PSYCHO CARDIOLOGY

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Abstract: Symptoms of depression and anxiety are very common among cardiac patients. Occasionally, the physician and even the patient and his surrounding think that progression of symptoms of depression and anxiety is expected and natural in the course of the disease.

Recent studies have shown that depression is a significant risk factor for cardiovascular diseases and for higher rates of mortality and morbidity after acute cardiac events.

More studies and publications in recent years in scientific literature dealing in interdisciplinary topic psycho - cardiology.

This discipline deals with the relation between depression and anxiety to cardiac diseases, and studies the bio-psycho-social mechanisms and processes which aim to the development of optimal therapeutic approaches. Despite the increasing trend in specializing in medicine, this new field represents integrative approaches which derive its sources from psychology, biological psychiatrics and cardiology all as a unit. This approach reinforces the psychosomatic concept in medicine which is gaining back popularity lately.

The article reviews the epidemiology, the hypothesis regarding etio-pathology and the therapeutic approaches.

Key words: psycho cardiology, depression, heart disease, anti-depression treatment, cognitive behaviour development.

INTRODUCTION

ACTUALITY OF THE ARTICLE

Cardiovascular diseases are the leading cause of mortality worldwide - according to WHO on average for 2/3 of cases. Rejuvenation of ischemic heart disease (IHD) and the fact that it occupies a permanent place in the statistics on causes of disability population not only determines special attention to this disease and predisposing factors and moderating it, but also a public necessity. Areas health and quality of life are complementary and interfering.

CAD forefront of the development of international and national action plan on chronic non-communicable diseases (NCDs). According to the World Health Organization psychosocial interventions are those that have a significant impact on public health and which are the most efficient in terms of cost-benefit do not require the addition of a great resource and easy to use.

EPIDEMIOLOGY

The first methodical proof – published already in 1937 by Malzberg, which noted an increased mortality in depressed patients. He compares the mortality between institutionalized psychiatric patients in New York and the general population. This pioneering study, which lasted for 3 years, showed the mortality rate among melancholic patients where 6-7 times higher than the general population. Furthermore, among melancholic patients, “disease of the heart” accounting for almost 40% of these deaths. The rate of heart disease among depression patients where 8 times higher than the general population (1). It should be noted that further scientific inquiry was delayed by historical causes.

In the late 1970s investigators returned to the topic. One of the impressive studies carried out by Weeke and co. in Denmark studied data of patients with either major depression or bipolar disease between 1974-1978 (2). 6000 patients were followed during these 5 years, investigating all reasons for natural death. Cardiovascular mortality was increased 50% above the general population.

This study raised concerns that the widespread use of the tricyclic anti-depressant drugs, known for their cardiac adverse effects, had an influence on the consequences. But proofs from scientific literature shows that mortality decreased nor increased.

Moreover, Weeke and co. showed that the increased cardiovascular death among depression patients was decreased after the onset of anti-depressant drugs. Data from large studies following thousands of patients for a long period in the 1980s and 1990s supported the relation between depression and increased cardiovascular mortality and morbidity.

Researches regarding clinical questions among hospitalized patients were limited because bias from the inclusion criteria for patients; the severity of the disease, environmental factors etc. Therefore, community-based studies have still shown increased cardiac mortality in patients with depression (1.5-2 times higher). Furthermore, studies show increased rates of atherosclerotic risk factors among patients with depression. For example, smoking rate is

higher in depression patients. Speculations were raised accusing smoking for the higher mortality rates in depression patients.

This issue was solved thanks to National Health Examination Follow-up study which involved over 3000 healthy individuals (at the start of the follow-up) over 45 years old for more than 12.5 years. After excluding the effect of smoking and other cardiovascular risk factors, chronic depression in the beginning of the follow-up predicted higher rates in fatal and non-fatal ischemic heart disease. Even though it is still controversial that a psychiatric disorder like major depression increases the risk for ischemic heart disease, and is still explained by the "intuitive" hypothesis that patients with psychiatric disorders have other risk factors for the development of heart disease. 15 prospective studies were published regarding depression as a risk factor for cardiovascular diseases.

