Cardiovascular disease and psychological disturbance

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Contents

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Introduction

In 1959, Friedman and Rosenman (1959) proposed a link between type 'A' personality and cardiovascular (CV) disease. Researchers have since examined the intricate links between the cardiovascular system and psychological disturbance. Their results show that variations in the neuroendocrine control of CV function can be related to psychological factors.

This essay examines the current literature relating glucocorticoid and autonomic nervous system (ANS) activity with CV morbidity. The information is presented as a psychoneuroendocrinological description of CV regulation, with a description of the possible mechanisms by which psychological disturbances can influence CV regulation and ultimately result in CV disease.

1. Psychoneuroendocrinology

Psychoneuroendocrinology or mind-body medicine, is a relatively new area of medicine that has developed due to the recognition that body systems, hereto thought of as being independent, are intimately linked. Watkins (1998. p. III) writes: "In the last 20 years there has been growing awareness amongst scientists and clinicians of how the different body systems within the body interact and how the breakdown in co-operation between these different systems can set the stage for the development and progression of disease".

Research into the activities of the heart in this inter-active-system approach to the human condition, have concluded that CV illness is intimately associated with psychological disturbances, especially depression, anxiety (Purcell & Mulcahy. 1994). These new ideas are not far removed from those of our forefathers. In an essay comparing the modern cultural perception of the heart to the pre-biomedical vision, Hillman (1979) writes: "The heart is still king, still the pace-maker, but now a tyrant, for heart and circulatory diseases are 'the number one killers', usually striking in the night. It cannot be trusted; we cannot have faith in the very organ which once was the source of faith".

2. Neuroendocrine influence on cardiovascular activity

Classical physiology has described in detail the extrinsic regulatory mechanisms of the heart and their effects on myocardial performance. These mechanisms have been described in terms of the activity of the ANS and its regulation by the catecholamines (see also appendix I, figs. 1 & 2 & appendix II, table 1).

Within the last decade, considerable attention has been devoted to the examination of other extrinsic endocrinological control mechanisms that influence CV activity. These pathways are intimately linked with psychological activity, and disturbances in these pathways have been implicated in the aetiology of CV illness (Gala et al. 1997).

2.1. Hypophysen-pituitary-adrenocortical axis

The catabolic glucocorticoids produced in response to hypothalamic-pituitary activity are known to have CV activities (see also appendix III table 2). Production of glucocorticoids occurs in response to stress and it has been recognised for nearly a century that this is a two way effect, as increased glucocorticoid levels can cause psychological disturbances (Thase & Howland 1995, p. 245).

The hypothalamic-pituitary-adrenocortical (HPA) axis constitutes the major *coarse* feedback control mechanism for glucocorticoid production (see also appendix IV). However, Thase et al. (1995, p. 246) write that: "The overall integrity of the HPA axis is controlled by an intricate feedback inhibition system, which receives input from both the limbic system and the cerebral cortex". These feedback mechanisms ultimately effect hypothalamic corticotropin-releasing hormone (CRH) production.

2.1.1. The role of Corticotropin Releasing Hormone

Specialised CRH responsive cells have been found throughout the cortex (Nemeroff 1992), and more recent studies have implicated increased levels of CRH with depressive disorders. Mitchell (1998) states: "…physical and psychosocial stressors, for example prolonged immobilisation or social conflict, down regulate CRH receptors in the anterior pituitary and hypothalamus. But may up regulate receptors in sites outside the HPA system". A study conducted by Weiss et al. (1994) linked anxiety with increased levels of CRH and excitement in the Locus Coeruleus (LC) cells. The LC has extensive projections, some of which innervate the dorsal vagal nucleus, and influence the preganglionic sympathetic neurones in the intermediolateral cell column of the spinal cord (Wilkinson 1988). This data would suggest that prolonged stressors could via the influence of CRH, have dysregulatory effects upon both the HPA and the ANS.

2.1.2. Dysregulation of the hypothalamic-pituitary-adrenocortical axis

Dysregulation of the HPA axis was observed by Yehuda et al. (1996) in a study comparing the basal pattern of cortisol release in patients suffering from post-traumatic stress disorder (PTSD) with patients with major depression. Their findings concluded that although both groups showed elevated cortisol levels, the group with major depression displayed a chaotic pattern of cortisol release. In the group suffering from PTSD, cortisol release patterns were better modelled by circadian rhythm.

