ORIGINAL ARTICLE

The role of some new factors in the pathophysiology of depression and cardiovascular disease: Overview of recent research

Eva Kitzlerová and Martin Anders

Clinic of Psychiatry, 1st Faculty of Medicine, Charles University and the General Teaching Hospital, Prague, Czech Republic

Correspondence to: Eva Kitzlerova, MD., PhD.
Clinic of Psychiatry, 1st Faculty of Medicine,
Charles University and the General Teaching Hospital
Ke Karlovu 11, Prague 2, 120 00, Czech Republic
PHONE: +420 2 24965358
FAX: +420 2 24923077
EMAIL: ekitzlerova@centrum.cz

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Abstract

Depressive disorders and cardiovascular disease are inter-connected by a whole range of pathophysiological mechanisms. Three biological mechanisms are fundamental: activation of the hypothalamus-hypohysis-adrenal axis with a subsequent increase in sympathetic-adrenal system activity, decrease in vagal tone with a decrease in heart rate variability, and alterations of thrombogenesis with increased platelet aggregability. Behavioural mechanisms and psycho-social factors are also integral to this common pathophysiology. Recently, research has focused mainly on studying various forms of stress, as well as changes and possibilities of influencing the autonomous vegetative system. Temporal aspects of the incidence and development of depressive episodes in relation to cardiovascular disease and subsequent cardiovascular morbidity and mortality are being studied, as well as general mortality risk factors. These findings are important for clinical practice. It is evident that in patients with untreated depressive disorder, the risk of developing cardiovascular disease is significantly higher than in patients suffering from a depressive disorder being treated with anti-depressants. From the data published so far, it may be surmised that depressive disorders in patients with cardiovascular disease may be reliably and safely treated with anti-depressants that act as inhibitors of serotonin re-uptake.

INTRODUCTION

It has been shown that depression may be both the cause as well as the consequence of physical illness. Depression increases the risk of mortality from cardiovascular disease, more significantly so in cardiac patients than in healthy individuals, and this risk depends on the degree of cardiac disease severity. This risk was approximately two times greater in persons with so-called minor depression (according to the DSM-IV classification, less pronounced symptoms of depression) and more than three times greater in persons with so-called major depression (according to the DSM-IV classification,

clear symptoms of depression). Cardiac patients with so called major depression were then designated as a high risk population group (Penninx *et al*. 2001).

An affective disorder may occur for the first time in an individual in direct association with e.g. myocardial infarction. This is then termed an organic depressive disorder (coded according to the ICD-10 as F 06.32). The effects and circumstances of cardiovascular disease may also induce depressive symptoms in an individual who has suffered from depression in the past or who is being treated for depression. In this case, the disorder is rather termed an exacerbation of a periodic depressive disorder (F 33), whereby the somatic disease represents a provoking factor for the already present psychiatric disease.

The increased mortality risk from cardiovascular disease was also uncovered in persons suffering from depression who have no cardiac disease. Depression is thus not only a marker of cardiac disease severity, but in itself contributes to its development and thus represents, together with "traditional" risk factors- hypertension, hypercholesterolemia, cigarette smoking, diabetes- an independent risk factor for its development (Carney *et al*. 1995, Penninx *et al*. 2001). Cardiovascular disease and depression thus represent two independent and in their way additive factors that increase mortality from cardiovascular disease. From this aspect, detection of a depressive disorder and its early and correct treatment in cardiac patients is extremely important.

PATHOPHYSIOLOGICAL RELATIONSHIPS BETWEEN DEPRESSIVE DISORDERS AND CARDIOVASCULAR DISEASE.

The exact mechanism by which depression affects the incidence and development of cardiovascular disease and vice versa is not as yet clear. It has been proven, though, that there is not a single mechanism involved, but rather that many factors play an interactive role.

Based on existing literary reviews, it may be presumed that a combination of biological and behavioural mechanisms is most probably involved. It has also been shown that psychosocial factors (Rozanski *et al*. 2005) and the induction of adverse psychological effects by certain cardiological preparation, e.g. alpha-blockers, methyldopa, clonidine etc. (Shapiro, 2005) also play a significant role in the common pathophysiology of these two diagnostic entities.