These studies included other risk factors (hypertension, hypercholesterolemia, smoking, reduced physical activity). Almost all recent studies indicate higher cardiovascular mortality and morbidity among patients with depressive symptoms or major depressive disorder. These studies highlight depression as an independent risk factor in the pathophysiologic development of cardiovascular disease and not consequence of cardiac disease.

Another important issue is the association of depression with heart disease in patients who already have heart disease. In 1988 Carney and co. were first to show that post-angioplasty patients who had major depression were in higher risk for heart attack, cardiac surgery or death in 12 months compared with those without major depression (4).

In 1990 Ahern and co. reported that patients after heart attack with mild to moderate cardiac arrhythmias were in higher risk to death in the following year in case they suffered depression after the heart attack. So, studies have shown strong relation between major depression and overall survival in ischemic heart disease. (5)

In 1991 Fasure-Smith and co. found that men with higher level of anxiety and depression after heart attack are at higher risk to die due cardiac events in the following 5 years. It is not only due to major depression, even symptoms of depression showed higher mortality rates the following year after myocardial infraction. Furthermore, 18 months follow-up showed that patients with moderate results in clinical scale of depression had the same risk as patients with major depression disorder. The risk of mortality was 3-4 times higher in both these groups compared to with patients without symptoms of depression. Even when

evaluated with other mortality causes (prior MI, level of heart failure, and frequency of premature ventricular beats) the risk remained the same. (6, 7)

Early epidemiological studies found much higher rates of depression among cardiac patients 18-60%. More recent studies showed stable rates of incidence around 16-23% even with the methodological weaknesses in some studies (different diagnostic scales, time of diagnosis, different populations, medical statue during hospital admission, kind of heart disease etc.). It should be emphasized, even that the severity of the physical disease is one the most influential parameters related to depression, studies in patients with heart diseases didn't indicate higher incidence of depression among those with progressive cardiac disease or high level of disability.

Moreover, a large meta-analysis of 55 studies in 1987 concerns the relation between personality and cardiovascular disease revealed that the type A personality (more competitive, ambitious, and impatient) had higher rates of depression. Those results were weak but still interesting.

BIOLOGY

The development of biological psychology points out series of neurochemical, neuroendocrine and neuroanatomical disorders in depression. Some could provide etio-pathological explanation to the development of cardiovascular diseases in depression.

- Increased sympathoadrenal activity
- Decreased heart rate variability
- Myocardial instability and ischemia secondary to mental stress
- Platelet function disorders.
- Immune system deregulation.

OVER-ACTIVITY ON HYPOPHESIS AND ADERNAL AND HYPOTHALAMUS (HPA)

The fight or flight response (acute stress response developed by Walter Cannon) has two major components:

1. HPA axix
2. Sympathoadrenal system

1. As a response to stress, the neurons in the hypothalamus secretes corticotropin-releasing factor (CRF) which stimulates the production and secretion of adrenocorticotropin hormone (ACTH), beta-endorphin and products of proopiomelanocortin (POMC) from the anterior pituitary. In major depression HPA-axis is hyperactive. Numerous studies have reported elevated cerebrospinal fluid concentrations of CRF, a blunted ACTH response to CRH administration, nonsupression of cortisol on the dexamethasone suppression test, and pituitary and enlarged pituitary and adrenal glands.

Furthermore, the number of hypothalamic neurons which contains CRF increased. Corticosteroids administration causes hyperlipidemia and hypertension. Furthermore, corticosteroids cause endothelial dysfunction and inhibit normal tissue repair. Indeed, studies have shown that high levels of cortisol were significantly associated with severe coronary disease in young and middle-aged men.

2. Deregulation of the system, which sympatho-adrenal contains the medulla of the adrenal and the sympathetic nervous system, is common among major depression patients. The hypothalamic neurons which contain CRF stimulate autonomic sympathetic centers and areas responsible for regulation and secretion of catecholamines. Excitation of this system occurs during physical activity, coronary ischemia, heart failure and mental stress (epinephrine- from the adrenal medulla, and norepinephrine from the sympathetic nervous system and the medulla of the adrenal).