These findings intimately relate the *status quo* of the HPA axis with psychological states, where dysregulation of the HPA axis is primarily related to prolonged psychological stressors. This relationship has been identified by Nielsen (1989), who described two types of stress response:

- The *active stress response* is characterised primarily by sympathetic autonomic activity.
- The *passive stress response* is characterised by high activity of the HPA system.

The *passive stress response* is a chronic state, which occurs when the individual is not able to react in a 'fight or flight' response (e.g. long-term anxiety leading to depression).

There have been many articles written implicating depression and anxiety to CV illness. A correlate with the ideas proposed by Nielsen is to be found in the studies of Hemingway and Marmot (1999).

They concluded that the major aetiological factors linking CV disease to psychological disturbances were; type A/hostility, depression, anxiety, work characteristics and social support. All of these factors fall within the remit of the *passive stress response* identified by Nielsen (1989).

It could therefore be assumed that the mechanisms that relate CV disease to psychological disturbance are to be found within activity of the HPA system. This idea would also implicate the ANS due to the interaction of CRH with the LC.

2.2. The autonomic nervous system

The ANS is considered as being the quick short-term regulator of CV dynamics, and is according to Nielsen (1989) responsible for the *active stress response.* The normal ANS regulatory control mechanisms are described in appendix II table 1. Autonomic activity also influences blood pressure, primarily via the sympathetic vasodilator system, which is principally controlled by the anterior hypothalamus and secondarily via the vasoconstrictor regions in the medulla.

Research into the ANS's role in the pathogenesis of CV disease related to psychological disturbances, has focused on blood pressure regulation. Autonomic regulation of blood pressure is mediated by both influence on the vasodilator system and by regulation of the heart rate.

2.2.1. Blood pressure variability – vasoconstrictor activity

In an article discussing the psychophysiological aspects of CV disease, Sloan et al (1999) presents the hypothesis that blood pressure variability (BPV) is a major factor in the development of coronary artery disease (CAD). Sloan proposes that psychological/behavioural factors, which can effect the capacity for CV autonomic regulation, indirectly effect BPV. This supports the argument that disturbances in the ANS are associated with CV morbity.

One of the main factors influencing BPV is autonomic vasoconstrictor activity. Julien et al. (1993) suggests that vasoconstrictor activity is an essential component of BPV, providing the background *tone* in the arterial system. The level of this *tone* dictates how transient sympathetic vasodilatory influences cause dynamic changes in arterial muscle tone, therefore dictating the BPV response.

It is known that projecting fibres from the vasoconstrictor regions in the brain descend in the intermediolateral columns of the spinal cord prior to emerging via the ventral roots to synapse in the paravertebral sympathetic chains. As mentioned previously, the effect of CRH on the LC can influence the preganglionic sympathetic neurones in the intermediolateral columns of the spinal cord Weiss (1994). This could be the pathway by which CRH influences the ANS in CV disease, as the dominant effect of fibres from the LC is inhibitory, which would explain the loss of vasoconstrictor tone as described by Julien et al. (1993).

Other possible mechanisms that could link elevated CRH levels with changes in vasoconstrictor tone are the effects of increased cortisol production. In a study on the effects of cortisol on renal blood perfusion, Matteo and May (1997) concluded: "… that cortisol acts directly on the kidney causing vasodilation and increasing renal blood flow". This would ultimately result in a disturbance of angi-

otensin II production. Cortisol also causes a direct decrease in the production of vasodilator prostaglandins.

2.2.2. Blood pressure variability – heart rate variability

Heart rate variability (HRV) is another mechanism by which dynamic changes in blood pressure can be regulated. HRV reflects autonomic activity, and measurements of HRV are used as an indicator to assess autonomic tone (see also appendix V, table 3.).

Clinical studies have shown that HRV analysis is a good prognostic tool for predicting mortality in post MI patients (Krittayaphong et al. 1997). Furthermore, depressed patients with CV disease have been shown to have a reduction in HRV, which relates to an increased risk of cardiac morbidity and mortality (Carney et al. 1988, Carney et al. 1999 and Thornton et al. 1999.). These findings could relate disturbances in the ANS with CV disease aetiology.