BIOLOGICAL MECHANISMS

Activation of the hypothalamus-pituitary-adrenal axis, imbalance of the autonomous vegetative system and the consequent changes in heart rhythm variability and decreased sensitivity of baro-reflexes, alterations of the immune system and of the composition of unsaturated fatty acids, and increased thrombogenesis are among the most important of these mechanisms.

Recently, research has focused mainly on the study of various forms of stress, changes and possibilities of influencing the autonomous vegetative system, the temporal aspects of the incidence and development of depressive episodes in relation to cardiovascular disease and subsequent morbidity and mortality, as well as the general study of mortality risk factors.

HYPOTHALAMUS–PITUITARY-ADRENAL AXIS (HPA)

The HPA axis represents a physiological system, which is involved in the stress response. Hyperactivity of this system is found in untreated patients suffering from moderate to severe depressive disorder (e.g. an increase in corticotropin releasing factor (CRF) in the cerebrospinal fluid (Musselman *et al*. 1998). Increased morning plasma concentrations of cortisol were considered to be associated with coronary atherosclerosis in young and middle-aged men. Increased plasma concentrations of catecholamines stimulate platelet activity directly and indirectly by inhibiting the synthesis of protective vascular endothelial eicosanoids, by elevating circulating lipid levels, and via haemodynamic changes that lead to endothelial remodelling. The pro-inflammatory effects of epinephrine and the alpha-2-adreno-receptor mediated cytokine enhance the damage to vascular endothelium and the formation of atherosclerotic plaques (Musselman *et al*. 1998).

Hyper-cortisolemia also plays a role in the distribution of body fat. The content of intra-abdominal fat, a well known risk factor of CHD, was two times higher in depressive women than in healthy controls (Thakore *et al*. 1997).

Dysfunction of the HPA axis in depressive patients reflects dysfunction of the sympathetic nervous system. Increased sympathetic-adrenal activity in patients suffering from depressive disorders leads to left ventricle dysfunction and to renal retention of sodium, which affects the progression of cardiac failure (Peppers, Lee, 1999).

Activation of the HPA axis during depressive disorders leads to the increased release of atrial natriuretic peptide (ANP). This is synthesised and secreted mainly in the heart atria and is involved in the regulation of blood pressure, diuresis and stress response. It has an inhibitory effect on the secretion of CRF and ACTH, and conversely CRF has a direct stimulatory effect on the secretion of ANP. It was repeatedly shown that ANP influences affective and anxious symptoms, especially in panic attacks and post-traumatic stress reactions.

ANP not only acts as a peripheral antagonist of CRF, but also directly in the CNS, where it has an anxiolytic effect. It inhibits hyperactivity of the HPA axis and sympathetic system domination (Wiedemann *et al*. 2001).

CRF pathways have extrahypothalamic channels that lead to the central components of the autonomous vegetative system. It has been shown (Brown *et al*. 1982) that

CRF, apart from its central role in the brain, stimulates the secretion of sympathetic nervous system mediators. Norepinephrine and epinephrine act on cardiac beta adrenergic receptors, increasing heart rate and myocardial contractility and decreasing heart rate variability, HRV (Schins *et al.* 2001).

Increased heart rate was also observed in depressive patients both with and without cardiovascular disease (Carney *et al.* 1999). Tachycardia and a decrease in HRV are associated with the risk of sudden death, myocardial ischemia, arrhythmia and heart failure, and together with other risk factors such as hypertension lead to increased body mass index (BMI) values and increased blood glucose concentrations, thus enhancing the development of atherosclerosis.

IMBALANCE OF THE AUTONOMOUS VEGETATIVE SYSTEM

Heart rate variability

Imbalance of the autonomous nervous system, the sympathetic and parasympathetic system, occurs in depressive disorders. Hyperactivity of the sympathetic nervous system dominates, which together with the disruption of vagal tone increases the risk of ventricular arrhythmia.

Heart rate variability reflects the ability of the cardiovascular apparatus to react immediately to haemodynamic changes.

