances (among others): (a) increased oxidative stress, (b) dyslipidaemia, (c) hyperhomocysteinaemia, (d) by the action of several infectious agents (*Chlamydia pneumoniae*, or cytomegalovirus for example). On the other hand, there are several types of inhibitors of NFκB such as the antioxidants and radical scavengers (*N*-acetylcysteine and analogues) or resveratrol (a polyphenolic compound identified as a constituent of the red wine). Also, the fatty acids of the omega-3 family inhibit NFκB activation via a peroxisome proliferators activated receptor α dependent pathway. There are also molecules that increase the activity of the NFκB specific inhibitory factor, IκBa.^{64 67} For instance, the induced COX2 generates substances called cyclopentenones, preserving the integrity of the IκBa; also curcumin or the epoxyeicosatrienoic acids have this property. The salicylates (in very high doses), binding to some kinases (IKK2), up-regulate the IκBa.^{64 67} The statin family can also stabilise IκBa.⁶⁸ Also the aminosalicylate drug mesalamine down-regulates NFκB by other unknown mechanism besides the upregulation of the IκBa inhibitory molecule.

QUANTIFYING PROBLEMS IN PSS

The construction of a comprehensive instrument that may quantify the PSS should range from emotion perceptions to behaviour in response to these stimuli. As not all people under PSS have the same somatic response and the causes of the PSS are heterogeneous, it has been difficult to design any psychological scale that may reflect the overall facets of this problem. Moreover, multiple factors influence response to stress. These include features such as duration of the emotional response, timing and causation, and features of the sufferers, such as age, intelligence, prior exposure to traumas, and pre-existing psychiatric disorders. Expected responses to PSS must be also outlined for each developmental stage. To exemplify this complexity, the comprehensive series on scales of Myers and colleagues, (related to emotional perceptions/reactions) can be reviewed.⁶⁹⁻⁷²

Therefore, for the moment, a unifying tool that may detect those people who are being damaged by PSS awaits the identification and validation of some biological variables (biomarkers) that can point out people with CVD fragility during PSS.

DEPRESSION AS AN EXAMPLE OF CHRONIC PSS

Few human diseases are as painful as depression. Reasons go from its inherent subjective suffering to its chronicity and insufficient recognition and treatment. Fortunately, successful therapeutic regimens exist (psychotherapy, drugs, or both) and when properly applied, most patients improve, although they are frequently forced to take drugs indefinitely so as to prevent relapses. However, this picture is not always true. Many depressed patients continue aging with cognitive damage or vascular damage in their brains related to their chronic depressive states. Depression also increases the mortality derived from CVDs.⁷³ Hence, we know that depression is a silent killer, but how and why? Can a deregulated stress response be one of the culprits?

The most conservative answer is affirmative. There are enough data to include depression among other chronic diseases with inflammatory components, as we do now with obesity or diabetes. On the one hand, many research articles prove the existence of molecular markers relating depression to atherosclerosis: (a) chronic endothelial activation,⁷³ monocyte activation,⁷⁴ high CRP levels, and increased inflammatory responses after a depressive episode, among others.^{47 75} On the other hand, about 50% of depressed patients are hypercortisolaemic, a situation that also may culminate in atherosclerosis. Why then, despite the weight of accumulated evidence, have some recent reports^{76 77} not found an association between depression and mortality?

Intensity of immune responses to stress can be of different magnitude among different patients. It has been shown that early attacks to the immune system led to immune hyper-reactivity thereafter.^{47 78} Thereby, it is reasonable to suppose that there are subgroups of depressed patients with intense immune activation. These patients may have a high set point for shutting down the stress response (or a deregulated stress response) forming an arteriosclerosis prone subgroup. Therefore, if we continue studying un-stratified depressed patients to disclose the effects of depressive related stress on CVD, many investigations will show inconclusive or negative results. Perhaps the already cited markers of inflammation in depressive patients may be used in future studies for a better selection of the high risk atherosclerotic prone depressive patients.⁷³⁻⁷⁵

