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# DEPRESSIVE SYMPTOMS AND WORKING MEMORY DYSFUNCTIONS IN PATIENTS WITH ISCHEMIC HEART DISEASE

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## SUMMARY

### Background:

The problem of depression among patients with Ischemic Heart Disease (IHD) especially after myocardial infarction (MI) is well documented. Various levels of cognitive dysfunctions also constitute a frequent problem in the clinical picture of IHD. The association of the two can be especially dangerous for the process of treatment and rehabilitation.

### Material/ Methods:

The study group consisted of 111 patients aged 41–65 years. Cognitive functions were evaluated by means of the Wisconsin Card Sorting Test (WCST). The mental status was assessed by means of the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HDRS).

### Results:

In the study group no elevated symptoms of depression were found, but subdepression could not be ruled out. The results of the Wisconsin Card Sorting Test (WCST) showed working memory dysfunction and executive functions impairment in the study group when compared with the control group. There was no statistically significant correlation between the depressive symptoms measured by HDRS and BDI and the cognitive dysfunctions obtained by WCST.

### Conclusions:

Although the etiology of these bidirectional associations between depression and cognitive dysfunctions comorbid with IHD is not well understood, a number of negative outcomes are visible and should be taken into the diagnostic process and treatment by physicians.

**Key words:** myocardial infarction. cognitive dysfunctions, depression

## BACKGROUND

Ischemic heart disease (IHD) tops the list of death causes, both in Poland and worldwide.

Relationships between psychological variables (particularly depression) are still being vigorously investigated especially in the lights of the World Health Organization prognosis suggesting that by the year 2020, IHD and depression will have become the two main causes of death and disability among people all over the world (Stetkiewicz-Lewandowicz, Goch & Borkowska, 2010; Guzińska et al. 2009).

In this paper the term 'depressive symptoms' refers to unipolar clinical depression measured by two types of standardized scales. Depression is a mental disorder characterized by a low mood accompanied by low self-esteem, and by a loss of interest or pleasure in normally enjoyable activities, there are also neurovegetative signs like body aches, problems with sleeping or eating. High scores on depressive mood scales are strongly correlated with the presence of unipolar clinical depression (Goldston & Baillie, 2008; Williams, Pignone, Ramiraz & Perez Stelato, 2002).

Depression among patients with IHD is a common problem. Clinically significant depressive symptoms were found in 17–65% of patients after myocardial infarction (MI) (Fauerbach, Bush & Thombs, 2005).

Depression is thought to be an independent risk factor in the etiology of IHD (Jiang, Krishnan & O'Connor, 2002; Kuper, Marmot & Hemingway, 2002; Lett, et. al, 2004; Nicholson, Kuper & Hemingway, 2006; Rozanski, Blumenthal, Davidson, Saab & Kubzansky, 2005; Wulsin & Singal, 2003).

There is evidence of the negative physiologic effects of depression including decreased heart rate variability (Comijs, Jonker, Beekman & Deeg, 2001; Gorman & Sloan, 2000), increased platelet aggregation (Musselman et. al., 1996; Pollock, Laghrissi-Thode, & Wagner, 2000), higher levels of inflammatory risk markers (Miller, Stetler, Carney, Freedland, & Banks, 2002) and glucose dysregulation (Ford, 2008; Katon et. al., 2003).

The consequences of depression among patients with chronic medical conditions like IHD include greater morbidity and mortality (Ferketich, Schwartzbaum, Frid, Moeschberger, 2000; Frasure-Smith, Lesperance & Talajic, 1993; Katon et. al., 2003).

The relationship between depression and IHD is complicated; a higher risk of depressive symptoms are observed in individuals with IHD, but there is also an increased probability of IHD in patients with depressive symptoms (Huang et. al., 2010).

Various problems affecting patients with IHD include disturbances of the cognitive functions that can be associated with various parts of the brain. Cognitive dysfunctions affect from 50% to up to 80% of cardiac patients (Callegari et. al., 2002; Wolfe, Worrall-Carter, Foister, Keks & Howe, 2006).

The evidence for links between depression and cognitive performance is inconsistent (Singh-Manoux et. al., 2008), some studies suggest an association

Breteler et. al., 1994; Miller, Stetler, Carney, Freedland, & Banks, 2002; Zuccala et. al., 2001) while others do not (Ahto et. a., 1999; Bursi et. al., 2006; Grubb, Simpson & Fox, 2000).

The most commonly observed disturbances affect short-term verbal memory, visual-spatial ability and abstract thinking (Callegari et. al. 2002; Farina et. al., 1997; Kilander, Andren, Nyman, Lind, Boberg & Lithell, 1998; Vingerhoets, Nooten & Jannes, 1997; Wolfe, Worrall-Carter, Foister, Keks & Howe, 2006).