This involves the determination of millisecond differences between R–R intervals on the ECG in patients with sinus rhythm, most frequently at rest. HRV is mainly controlled by the parasympathetic nervous tone and it is also affected by neurotransmitters of both the peripheral and central nervous system (norepinephrine, dopamine, acetylcholine, serotonin) (Carney *et al.* 2001). A high degree of HRV occurs in healthy persons, while patients suffering from CHD or heart failure have a significantly low HRV. A low frequency of HRV is a marker of sympathetic tone predominance, while a high frequency is a marker of vagal tone predominance (Musselman *et al.* 1998). Both low and high HRV predispose to sudden cardiac death in patients suffering from myocardial infarction (MI), congestive heart failure and hypertension.

Indicators of autonomous imbalance include high variability of ventricular depolarisation, increased heart rate, low HRV and low baro-receptor sensitivity.

All these indicators are associated with an increased risk of cardiovascular mortality and morbidity in patients suffering from CHD (Carney *et al.* 2005).

Ventricular depolarisation is defined by the QT interval. Variability of the QT interval, just as sympathetic tone predominance, differs in patients suffering from depression and in non-depressive individuals, and shows circadian characteristics, especially during the early morning, around six o'clock. This is associated with the frequent incidence of myocardial infarction and sudden cardiac death in the early morning hours. (Carney *et al.* 1999, Muller, 1999).

Depressive disorders increase heart rate at rest, decrease HRV in both patients suffering from CHD and patients without CHD (Carney *et al.* 1995), disrupt vagal control, increase epinephrine plasma levels and lead to the long-term activation of the sympathetic nervous system (Curtis, O´Keefe, 2002). Currently, it has been shown that there is a clear association between low HR in depressive patients following a MI, but the question remains whether this is also true for depressive patients suffering from a stable form of CHD. A study conducted in 2005 demonstrated that, in view of the different pathophysiological signs of atherosclerotic plaques in stable and unstable CHD, it may be presumed that decreased HRV will be present in depressive patients suffering only from unstable forms of CHD and not those suffering from stable forms of CHD (Gehi *et al.* 2005).

According to the so-called reactivity hypothesis, the natural reactivity of individuals to common physical and psychological stress stimuli may be continually elevated on three levels (cognitive-emotional, hypothalamus-brain stem, peripheral autonomous system).

The reaction of the peripheral autonomous system may lead to an increased risk of developing cardiovascular disease in specific patient sub-groups, although reactions at the cognitive-emotional and hypothalamus-brain stem level are otherwise normal (Lovallo, Gerin, 2003).

The questions that arise regarding preventive measures are thus: can the autonomous vegetative system be "trained" in some way, and can persons at risk of vegetative imbalance be recognised before the development of cardiovascular disease, and can "training" of their disrupted vegetative balance preclude their subsequent cardiovascular morbidity and mortality?

These questions are partially answered by a study from 2005, which showed that an abnormal heart rate profile when recuperating from physical exercise (a sign of vegetative imbalance) is a predictive factor for the risk of sudden cardiac death (Jouven *et al.* 2005). The increased risk of death is associated with so-called chronotropic incompetence (Lauer *et al.* 1999), which is the inability to increase the heart rate suitably in response to physical stress.

Patients with such a high-risk heart rate should be included in preventive rehabilitation programs. Autonomous imbalance can be influenced by regular kinetic and motor training, which adjusts autonomous balance in favour of vagal activity and thus may significantly improve the long-term prognosis of patients (Aláčová *et al.* 2005, Karacabey *et al.* 2005, Ozcan *et al.* 2006).

Regular exercise decreases sympathetic system activity via many indirect mechanisms such as e.g. weight loss, reduction of anxiety and depression, improvement of insulin sensitivity and abstention from smoking (Curtis, O ´Keefe, 2002).

Another issue regarding therapeutic measures is the possibility of pharmacological intervention in vegetative imbalance. It has been shown that beta-blockers reduce circadian variations of catecholamine plasma concentrations, equilibrate vegetative imbalance, slow the development of atherosclerosis and improve the prognosis of congestive heart failure. Reduction of the heart rate is one of the most important predictors of survival in patients treated with beta-blockers in both short-term and long-term intervention studies (Peters, 1990). Their use is limited, though, by the induction of depressive symptoms. These results are not unequivocal and significant, similarly as the issue of whether lipophilic types of beta-blockers penetrate more easily through the haemato-encephalic barrier and thus are more capable of inducing depression (Peters, 1990).