It was previously suggested that the *passive stress response* could implicate the ANS and HPA in CV disease pathogenesis. This hypothesis can be further supported by the findings of Sloan et al. (2001), who confirmed a reduction in HRV in subjects demonstrating hostility.

The pattern then arises that psychological disturbances related to *passive stress response* can disturb the neuroendocrine control mechanisms of the CV system. The question then arises as to the nature of the pathological mechanisms involved.

3. Dysregulation of the neuroendocrine system and mechanisms in the development of cardiovascular disease

The psychoneuroendocrinological factors relating to CV disease presented in this essay are summarised in appendix VI. The principle resulting factors are:

- Increase in dynamic changes in blood pressure (as a result of disturbances in the autonomic control of BPV)
- Increase in dynamic changes in blood pressure (due to decreased HRV)
- Increased circulatory cholesterol
- Increased circulatory triglyceride
- Increased platelet activity

It can be seen that the physiological results of psychological disturbance produces a cardiovascular scenario, which predisposes to the development of CV disease (see also appendix VII, fig 5). Sloan et al. (1999) describes how increases in BPV may have pathogenic effects on the coronary arterial endothelium. Disturbances of the autonomic control of BPV along with decreased HRV causes instability in the blood pressure, which predisposes to endothelial damage and is the first stage of plaque formation. The blood chemical profile in the *passive stress response*, with increased triglycerides and cholesterol would promote plaque formation (see also appendix VIII, fig. 6) ultimately resulting in artherosclerosis.

A sequel to this scenario explaining acute ischaemic heart disease has been described by both Sloan et al. (1999) And Musselman et al. (1998). Sloan (1999) states that: “Damage to the fibrous cap [that

covers the atherosclerotic plaque] exposes underlying plaque material to the lumen of the coronary artery, stimulating platelet aggregation and thrombus formation". Increased platelet activity would help facilitate this process. Thrombus formation is one of the major factors in the development of ischaemic heart disease.

Another aspect that could also play a role is the direct action of increased sympathetic tone upon the heart, causing coronary vasoconstriction. This would amplify the effects of the previously mentioned mechanisms.

4. Conclusion

The present state of research into the relationships between psychological disturbance and CV disease has firmly established that disturbances correlating with the *passive stress response* described by Nielsen (1989) are linked to CV disease morbidity. Much research has been carried out to examine the various mechanisms that could be responsible for these phenomena. However, a cohesive picture of how these mechanisms are related is only just beginning to reveal itself. Research into psychological disturbance and CV disease requires a multi-specialist approach, as the nature of the problem reveals an intricate interaction between endocrinological, neurological, psychological and cardiological mechanisms. The field of psychoneuroendocrionology has developed out of a need to combine specialities in order to understand fully the multi-factorial aspects of the human organism in both health and disease. Hopefully the medical textbooks of the future will discuss illness in terms of the emerging holistic understanding of the life processes.

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Appendices

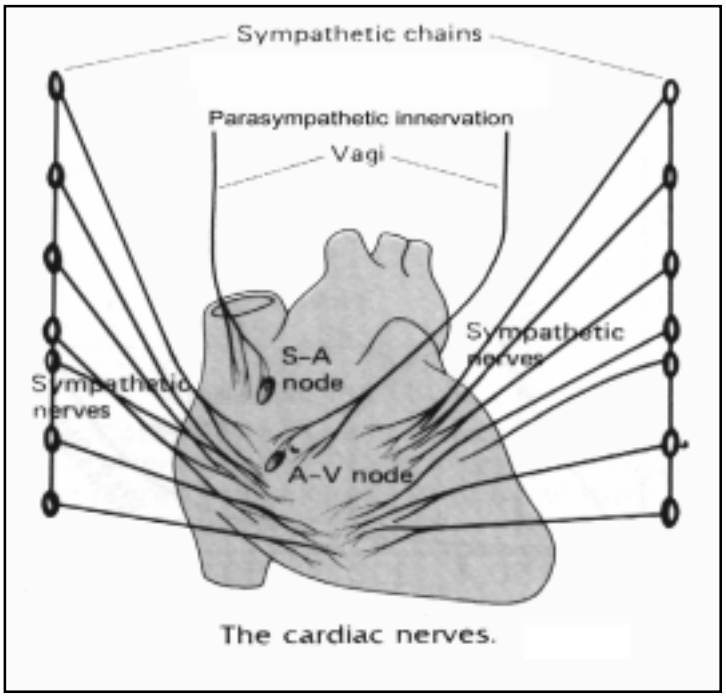


Figure 1: The cardiac nerves

Source: Guyton (1986)