Elevated norepinephrine levels were found in the plasma of major depression disorder patients, especially those with melancholia. The hyper-active sympatho-adrenal system contributes to the development of cardiovascular diseases, when affecting the heart, blood vessels and platelets.

HRV – (HEART RATE VARIABILITY)

DECREASE A VARIATION

Decrease in the HRV level indicates disruption in the nervous system, autonomic ANS (nervous system) and another possible explanation regarding the low survival of patients with major depression. This hypothesis came from cardiology.

In the 1980s a reduction in HRV after myocardial infarction was found to be a prognostic factor for increased mortality. The idea is that decreased vaginal control and symptomatic control increases the threshold for fatal arrhythmia. This finding was also

confirmed in animal experiments. Because depression involves increased mortality, the hypothesis of autonomic dysfunction may help to understand the etiopathology of increased cardiac mortality in depressed states in people with a healthy heart.

In studies measuring heart rate variability in patients with major depression, HRV was reduced. About 50 works were published on the subject, and their results are not decisive. The reason for this is methodological failures (tricyclic drugs, additional morbidity, cross-sectional design, etc.).

There are several approaches to assessing HRV. In the traditional approach, we find two main methods: the time domain, which calculates statistical variables of the heart rate, and the frequency domain, which reveals the contributions of the two arms of the ANS (viral and sympathetic). Only one study demonstrated normalization of HRV in patients with major depression after antidepressant therapy (8).

In a joint study conducted by the Geha Hospital and the Heart Institute at Beilinson Hospital, there was a significant increase in HRV in patients treated with electroencephalopathy (9,10). In this study, there was a significant increase in the degree of vaginal control, which had a protective effect on the heart from arrhythmia, and decreased sympathetic control. In another study, which was also conducted at the Geha Hospital, the QT Dispersion Index was used for the first time in a group of patients with major depression and no physical illness, compared with healthy subjects.

This index, which can be calculated from the EKG chart, measures the diffraction of ventricular resarpulation, which indicates an increased risk of fatal arrhythmia, which is affected by a number of factors including heart muscle injury (as in patients with myocardial infarction) The autonomic nervous system, i.e. low and sympathetic nervous activity, and we also found significantly higher scores among depression patients in relation to the control group, in addition to the values reported in the cardiology literature for cardiologic patients at risk (11).

In another study, conducted in collaboration with a Heart-Lung Transplant Unit at the Bilinson Hospital, with Dr. Danny Aravot, we calculated the HRV indexes in physically healthy patients with major depression, compared with psychiatric patients without psychiatric illness, and healthy subjects. We expected that the HRV indexes of patients with depression would fluctuate between those of the heart transplant recipients who had low rates of autonomic neural wiring and the healthy subjects.

In fact, the guiding logic was that the transplanted heart is a paradigm of denervated heart. To our surprise, the HRV indexes of the transplanted patients and patients with major depressive disorder (MDD). Were not statistically different, and both were significantly lower than those of healthy subjects (12).

It should be noted that in some of these studies and in others, an innovative HRV assessment method was developed, based on the principles of chaos theory (non-predictive systems research), in addition to the traditional analysis approaches.

Thus, our study, added to previous studies, clearly indicates cardiac autonomic imbalance. Thus, the aetiopathology of increased cardiac mortality in patients with MDD appears to involve low wavy activity, which in turn reduces the threshold for fatal arrhythmias. Also, in patients with coronary disease who are depressed, HRV is significantly lower than in non-depressed coronary patients.

MYOCARDIAL ISCHEMIA AND NON-CARDIAC UNDER PRESSURE MENTAL PAUSE

Jiang et al. (JAMA 1996), who followed 126 patients with CHD for 5 years, demonstrated the effect of mental stress on myocardial ischemia. Mental stress was found to be significantly associated with fatal and non-fatal cardiac events regardless of age, excretion rate, and myocardial infarction in the past (13). It is hypothesized that psychological pressure lowers the threshold for ventricular fibrillation, which is the leading arrhythmia, the most common cause of death in coronary patients. Here too, the hypothesis is related to wavy activity, which has an anti-arithmetic effect.