A recent study from 2006 has shown that the use of beta-blockers in patients who had suffered a myocardial infarction is not associated with an increased incidence of depressive symptoms during the first year (van Melle *et al*. 2006). These results were also supported by an extensive meta-analysis of 10 000 patients, followed for at least six months, which showed that the incidence of depressive symptoms was the same in the group of patients receiving beta-blockers as in the group of patients receiving placebo, and the incidence of depressive symptoms did not differ between lipophilic and hydrophilic types of preparations (Ko *et al*. 2002).

Beta-blocker treatment is undoubtedly an integral part of current guidelines for the management of patients with acute myocardial infarction. It significantly decreases morbidity from ventricular fibrillation and it reduces mortality by 23% in patients post myocardial infarction (van Melle *et al*. 2006).

Positive effects on vegetative imbalance have also been observed during treatment with selective serotonin re-uptake inhibitors (SSRI) e.g. fluoxetine, whereby there were indications of increased 24-hour HRV in depressive patients (Khaykin *et al*. 1998). The same effect has been observed during treatment with SSRI of patients with anxiety and post-traumatic stress disorder (Cohen *et al*. 2000). A similar increase in HRV at the end of successful anti-depressant therapy is documented by the SADHART and ENRICHD studies (Glassman *et al*. 2002; Writing Committee for the ENRICHD Investigators 2003).

Cardiac baroreflex

The cardiac baroreflex reflects the combination of sympathetic and parasympathetic activity and fulfils the function of a cardiovascular control mechanism. The baroreflex responds to changes in arterial blood pressure by altering cardiac parameters such as heart rate, contractility and vascular tone. For a duration of ten seconds to a few minutes, blood pressure is maintained by the autonomous vegetative system and by modulation of the sympathetic tone in various vascular beds (skin, heart, kidney and brain). A fall in blood pressure may be countered by tachycardia, increased contractility and vasoconstriction (activation of the sympathetic system), as well as by the elimination of the inhibitory effect on heart rate and contractility (vagal mechanism). Patients with low baroreflex control of heart rate are less capable of equilibrating common fluctuations of the sympathetic nervous tone via vagal mechanisms.

In one of the first studies to investigate baroreflex sensitivity (Watkins *et al*. 1998), depressive patients suffering concurrently from cardiological disease were found to have decreased baroreflex control of heart rate, compared to similar patients without a depressive disorder.

Another study that focused on the investigation of autonomous reflexes recorded decreased baroreflex sensitivity in patients who had suffered a myocardial infarction and in patients suffering from an as yet untreated depressive disorder (Vacarino, 2000).

The so-called concept of blood pressure oscillation is mentioned in connection with haemodynamic changes, depressive disorders and impairment of the vegetative tone. This occurs as a consequence of sympathetic nervous system predominance during depressive disorders. During blood pressure oscillation, damage is incurred by the vascular endothelium due to as yet unclear mechanisms. It is presumed that blood turbulence in large vessels leads to "shear stress", which in turn damages the vascular intima thus accelerating the atherosclerotic process in patients suffering from depression (Sloan, Shapiro *et al*.1999).

The role of inflammation

Major and moderate depressive episodes may modify immune functions, and conversely abnormalities of the immunes system may play a role in the aetiology of depression (Irwin, 2002, Musselman *et al*. 1998). The depressive episode is associated with the activation of a non-specific immune response, the secretion of interleukin 1-beta, TNF-alpha and interferon. It has been demonstrated that white blood cell counts are higher in depressive patients compared to normal controls. Upon recovery, the number of monocytes in depressive patients decreases and concurrently monocyte phagocytary activity increases. In contrast to the activation of non-specific inflammatory response, a concurrent suppression of cell-mediated immunity occurs in depressive patients. This is demonstrated by low NK cell, T helper cell, T cytotoxic cell and B cell counts. Thus far, it is unclear whether changes in the immune system are the aetiological agent of depressive disorders or vice versa. Cell-mediated immunity may also be disrupted by the high concentrations of cortisol often seen in depressive patients. The disrupted cell-mediated immunity may be the result of increased sympathetic system activity or the increased catecholamine turnover. Catecholamines subsequently inhibit immune reactivity via their direct binding to the surface of lymphocytes or via the release