Dysfunction of the prefrontal cortex is particularly important with regard to normal, everyday life functioning. This part of the brain is responsible for the integration and coordination of higher mental functions, especially for working memory and executive functions (Stetkiewicz-Lewandowicz, Goch, & Borkowska, 2010). Executive dysfunction is thought to be a core syndrome in many neuropsychiatric disorders, including various forms of dementia, schizophrenia and bipolar disorder and impairs the patients' ability to cope with everyday problems.

The co-existence of both depression and executive dysfunction has been fully discussed in the subject literature and even the term "depression-executive dysfunction syndrome of late life" (DES) has been coined (Vataja et. al., 2005).

The risk of cognitive disturbances in the group of patients after MI increased two-fold those who also suffered from depression. Depression can lead to memory and attention disturbances, dysfunctions of the prefrontal cortex functioning and psychomotor retardation. Depression can also have a secondary and reactive effect, i.e., it can lead to an increase in the degree of cognitive dysfunctions in patient after MI (Degl'Innocenti, Agren & Backman, 1998; Mialet, Pope & Yurgelun-Todd, 1996; Veiel, 1997). This situation is especially dangerous because it can affect the process of treatment and rehabilitation.

In the present study we have tried to look for possible co-existing emotional and cognitive phenomenon in the group of patients with IHD and speculate on their possible roots.

## **MATERIAL AND METHOD**

The study comprised 111 patients (22 women and 89 men) in the 41-to-65-year old age group (the mean age: 55.4±5.6 years) with diagnosed IHD, and it was conducted by means of standard clinical criteria. A control group consisting of 50 healthy subjects (10 women and 40 men), was matched by sex and age with the study group. The proportion of men and women in the study group reflects the prevalence of IHD in the population, in this age group. In the study group, 69 patients had experienced myocardial infarction, while no infarction records were found in the medical documentation of the other 42 subjects. All patients were in stable clinical condition at the time of the psychometric testing. Exclusion criteria were a history of psychoactive substance addiction, psychiatric and neurological diseases, and a history of strokes.

This study was accepted by the Bioethics Committee of the University of Lodz (RNN/127/06/KE). All the subjects were informed about the study goal, their char-

acter and of the methods for performing the examination. All the participants gave their informed consent for the examination to be performed.

The psychometric assessment of the intensity of depressive symptoms was performed using Beck's Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HDRS). Beck's Depression Inventory (BDI) is a subjective self-related interview consisting of 21 questions.

For BDI the higher the scores the more depressive the symptoms. Usually scores higher than 12 are thought to indicate the presence of a clinically significant level of symptoms (depressive episode). The Hamilton Depression Rating Scale (HDRS) is an objective assessment by the raters, which consists of 17 items. The HDRS is used for the evaluation of the intensity of depression. It uses the following scoring scheme: 0–7: no depression; 8–12: mild; 13–17: moderate; 18–29: severe; and 30–52: very severe depression (Stetkiewicz-Lewandowicz et. al., 2011).

Working memory in the study population was evaluated by means of the computerized version of the Wisconsin Card Sorting Test (WCST).

The WCST was administered with the use of a computer version of the test (WCST Research Edition, Version 3, Psychological Assessment Resources, Inc.) in accordance with the standard WCST administration procedure. In turn the WCST consists of 4 stimulus cards and 128 response cards that depict figures in different forms, colours, and numbers. The subject faces a set of 4 stimulus cards at the top of the screen, with the first response card displayed in the bottom center. The subject is instructed to match the response card to one of the stimulus cards using the computer mouse. The cards can be matched according to 1 of the 3 sorting principles: colour, form, and the number of depicted figures. The subject is never told which sorting principle to use and has to find the correct sorting strategy based on visual feedback provided by the program (a right or wrong message, which appears on the screen after the subject matches the current response card to one of the stimulus cards). After 10 consecutive correct matches according to the initial sorting principle (colour), the sorting principle is changed without warning, requiring the subject to develop a new sorting strategy based on the feedback provided. Test administration ends after the subject successfully completes 6 categories or uses up all of the 128 consecutively administered response cards prior to completing the 6 categories.

The following standard WCST scores were used:

- percentage perseverative errors (%PE), indicating thinking rigidity;
- percentage non-perseverative errors (%NPE), showing chaotic, uncontrolled reactions;
- the number of categories completed (CC), which shows the index of thinking efficacy;
- conceptual level responses (CON), which reflect the ability to connect new information and previous experience;
- trials to complete 1st category (TC1STC), which indicates the ability to formulate logical conception (Heaton, Chelune, Talley, Kay & Curtis, 1993; Jabłkowska, Karbownik-Lewińska, Nowakowska, Junik, Lewiński & Borkowska, 2009).