Further studies indicate an increase in the activity of the ventricular ventricle, under mental pressure, and therefore an increased risk of ventricular fibrillation. In patients with coronary heart disease, mental stress reduces the movement of the heart and the left ventricular emission segment. It was found that mental stress ischemia was "quiet" in 83% of patients with congestive heart failure and had lower heart rates than physical ischemia. A speech in which emotional elements increase heart contraction disorders rather than a cognitive effort that causes mental stress without an emotional component. The intensity of the injury to the contraction of the heart muscle as a result of speech was similar to that of physical exertion. In a study examining changes in ST sections from Holter records of

patients with coronary heart disease, it was found that among those who experienced mental stress, there were more "quiet" ischemia events (no pain).

Frasure-Smith and Hubbard claim that depression worsens prognosis after myocardial infarction using another ventricular Premature Beats mechanism (7). They found that the risk of sudden death associated with depression was highest in patients with 10 or more VPBs per hour - 60% of these patients died within 18 months. This suggests a possible role of arrhythmia as a link between depressive onset and sudden death. In patients with myocardial infarction and with VPBs who were not depressed, mortality was also low when the left ventricular segment was low. Therefore, it can be assumed that the prognostic value of VPBs may be more related to depression than to VPBs in their bodies. This is reminiscent of the famous Cardiac Arrhythmia Suppression Trial-CAST (14), which attempted to reduce mortality following myocardial infarction by means of antidepressants to reduce the rate of VPBs, Which necessitated the discontinuation of the study, suggesting that depression may be an essential component for improving the survival of patients with VPBs.

INTERFERNCE IN PLATELETES ACTIVITY

The effect of depression on cardiovascular disease may also be associated with platelet-related mechanisms. Markovitz & Matthews were the first to argue that platelet response increased due to mental stress and could trigger ischemic events (15). The results of CVA-Cerebrovascular Accident (CVA) studies indirectly support the association between depression and vascular disease. In a 6-year study of 10,294 people (aged 65 years) to determine the frequency of brain events, the risk was 2.5 times higher among those with severe depressive symptoms than those with low symptoms. In 103 patients with stroke, depression was evaluated two weeks after CVA.

It was found that in subjects who were depressed, the risk of mortality was 3.4 times over 10 years, compared with those who were not depressed. Platelets central role in the pathogenesis of thrombosis (thrombosis the development of atherosclerosis and events in coronary sharp. This is a complex interaction with components sub-endothelial damaged walls of blood vessels and clotting factors, and especially thrombin. Platelets in humans contain adrenergic receptor, Srotonrgiim and Dofminrgiim. An increase of Ktcolaminim plasma, causing irritation alpha -2 receptors on the membrane of platelets and allows the effects of agonists.

At high concentrations, there is a reaction of the platelet response, which includes excretion, Igor and operation of the archidon route. Vascular endothelial damage was also caused. Platelets and leukocytes adhere to the sub-endothelial layer. Clinging to collagen and thrombin stimulates operation, which causes the complexes on the GPIIb \ IIIa membrane to become functional receptors for fibrinogen. The operation is also accompanied by the provision of storage granules for extracellular space. Platelets in the damage zone accelerate the local formation of thrombin and secretion of storage granules of a range of products - mitogens and chemotaxes, while stimulating leukocyte migration from the bloodstream and proliferation of cells in the walls of the blood vessels. These factors, PF4, beta thromboglobulin and serotonin, recruit additional platelets and cause irreversible platelet aggregation. Thus formed platelet thrombus. Platelets cause additional vascular damage by stimulating uptake of lipoproteins by macrophages, and mediating of vasoconstriction by creating and releasing substances such as thorboxcan A2, PAF, and serotonin.