of mediators that enhance the function of suppressor lymphocytes. Immune system components affect platelet activity and this may then lead to the occurrence of adverse cardiovascular incidents. Cytokines may affect cardiovascular regulation via their interaction with the CNS; IL-1 and IL-6 stimulate the activity of the HPA axis, which leads to hyper-cortisolemia. Hyperactivity of the HPA axis leads to a change in the sympathetic tone and to a decrease of heart rate variability.

Pro-inflammatory cytokines also affect the serotonergic system, which is linked to the pathophysiology of depression. IL–1 and interferon alpha induce the enzyme, indole-amine-2,3 di-oxygenase, which converts tryptofane (the precursor of serotonin) to quinurenine and quinolinine acid. This leads to the depletion of plasma tryptofane and thus to the reduction of serotonin synthesis in the brain. Reduced serotonin availability facilitates the development of depressive symptoms and leads to the occlusion of coronary arteries via serotonin regulated platelet aggregation, fibrinolysis and constriction of the coronary arteries (Maes, 1999).

Pre-clinical data from animal studies indicate that the immune response following a myocardial infarction leads to the formation of immuno-complexes in the serum and their extra-vasation across the haemato-encephalic barrier into distant parts of the brain (pre-frontal cortex, anterior cingulum, enthorinal cortex, hippocampus and substantia nigra). These findings were confirmed by the findings of hyperdense foci in the white matter and hypodense foci in the grey matter of clinically depressive patients (Honig, Maes, 2000).

Unsaturated fatty acids

Inflammation-induced alterations in the metabolism of fatty acids and changes in the composition of fatty acids in the serum phospholipid fraction and erythrocyte membranes must be included in the pathophysiology of episodes of depression and ventricular arrhythmia (Peet *et al.* 1998). Lack of unsaturated fatty acids alters the distribution of fatty acids in the membranes of various organs, including the brain. Changes in membrane composition affect the metabolism of serotonin (by modulating the activity of tryptofane hydroxylase- the enzyme limiting the synthesis of serotonin), and are associated with reduced calcium channel blockade, a decrease in pro-inflammatory cytokines and inhibition of 2nd messenger associated G proteins. The depressive episode is associated with depletion of omega-3-unsaturated fatty acids in erythrocyte membranes and serum (Carney *et al.* 1995), and with increased concentrations of homocysteine (Severus *et al.* 2001). Homocysteine plasma concentrations greater than 9 – 10 μmol/l represent an independent risk factor for the development of atherosclerosis. Increase of total plasma homocysteine concentration by 5 μmol/l increases the risk of CHD as significantly as an increase of plasma cholesterol concentration by 0.5 mmol/l. Thus, immune activation during depression is associated with an increase in the omega-6 (pro-inflammatory): omega-3 (anti-inflammatory) fatty acid ratio. Omega-3 unsaturated fatty acids have an immuno-regulatory and protective anti-arrhythmic effect. Increased intake of omega-3 fatty acids decreases the production of pro-inflammatory cytokines – IL-1, IL-6, TNF-alpha, suppresses lymphocyte proliferation, T cell-mediated cytotoxicity, NK cell activity, macrophage-mediated cytotoxicity, monocyte and neutrophil chemotaxis, and expression of adhesive molecules (Calder, 1999).

Thrombogenesis

Elevation of cortisol and norepinephrine during activation of the HPA axis in depressive patients accelerates the development of atherosclerosis, possibly by disrupting the intima, which leads to increased platelet aggregation and the formation of atherosclerotic plaques at the site of damage, or even to acute occlusion and development of acute coronary syndromes (Musselman *et al.* 1998).

Changes in the platelet serotonin system that enhance platelet aggregation have been uncovered in patients with depressive disorders. Reduced platelet serotonin uptake, increased expression of the serotonin 5-HT2 receptor and increased concentration of intra-cellular calcium compared to healthy controls were observed (Sheps a Scheffield, 2001).