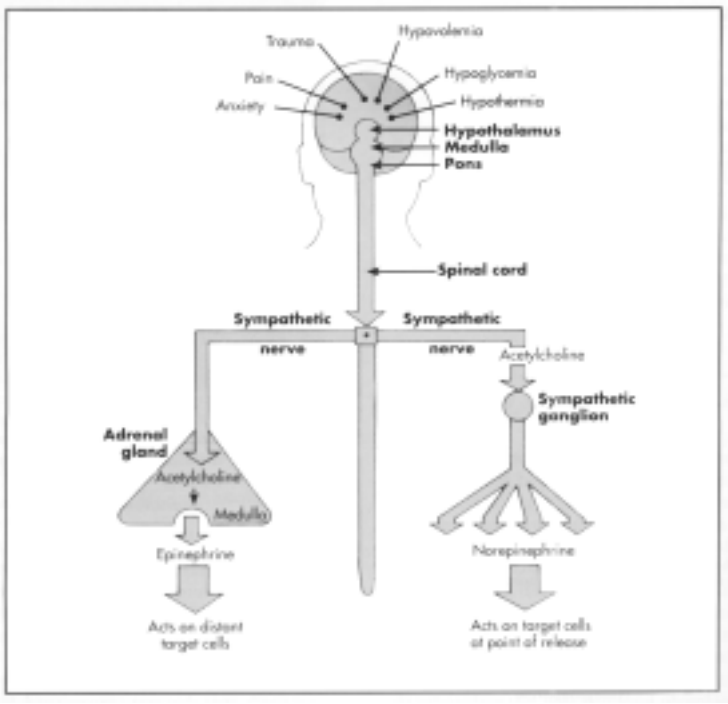


Figure 2: The catacholamines

Source: Berne et al. (1998)

Classical cardiac control mechanisms

Parasympathetic influence

Parasympathetic autonomic innervation of the heart arises in the medulla oblongata (dorsal motor nucleus of the vagus, or in the nucleus ambiguus). From this origin arise the left and right nn. vagi.

The right vagus nerve has an inhibitory effect on the SA node, which slows down SA nodal firing. The left vagus nerve impedes AV conduction. The high concentration of cholinesterase at the SA and AV nodes, causes the rapid decay of vagal stimulation, due to breakdown of the acytylcholine neurotransmitter.

Sympathetic influence

The preganglionic cardiac sympathetic fibres have their origin in the intermediolateral columns of lower cervical and upper thoracic segments of the medulla spinalis. They synapse with the post-ganglionic fibres in the stellate or middle cervical sympathetic ganglia. The heart receives post-ganglionic fibres its apex, which form an extensive epicardial plexus prior to entering the myocardium.

Sympathetic activity, unlike vagus activity, is slow to decay and most of the norepinephrine neurotransmitter is taken up by the nerve terminals. Similarly, the heart responds slower to initiatory sympathetic stimulation than it does to initiatory parasympathetic stimulation.

The right and left sympathetic fibres are distributed to different areas of the heart. It is thought that the left fibres have a more pronounced influence upon myocardial contractility, whilst the right fibres have more influence on heart rate.

Cardiovascular influence upon autonomic activity

Autonomic activity of the heart is influenced by the hydrodynamic and chemical state of the blood. Afferent signals from chemoreceptors in the cardiovascular system regulate vagal activity via the medullary vagal center. Afferent signals from baroreceptors in the cardiovascular system regulate both vagal and sympathetic activity.

Catecholamine influence

Epinephrine primarily initiates the cardiovascular systems metabolic activity, increasing heart rate, contractile force and cardiac output. Due to epinephrine action on the β_2 receptors, arteriolar vasodilation occurs in the skeletal muscles.