The question arises whether depression in a healthy person can be a risk factor for mortality due to vascular reasons. Platelets with major depression without physical illnesses were found to be more effective, and had greater responsiveness than normal subjects. Moreover, in comparison with heart disease patients with depression and non-depressed heart patients, significantly higher levels of PF4 and beta-thromboglobulin were found in the depression group. Serotonin secreted from platelets up Igor platelets and blood vessel contraction - through 5HT2 receptors. In recent years, there has been a great deal of evidence that supports the hypothesis of dysfunction in serotonergic function, both in the central nervous system and platelets. Although platelet activation by serotonin is relatively weak, it greatly increases platelet response to other agonists - ADP, thromboxan A2, catecholamines and torombin (16).

Several studies have reported an increase in the link density of 5 HT2 in platelets of patients with depression. It was found that this condition is reversible and is returning to normal with the improvement in depression. In addition, depression was found to be significantly associated with serotonin, both in the central nervous system and platelets. This combination actually reduces the uptake of serotonin and exposes the high numbers of 5HT2 receptors to serotonin outside platelets. In addition, platelets of depressed patients have increased levels of free calcium after serotonergic stimulation. Even a small increase of free

calcium in the platelets increases the response of platelets to weak agonists (such as serotonin) or even to an increase in blood flow (17).

INTERFERENCE WITH THE IMMUNE SYSTEM ACTIVITY

In depression situations, there was evidence of disorder in regulation of the immune system. For example, there is evidence indicating an increase in signs of inflammation (white blood cells, C-reactive protein, various cytokines, and even changes in the relative distribution of B and T cells). These findings indicate that both arms of the immune system are active: the humeral and the cellular. These processes can be linked to additional findings related to disorders of fatty acid metabolism in depression.

For example, omega-3 fatty acid deficiency, which occurs during depression, can cause an increase in the production of inflammatory cytokines. These complex processes can lead to the development of coronary heart disease, disorders of the HPA axis activity, and increased risk of arrhythmias.

On the other hand, one of the ethopathological features of coronary heart disease is chronic sub-chronic inflammatory processes involving C - reactive protein (CRP) and cytokines. The rise of these markers can induce "behavioral behavior," a syndrome characterized by decreased energy, decreased appetite and weight, sleep disorders, anhedonia (inability to enjoy things that normally cause pleasure) and general feeling bad. These signs are part of the diagnosis of depression. Therefore, depression can be a cause or a consequence of inflammatory processes that also appear in the development of coronary heart disease.

The challenge of future research is to link all the strands of pathophysiological mechanisms - hyperimmunotropic and autonomic disorder, over reactivity of platelets, serotonergic system disorders, and immune system activity - into a complete ethotypological model from which best therapeutic approaches can be derived.

OTHER APPROACHES

The decision to treat depression depends on several factors: the severity and duration of the depressive episode, the history and severity of episodes of depression in the past, the degree of functional impairment, evaluation of various stressors, other diseases and the degree of social support. It is important to remember that every patient with suicidal thoughts, even in the context of physical illness, must be examined by a psychiatrist. In general, the approach

to depression is divided into two phases: in the first phase we try to relieve depressive symptoms and improve the functioning of the patient. The prevention phase, in which the patient takes prophylactic treatment, too early discontinuation of the treatment can cause the recurrence of the depressive state, and in the treatment process it is important to share the patient's schedule and expectations with respect to the rate and chances of success in the treatment of depression.

The therapeutic approaches are divided into psychological approaches and psychopharmacological approaches. An approach combining the two is recommended. In the psychological approach, research literature specifically demonstrates the effectiveness of two types of psychotherapy: the cognitive-behavioral approach and the interpersonal approach. In the cognitive-behavioral approach, the therapist attempts to clarify thought processes and perceptions that contribute to the patient's ability to function regularly.

The goal is to change thinking and behavior processes that will enable better coping with daily stresses. On the other hand, in the interpersonal approach, the patient's interaction with the various circles in his life: family, employment, and social are assessed. Here, the goal is to assist the patient in achieving maximum compatibility in his interpersonal relationships, which will help him solve his emotional and behavioral needs.

The results of the largest psychotherapy study ever conducted in patients with coronary heart disease have recently been published, in which this important issue was examined in cardiac patients (19).