Pro-thrombogenic factors released from platelets (platelet factor 4 and beta thromboglobulin) are elevated in patients with myocardial infarction, unstable angina and in depressive patients. This supports the pathophysiological function of platelets in the pathogenesis of acute coronary syndromes.

It has been documented that preparations of the SSRI type adjust platelet activity. Anti-depressants of the SSRI type do not affect only the re-uptake of central serotonin, but also that of peripheral serotonin. Fluvoxamine, fluoxetine, sertraline and paroxetine reduce platelet and plasma serotonin concentrations.

Effective anti-depressant treatment may thus reduce risk of mortality following a myocardial infarction, as shown e.g. by three studies using antidepressants of the SSRI type in depressive patients with serious cardiovascular disease: fluoxetine (Glassman, Shapiro, 1998), paroxetine (Roose *et al.* 1998), sertraline (Shapiro *et al.* 1999). A recent extensive "case-control" study involving patients-smokers after their first episode of myocardial infarction indicates that, in general, the administration of antidepressants of the SSRI type, or serotonergic antidepressants with high affinity for the serotonin transporter, statistically significantly reduced the risk of developing another myocardial infarction compared to the administration of other types of antidepressants. Although the non-smoker population was not studied in this trial, it may be expected to benefit similarly (Sauer *et al.*2001).

The temporal aspect of depressive disorder development in relation to the prognosis of cardiovascular disease

At this time, there is insufficient information as to when the incidence of depressive symptoms in association with cardiovascular disease is most frequent.

Recent facts from available literature indicate, though, that from the aspect of the frequency of incidence and development of a depressive disorder, the period around the first to sixth month following the cardiovascular episode may be assumed to be that of greatest risk (Jonge *et al*. 2006, Parashar *et al*. 2006). There exist long-term studies that show that the same high risk exists even in a period e.g. five years following a cardiovascular episode (Grunau *et al*. 2006).

It has been shown pathogenetically that recurrent depressive symptoms may increase the risk of developing atherosclerosis in women by inducing or maintaining increased platelet reactivity and hyper-cortisolemia. On the other hand, depressive symptoms that appear as an immediate consequence of a cardiac episode may lead to the development of other cardiac episodes by way of vegetative imbalance and the consequent decrease in vagal tone (Rozanski *et al*. 1999).

A study from 2006 evaluated the prognostic significance of acute and recurrent depression on clinical results during the period of six months following a myocardial infarction. In both cases of depressive episodes, a worse prognosis was observed than in patents without depression (Parashar *et al*. 2006).

Half of all depressions that develop after a myocardial infarction represent a truly new depressive episode, the other half are recurrent depressive episodes (Jonge *et al*. 2006). Patients with a first depressive episode had a greater risk of developing another cardiovascular episode and a worse prognosis, compared to patients without depression and patients suffering from a relapse of depressive symptoms as part of a recurrent depressive disorder yet who responded well to therapy with anti-depressants of the SSRI type. This is in accordance with the results of the SADHART study (Jonge *et al*. 2006, Glassman *et al*. 2002).

The message of the aforementioned studies is that depressive symptoms must always be treated, regardless of when they develop!

Behavioural mechanisms

Due to their course, depressive disorders are often inadvertently linked to a change in patient lifestyle. Depressive patients are forced to change a whole range of habits and routines, both harmful and beneficial. They take this change in behaviour hard, they find dealing with daily tasks, obligations and stereotypes more difficult, they change their habits in caring for themselves and their surroundings.

They cannot cope with work; ordinary physical activity, including regular walks and sports, is unthinkable. They change dietary habits, smokers increase the number of cigarettes they smoke. They feel that their life and existence are threatened, as they are cut off from fulfilling their occupational and social roles. If we look at these symptoms from another aspect, they are also forcibly induced in serious cardiovascular disease.

Depressive disorders represent an important predictor of inferior compliance. This relates not only to psychiatric medication, but also to long-term medication. "Lack of discipline" when taking cardiological or other internal medication may lead to deterioration of cardiological functions, acceleration of hypertension, blood glucose oscillation hyperlpidemia, all of which increase the risk of sudden cardiac episodes.