For statistical analysis, a non-parametric analysis of Kruskal-Wallis variance with a post-hoc U Mann-Whitney test with Bonferroni modification for comparisons between the groups was used. The significance of differences between the groups was evaluated with chi-square tests for dichotomized variables.  $P < 0.01$  was adopted as the statistical significance of difference.

## RESULTS

### Depression

None of the patients was suffering from any depressive episode at the time of the psychometric testing. Consequently, the scores of both measures applied reflected a low level (if any) of depressive symptoms in both the IHD and control groups. However, the raw scores of BDI and HDRS were still significantly higher in the clinical group when compared to the controls (Table 1). As expected, more pronounced depressive symptoms, measured by BDI as well as by HDRS, were observed in women (BDI=14.3; HDRS=8.2) when compared with men (BDI=8.9; HDRS=6.2), respectively (Table 2).

### Working memory

Patients with IHD demonstrate a statistically worse execution of WCST in comparison with the control group in every considered WCST scale: %PE=13.8±7.4; 8.4±3.0, %NPE=13.2±6.6; 7.9±2.6, CC=5.1±1.5; 5.9±0.3, CON=66.4±16.2; 80.7±6.8, TC1STC=19.8±19.5; 13.2±4.1 (Table 3).

Table 1. The intensity of depressive symptoms in the study group patients with IHD and the control group

	Study group N=111		Control group N=50		Significant p
	Average ±SD	Median (QR)	Average ±SD	Median (QR)	
BDI	9,9±7,5	8,0(5,0-14,0)	3,2±2,7	3,0(1,0-5,0)	<0,001
HDRS	6,6±4,6	6,0(3,0-10,0)	3,1±2,9	2,0(1,0-5,0)	<0,001

QR – quartile range; SD – standard deviation; N – number of the group; p – value of testing probability for U-Mann-Whitney test.

Table 2. The intensity of depressive symptoms in investigated group of patients with IHD according to sex

	Women N=22		Men N=89		Significant p
	Average ±SD	Median (IQR)	Average ±SD	Median (IQR)	
BDI	14,3±9,6	9,5(8,0-21,0)	8,9±6,4	7,5(4,0-13,0)	<0,01
HDRS	8,2±4,6	7,5(6,0-11,0)	6,2±4,5	4,0(3,0-10,0)	<0,05

QR – quartile range; SD – standard deviation; N – number of the group; p – value of testing probability for U-Mann-Whitney test

Table 3. The results of the WCST in the study group, patients with IHD, and the control group

	Study group N=111		Control group N=50		p
	Mean±SD	Median (QR)	Mean±SD	Median (QR)	
WCST_%PE	13,8±7,4	12,0(9,0-16,0)	8,4±3,0	8,0(6,0-10,0)	0,0000
WCST_%NPE	13,2±6,6	12,0(9,0-16,0)	7,9±2,6	8,0(6,0-9,0)	0,0000
WCST_CC	5,1±1,5	6,0(4,0-6,0)	5,9±0,3	6,0(6,0-6,0)	0,0152
WCST_%CON	66,4±16,2	72,0(56,0-78,0)	80,7±6,8	80,0(76,0-86,0)	0,0000
WCST_TC1STC	19,8±19,5	14,0(13,0-19,0)	13,2±4,1	12,0(11,0-13,0)	0,0000

QR – quartile range; SD – standard deviation; N – number of the group; p – value of testing probability for U-Mann-Whitney test.

WCST\_%PE - percentage perseverative errors

WCST\_%NPE - percentage nonperseverative errors

WCST\_CC - number of categories correctly completed

WCST\_%CON - conceptual level responses

WCST\_TC1STC - number of cards needed to complete first category

Table 4. r-Spearman correlations between WCST results and age, and years of education in the study group

	Years of education	Age
	R	R
WCST_%PE	-0,34*	0,24*
WCST_%NPE	-0,30*	0,27*
WCST_CC	0,30*	-0,22*
WCST_%CON	0,37*	-0,30*
WCST_TC1STC	-0,05	0,04

\* Statistically significant correlations

Correlation between working memory and depression

There was no statistically significant correlation between HDRS and BDI scores and WCST

In the study group statistically important correlations were found between WCST results and years of education and between WCST results and patient age (Table 4).

Sex, working status and the course of the IHD (the existence/or not of myocardial infarction in the history) did not differentiate the groups on the basis of working memory and executive functions.

## DISCUSSION

The scores of depressive symptoms were significantly higher in the study group (BDI=9.9; HDRS=6.6) when compared with the control group (BDI=3.2; HDRS=3.1). But in general no depression was detected in the group of patients, although the results may indicate a subdepressive disorder that can be significant for treatment and rehabilitation (Frasure-Smith, Lespérance & Talajic, 1995; Ziegelstein, Feuerbach & Stevens, 2000).