This research called ENRICHD (Enhancing Recovery in coronary heart disease), included about 2,500 patients from 73 hospitals in the United States and lasted for 8 years and examined the results of psychosocial intervention in cognitive-behavioral approaches compared to conventional therapy in patients diagnosed with depression and Or low social support The study hypothesis was that patients in the treatment group would have a longer life expectancy and fewer cardiac events than the control group.

But the findings were negative and no effect was found on life expectancy or a decrease in the number of cardiac events during a 29-month follow-up period.

However, a segmentation of the patient population showed that patients who were treated with serotonin reuptake inhibitors in both groups had a lower risk of death or myocardial infarction. Although the use of antidepressants was not random but was given according to clinical need, this finding raises new questions. It may be the mechanism of

influence of serotonin reuptake inhibitors on IgG platelet processes, which begin to function immediately at the cellular level, that is, even before the onset of behavioral changes in depression. Conversely, in the case of cognitive behavioral therapy, behavioral change can be achieved before the decline of the physiological risk factors. Hence, psychotherapy may take too long to induce changes at the cellular level, which will reduce the risk of death and morbidity during the critical period close to the heart attack.

In the psychopharmacologic treatment of depression, all approved antidepressants are effective. The difference between them lies in the profile and safety of side effects for the patient. This aspect is of particular importance to heart patients.

For many years, tri-cyclic drugs have been a cornerstone in effective treatment of depression. But these drugs may be toxic to heart and cardiovascular systems. So it is best to avoid using them in heart disease. The side effects reported in the literature that are derived from the reactive activity of the tricyclic drugs include: tachycardia, orthostatic blood pressure, extension of the PR, QRS and QTcB segments in the ECG diagram, similarity to the activity of C1 anti- In one of the most recent studies evaluating the effect of the use of tricyclic antidepressants, an increased risk of myocardial infarction was reported (20).

Therefore, in the treatment of depression in heart patients, there is a clear preference for the new generation of antidepressants belonging to the selective serotonin reuptake inhibitors (SSRIs) family. These drugs have few cardiac side effects and can be started with the guidance of a community physician. All of these drugs are similar in treating depression. In a study published in 2001 by Sauer et al., in which 653 patients were examined after a first myocardial infarction against a control group of 2,990 subjects, use of SSRIs (sertraline, fluoxetine, fluvoxamine, and paroxetine) was a protective factor against recurrent heart attack(21).

In a small-scale double-blind trial comparing paroxetine and nortriptyline, considered to be the least tri-cyclic tericyclic drug in patients with ischemic heart disease and depression, a significant reduction in β-thromboglobulin -platelet factor 4) in the paroxetine administration from the first week onwards (22). It was also reported that the rate of cardiopulmonary adverse events among those taking paroxetine was significantly lower than among those taking nortriptyline. A recent large-scale study (SADHART - Sertraline AntiDepressant Heart Attack Trial) has shown that sertraline is safe and effective in treating depression in patients with ischemic heart disease (23). It should be noted that the significant

efficacy in the treatment of depression was prominent in cases of patients with depression or severe depression. There was no reported decrease in the mortality rate and the cardiovascular morbidity relative to the control group.

As a result, SSRIs in the treatment of depression in patients with heart disease appear to be effective and have a low risk of side effects in relation to tricyclic drugs. However, it is important to keep in mind the issue of drug interactions because some SSRIs tend to inhibit P450 isoenases (such as beta-blockers, anti-arithmetic drugs, calcium blockers, comadine, etc.).

RESEARCH FOR THE FUTURE

In light of the growing research results in the field of psychodirology, we remain with the main questions dealing with the etiology, treatment and prediction of the effectiveness of treatment. We do not yet have a socio-demographic profile or biomarkers that can predict the development of depression after a cardiac event. For example, will it be possible to use state markers that are normalized by successful treatment, such as inflammatory markers, endocrine markers, HRV components ...? We do not have an integrative model, but the biopsychosocial findings are accumulating. In the future, we may be able to predict new therapeutic approaches in depressed patients, and not only will their quality of life rise, but we may also reduce morbidity and improve long-term survival.

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