Decreased patient physical activity is one of the potential behavioural mechanisms involved in the pathophysiology of depressive disorders and cardiovascular disease that deserve mention.

The relationship between depressive symptoms, cardiovascular disease and decreased physical activity is clear and undisputable. Restriction of physical activity need not be only due to the symptoms of the depressive disorder per se, but may be also due to fatigue that plays a specific role in the relationship: mood changes versus cardiovascular deregulation.

Fatigue need not be the direct cause of cardiovascular disease, but it may interact with other risk factors. Massive fatigue usually precedes a myocardial infarction and sudden death. Exhaustion is considered to be a short-term risk factor for recurrent myocardial infarction, independent of blood pressure, cigarette smoking, cholesterol, age and use of anti-hypertensive medication.

The fact that fatigue and physical inactivity are concurrently associated with depressive disorders and cardiovascular disease is also documented by therapeutic programs for patients suffering from psychiatric and cardiovascular disease, where physical exercise is stressed in the first place. Physical training positively affects mood, reinforces self-confidence in cardiac patients and moreover significantly increases HRV and baro-reflex sensitivity (Watkins *et al*. 1998).

Psychosocial factors

A detailed review of psychosocial factors and their relationship with the development of cardiovascular disease is presented in the work of Rozanski *et al*, but in practice, complex assessment of patients, including screening for these risk factors, is still lacking. Usually, patients are mainly assessed for biological factors that are well established.

It must be admitted though, that proper or rather standardised screening tools for recording psycho-social factors are not as yet available (Rozanski *et al*. 2005).

Apart from type A personality, a well-known predisposing factor for the development of coronary heart

disease, other personality traits are being intensively studies e.g. hostility, chronic anger. Some studies indicate a relationship between hostility and the incidence of subclinical forms of atherosclerosis and its progression on repeated coronarography. The relationship between hostility and mortality from cardiovascular disease is not as yet conclusive (Surtees *et al*. 2005). Another study showed that patients with a great degree of hostility and concurrent metabolic syndrome had a 4 x greater risk of developing a myocardial infarction than patients with a low degree of hostility and no metabolic syndrome. Hostility may, in such patients, represent an additional prognostic factor for evaluating the risk of developing CHD (Todaro *et al*.2005).

Stressors such as e.g. unemployment, low socioeconomic status, long-term stress at work or in marriage etc. may disrupt neurochemical processes in the brain, such as changes in the utilisation and synthesis of norepinephrine, changes in dopamine activity, increased synthesis of serotonin, increased release of cortisol (Harl *et al*. 2006, Takahashi *et al*. 2005). The presumed central mechanism that leads to the development of depressive symptoms due to such stressors is damage to the hippocampus with subsequent interference with HPA axis activity (Vaidya, 2000, Umegaki *et al*. 2006).

At the same time, stressors may induce hypertension and contribute to the development of subsequent atherosclerosis via repeated blood pressure elevation, stimulation of nervous system production of vasoconstrictive substances, and changes in vascular resistance (Bedi *et al*. 2000). According to carotid artery ultrasound findings, there is an evident relationship between stressors and the incidence of subclinical forms of atherosclerosis (Carney *et al*. 1999).

It has been demonstrated that stress stimuli decrease the cardiac threshold for developing ventricular arrhythmia. A decreased threshold for ventricular fibrillation then represents a basic mechanism of sudden cardiac death (Follick *et al*. 1988, Verrier, Lown, 1984). Also frequent is the close link with an unhealthy life style.

The task of behavioural cardiology should in future involve not only the identification of unhealthy behaviour within a person's lifestyle, emotional factors and chronic life stressors, but also the motivation of patients for behavioural intervention.

Lifestyle adjustment, combination of physical exercise and multifactorial cardiac rehabilitation complemented by psychosocial intervention may lead to a reduction in the incidence of new cardiac events. Despite these findings, clinical guidelines for the management of psychosocial interventions are still lacking in practice (Rozanski *et al*. 2005).