Norepinephrine primarily causes an increase in the hearts contractile force, and due to epinephrine action on the α_1 receptors, arteriolar vasoconstriction occurs in the renal, splachnic and cutaneous beds.

Stimulation of α_2 adrenoreceptors on platelet membranes increases circulatory catacholamines and with increasing catecholamine concentrations, activate platelet activity.

Table 1: Cardiac control mechanisms

References: Guyton 1986 & Berne et al.1998

Appendix III

Cardiovascular activity of the glucocorticoids

The Glucocorticoids particularly cortisol, produced by the adrenal cortex are known to have various actions upon the cardiovascular system, these are:

- To sustain myocardial performance
- To facilitate the vasoconstrictive activities of the catecholamines and angiotensin II
- To decrease production of vasodilator prostaglandins, and reduce vascular endothelium permeability

Table 2: Cardiovascular activity of the glucocorticoids

References: Berne et al.

Appendix IV

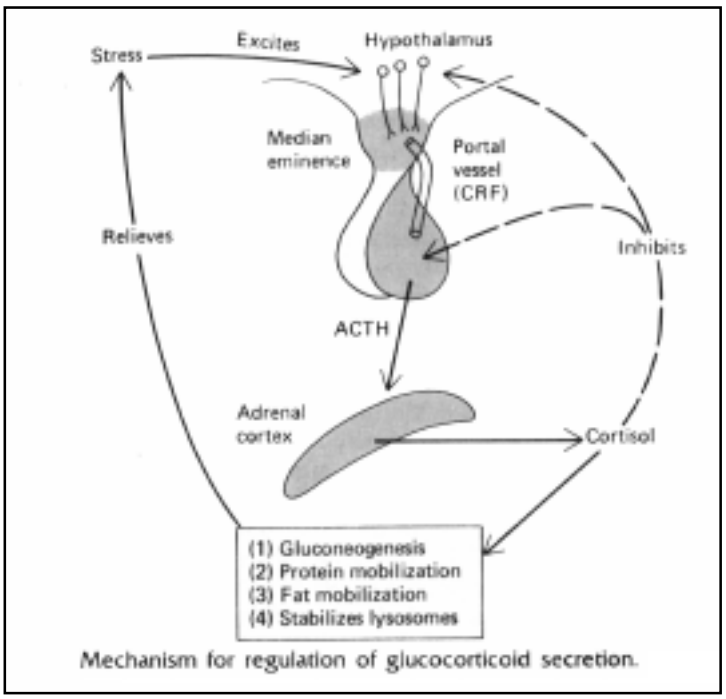


Figure 3: Regulation of glucocorticoid secretion

Source: Musselman et al., 1998.

Appendix V

Heart rate variability

The heart rate variability spectrum is measured by the standard deviation of succesive R-R interval, R being the first positive deflection in the QRS complex.

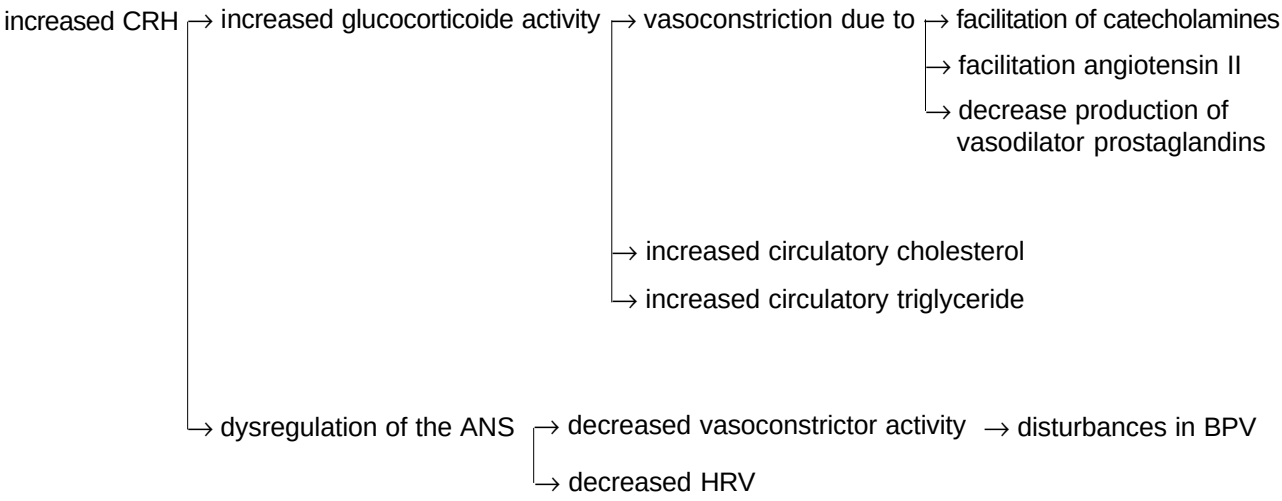
Heart rate variability is measured using fourier or autoregressive analysis, and devides the variability spectrum into high and low frequency components.