PSS AND CVD: THE PROBLEM OF THE NEGATIVE REPORTS

This review summarises the scientific basis underlying the relation between PSS and CVD. Its limitations are

represented by the selective review of a complex area of human behaviour and biology. Nevertheless, we have now enough hard data to accept that the PSS is associated to CVD; but, what percentage of patients with PSS will have an important or fatal CVD problem? In the case of acute PSS, authors do not disagree, probably because outcomes take place in people already damaged by arteriosclerosis. The problem exists during chronic PSS, where negative reports should be understood before proper clinical decisions can be adopted. Hence, I propose the following theoretical approaches:

(1) Rejecting the PSS effects on atherosclerosis because not all stressed people have deleterious consequences is equivalent to discarding the risk that being overweight has on CVD, because some people do not suffer the related consequences. Unfortunately, this is exposed in conclusions like "... there is no association between psychological stress and the CVD ...".⁷⁶ We can hypothesise that PSS does not predict CVD fatalities, but not that there is no association between mental stress and CVD.

(2) CVD risk factors may cause fatal atherothrombotic accidents in some diseases, while other risk factors can act as moderators or mediators.⁷⁹ The unremitting PSS may be located in the second category.

(3) Fatal outcomes in CVD patients with PSS may be selectively related to the presence of un-modifiable factors (as occurs in common inherited abnormalities in blood coagulation). Additionally, there exist subgroups of atherosclerotic prone people that can react severely during PSS, such as those with vascular vulnerability acquired by a long term effect of early prenatal events (programming).⁸⁰ Postnatal growth acceleration can also have a programming effect that, interacting with adverse life events situates the patients in risk for CVD.⁸¹ Also, early attacks to the immune system lead to immune hyper-reactivity thereafter.⁴⁷

WHERE DO WE STAND NOW?

The theme of PSS and CVD is a goal actively pursued in the scientific literature from past decades until now. However, as not all prospective studies have reported a significant relation between psychological stress and ischaemic heart disease, a definite direction towards the search of biological markers has not been outlined yet. Most international ongoing researches are still dealing with the demonstration of good evidence for the association. This is the case of: (a) the INTERHEART study group, or (b) the respective section of the Framingham study, or the works in different countries: (c) Ismail, (d) Bluzhas, (e) Wamala, and many others.⁸²⁻⁸⁶

CONCLUSIONS

Nowadays, we do not know what percentage of patients can sustain, despite persistent PSS, a low set point for stopping their immune suppressive/immune activating response. These people will have few complications derived directly from their mental stress. For the others, a deregulated response will result. Their consequent disease can be skewed towards immunosuppression or towards the inflammatory side. Finally, some patients may conserve the equilibrium between both arms of the stress response, but with an abnormally high set point for stopping the response, a pro-atherosclerotic process also (see fig 1). So, several suggestions to patients with PSS can be advanced (besides intending to help them in reducing it when possible).

(1) As it is well reported that healthier lifestyle delays or reduce the atherosclerotic risks, the emphasis on modifying unhealthy habits like smoking, alcoholism, overweight, high fat diet, sedentary life, etc, is of paramount importance for these patients. (2) Addition of appropriate doses of fish or omega-3 fatty acids in diet is not harmful and may delay

endothelial dysfunction. (3) Should we still prescribe drugs such as the non-steroidal anti-inflammatory agents or statins? Although these substances may be beneficial for some stressed people, because of the uncertain knowledge about patients that can be undoubtedly helped, we are not yet in the possibility of advising their general use. (4) Patients with other risk factors for CVD (diabetes, hypertension, obesity, etc) in addition to PSS, should be advised not only to take the best lifestyles to promote their health, but to receive the secondary prevention measures for treating their overlapping risk factors for CVD. (5) The PSS is probably a mediator or moderator risk factor (an intervening causal variable) among the chain of causal risk factors for CVD. Consequently, specific biological markers to stratify adequately PSS patients who are prone to suffering a severe CVD are needed with urgency.

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