In connection with the position of stress among the pathophysiological mechanisms of depression and somatic disease, recent studies have brought information regarding individual genetic differences in stress tolerance (e.g. chronic somatic disease = chronic stressor) and have shown a relationship between the incidence of depressive disorders and the amount of stressful incidents experienced depending on the functional polymorphism in the serotonin transporter gene. Genetic information determined by the short allele of the serotonin transporter promoter gene region is associated with a greater sensitivity of individuals to stress and thus with a greater probability that the experienced stressful incidents will induce a depressive disorder (Grabe *et al*. 2005). Only time will show the contribution of similar association studies to the field of medicine, based as it is on evidence.

It seems that the relationship between negative emotional states and stressors, and the development of cardiovascular disease is well documented. Nonetheless there is still an insufficient number of studies dealing with positive psychological factors. The largest, a ten year study conducted by Kubzansky showed that participants naturally predisposed to optimism achieved better clinical results following bypass surgery (Kubzansky *et al*. 2001). A new outlook is brought by a study that explains so-called "flexibility" paradigms. It presumes that "vitality" (a state of positive energy and enthusiasm potentially beneficial to health) is promoted by the ability to show emotion and subsequently flexibility.

In contrast, "inflexibility", expressed e.g. by depressiveness and other negative emotions, reduces vitality. Preliminary data hint at a direct relationship between a wide scale of "inflexible" life situations and the development of cardiovascular disease (Rozanski, Kubzanski, 2005).

Social factors undoubtedly include environmental aspects, especially fine particulate air pollution (particles smaller than 2.5μm in their aerodynamic diameter), whose increased concentration is clearly associated with the risk of developing cardiovascular disease, more so in women than in men (Dockery, Stone, 2007, Miller *et al*. 2007). The mechanism by which dust particles of the polluted air affect the development of cardiovascular disease is still the subject of research. It is evident that inhalation of harmful substances induces and aggravates both the pulmonary and systemic inflammatory response, and concurrently leads to oxidative stress, which induces direct damage to arteries, atherosclerosis and autonomous dysfunction.

Dust particles lead to a rapid and significant rise in fibrinogen levels, of plasma viscosity, to the activation of platelets and the release of endothelins (a group of potentially vasoconstrictive molecules) (Dockery, Stone, 2007).

This means that the concurrent presence of other cardiovascular risk factors has a significant influence on vulnerability to the adverse effects of fine particulate air pollution.

The results of a completely new study that dealt with the co morbidity of depression and anxiety are interesting from the aspect of cardiovascular disease morbidity and mortality (Mykletun *et al*.2007).

The co morbidity of depression and anxiety is very frequent (Kessler *et al*. 1999) and is associated with

somatic morbidity more significantly than anxiety or depression alone (Stordal *et al.* 2003). This study dealt with data from "Nord-Trondelag County" (one of 19 counties in Norway) in the years 1995–1997, and data on mortality from the "National Mortality Registry". It was discovered that the presence of anxiety alone or of states of concurrent depression and anxiety was associated with a generally lower mortality than in the case of depression alone. One explanation for the increased mortality in depressive disorders without anxiety could be the so-called help-seeking behaviour (Roness *et al.* 2005). "Help-seeking behaviour" is typical of patients suffering from anxiety who often seek the medical help of various specialists for their vegetative somatic symptoms. In depressive patients, such behaviour is practically missing. Depression in this case represents an equally significant risk factor for both general and cardiovascular mortality.

CONCLUSION

Depressive disorders represent an independent risk factor for the incidence and development of cardiovascular disease in both healthy individuals as well as in patients suffering from cardiovascular disease. Depression plays an equally significant role in the development of these diseases as e.g. lipid spectrum disorders, hypertension, older age, female sex or smoking.

Depression and cardiovascular disease clearly have common pathophysiological correlates. These include a combination of biological and behavioural mechanisms, with psycho-social factors, the subject of continued intensive research, today playing an undisputable role. From the data published so far, it may be concluded that a depressive disorder in patients with cardiovascular disease may be reliably and safely treated with antidepressants of the SSRI type. Efficacy in treating depression and the favourable cardiovascular effects of SSRI in this patient population have been manifestly documented (SADHART study).

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