Analysis of the spectrum reveals a high freqency (>0,20 Hz) and a low frequency (<0,10) Hz components. The high frequency component is a reliable indicator of parasympathetic efferent activity. The low frequency component, or the ratio of low to high frequency is thought to be a reflection of sympathetic activity.

Table 3: Definition of heart rate variability.

References: Musselmann et al. (1998), Sloan et al. (1999), Houle et al. (1999)

Appendix VI



increased catecholamine activity → increased platelet activity

Principle factors in the development of cardiovascular disease

- Increase in dynamic changes in blood pressure (as a result of disturbances in the autonomic control of BPV)
- Increase in dynamic changes in blood pressure (due to decreased HRV)
- Increased circulatory cholesterol
- Increased circulatory triglyceride
- Increased platelet activity

Figure 4: The psychoneuroendocrinological factors relating to CV disease

Appendix VII

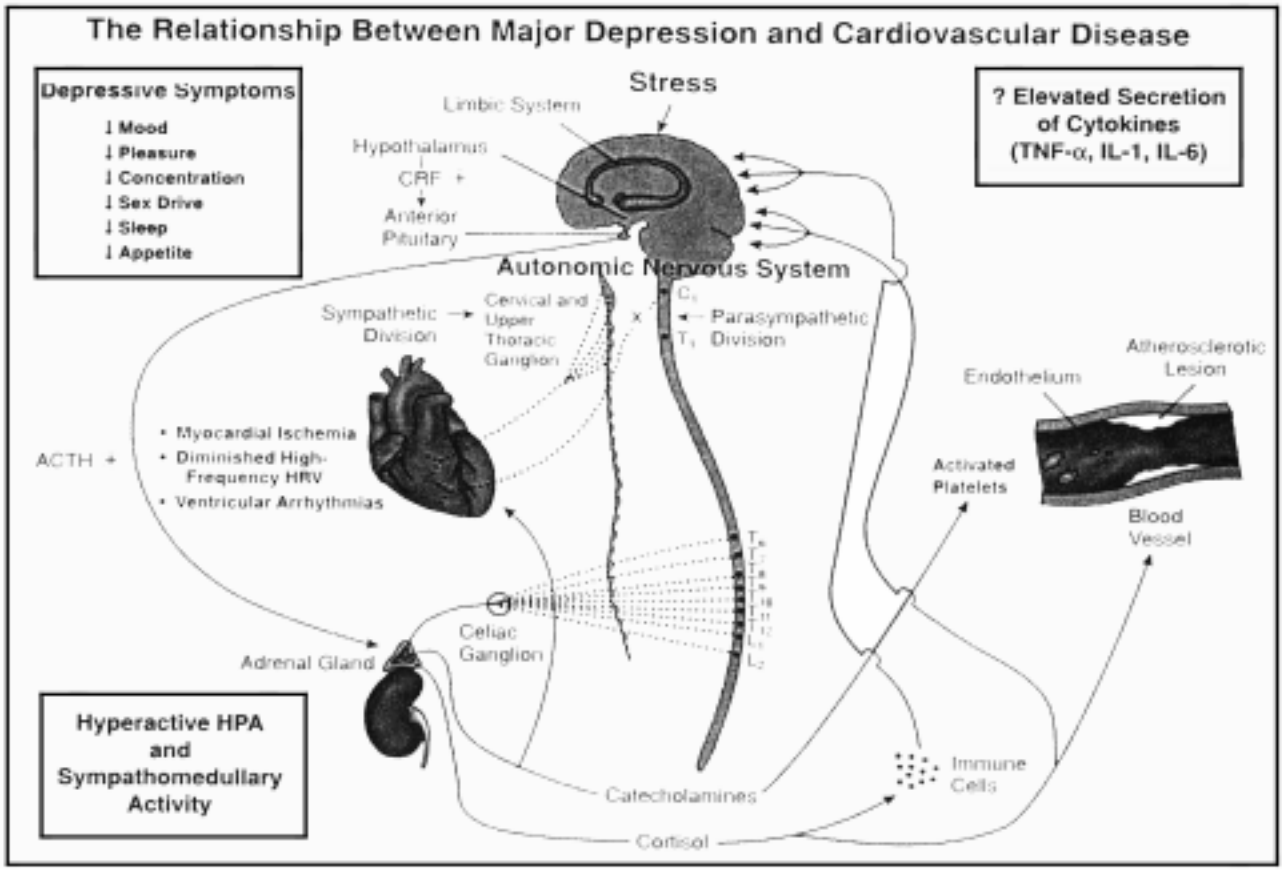


Figure 5: Pathophysiologic alterations associated with depression

”Hypothetical schema of pathophysiologic alterations associated with depression that likely contribute to increased vulnerability to cardiovascular disease (CVD). Autonomic nervous innervation of the heart via parasympathetic vagus (X) and sympathetic (postganglionic efferents from cervical and upper thoracic paravertebral ganglia) nerves is shown. CRF indicates corticotropin-releasing factor; ACTH, corticotropin; TNF-α, tumor necrosis factor a; IL-1, interleukin 1; IL-6, interleukin 6; HRV, heart rate variability; and HPA, hypothalamic-pituitary-adrenocortical axis”.

Source: Musselman et al., 1998.

Appendix VIII

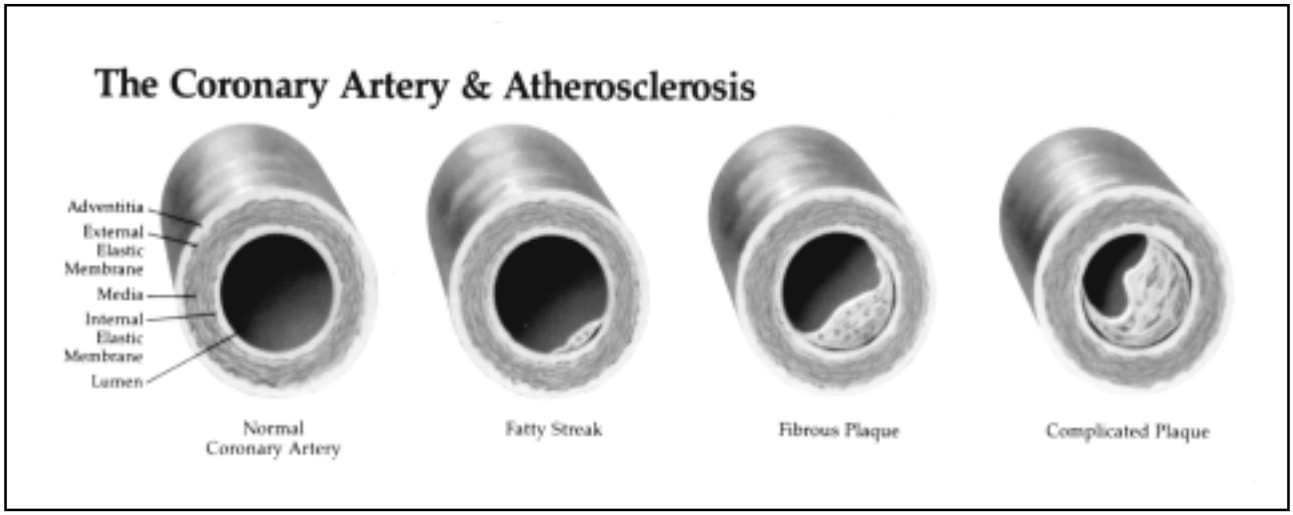


Fig 6: The coronary arteries and atherosclerosis

References: Anatomical Chart Co. (1993)

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