In the study group more pronounced depressive symptoms, measured by BDI as well as by HDRS, were observed in women (BDI=14.3; HDRS=8.2) when compared with men (BDI=8.9; HDRS=6.2). This regularity is characteristic not

only of the general population but also among patients with IHD (Mallik et. al., 2006; Whang et. al., 2009).

The results of the Wisconsin Card Sorting Test (WCST) show working memory dysfunction and executive functions impairment in the study group. Patients with IHD demonstrated difficulty expressing logical conceptions and problems using new information and new experiences (Stetkiewicz-Lewandowicz et. al., 2010).

In the analyzed groups significant differences were observed according to years of education and WCST results. People with higher education achieved better test results (Boone et. al., 1993).

The WCST results are strongly affected by age; in people above 60 the values of the test scales decrease (Strauss, Sherman, & Spreen, 2006). In our study group age correlated positively with the %PE ( $R=0.24$ ;  $p<0.05$ ) and %NPE ( $R=0.27$ ;  $p<0.01$ ), but it correlated negatively with CC ( $R=-0.22$ ;  $p<0.05$ ) and CON ( $R=-0.30$ ;  $p<0.01$ ).

In the subject literature, cognitive dysfunction has been reported in patients with a variety of cardiovascular disorders. It is well documented among hypertensive patients and after coronary bypass graft (CABG) surgery (Ho et. al., 2004; Millar, Asbury & Murray, 2001; van Dijk et. al., 2000) but in general little is known about the relationship between heart disease and cognition.

Heart disease manifests itself in middle age. Dementia occurs late in life but it is being increasingly diagnosed and there is a long preclinical phase characterized by progressive neuropathological changes (Singh-Manoux et. al, 2008).

Vascular risk factors and indicators of vascular disease are associated with both cognitive impairment (Breteler et. al., 1994; Launer, Masaki, Petrovitch, Foley & Havlik, 1995) and dementia (Breteler, 2000; De la Torre, 2002). The atherosclerotic process and the related hypoperfusion are believed to be responsible for this association (Breteler, 2000; Singh-Manoux et. al., 2008).

In recent years, growing attention has been given to the clinical importance of the relationship between depression and cognitive processes especially executive functions (Alexopoulos, 2003; Cui, Lyness, Tu, King & Caine, 2007; Lockwood, Alexopoulos & van Gorp, 2002) although not all studies have confirmed this association (Butters et. al., 2004; Mast, 2005).

In one study patients after MI with depression demonstrated paradoxically better cognitive performance than patients after MI without depression and the control group (Dijkstra et. al., 2002). This result can be explained by the procognitive stimulation of pharmacotherapy.

According to Freiheit et al. (2012) older patients who suffered from coronary artery disease with persistent depressive symptoms performed significantly greater declines at 30 months in attention/executive function, learning/memory, verbal fluency and global cognition in comparison with subjects with no or baseline-only depressive symptoms.

In another survey depressive symptoms were associated with a decline in the pace of processing information over a three-year period (Comijs, Jonker, Beekman & Deeg, 2001).

In our study there was no statistically significant correlation between depressive symptoms as measured by HDRS and BDI and cognitive dysfunctions obtained by WCST. This can be caused by the specific picture of depression in somatic diseases which is usually characterized with pain and with psychosomatic complains.

The relationship between depression and cognitive dysfunctions in IHD is clearly observed in elderly patients. Patients with old-age depression often suffer from vascular depression, which is related to ischemic white-matter changes. Vascular depression should probably be considered as a warning sign for emerging vascular dementia (Vataja et. al., 2005).

The cognitive profile of patients with cardiological disease especially after MI with coexisting depressive symptoms can be different when compared with depressed patients without somatic problems.

There are many overlapping problems still waiting to be solved: depression as a cause and as a result of IHD, cognitive dysfunctions as a prodromal phase of IHD and a consequence of neuropathological changes and hypoperfusion and, the association between depressive disorders and cognitive dysfunctions in middle-aged patients. This group is particularly prone to be affected by a pre-clinical phase of dementia that itself might modify the risk factors for heart disease (Singh-Manoux et. al., 2008; Stewart, White, Xue & Launer, 2007).

Although the etiologies of these associations are not well understood, a number of negative outcomes are visible. Healthcare systems providers will have to make efforts to recognize and treat depression and cognitive dysfunctions in patients with IHD more effectively (Ford, 2008).

The results of our study show interesting tendencies. Nevertheless, further research into these aspects is needed.

## **CONCLUSIONS**

A higher degree of depressive symptoms, working memory dysfunction and executive function impairment were observed in the study group than was in the control group. There was no significant correlation between depressive symptoms and cognitive dysfunctions. This fact can be explained by the different cognitive profile of patients with cardiological disease in comparison to depression patients without somatic problems or on the basis of other factors like the influence of pharmacology, personality or sociological factors.

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