Personalized Psychiatry and Neurology

Article

Relationship Between Cognitive Functions and Oxytocin Levels in Patients with Multivessel Coronary Artery Disease

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Citation: Mikhailova, O.V.; Petrova, M.M.; Lopatina, O.L. Relationship Between Cognitive Functions and Oxytocin Levels in Patients with Multivessel Coronary Artery Disease. *Personalized Psychiatry and Neurology* **2025**, *5 (2)*: 26-30. https://doi.org/10.52667/2712-9179-2025-5-2-26-30

Chief Editor: Nikolaj G. Neznanov, DMedSci, Professor

Received: 15 May 2025
Accepted: 11 June 2025
Published: 15 June 2025

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Abstract: This study investigates the relationship between cognitive function and oxytocin levels in blood and saliva among male patients with multivessel coronary artery disease (CAD). Existing literature highlights a significant association between CAD and cognitive impairment, with prevalence rates varying widely due to inconsistent diagnostic criteria. **Objective:** To determine the relationship between cognitive function and oxytocin levels in blood and saliva among patients with multivessel coronary artery disease. **Methods:** Our research involved 91 male patients undergoing coronary artery bypass grafting, excluding those with concomitant diseases or significant cognitive deficits. Neuropsychological assessments were conducted using validated screening scales, including the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB). Oxytocin levels were measured through enzyme-linked immunosorbent assay (ELISA). Results indicated significant correlations between cognitive performance and oxytocin levels, with direct relationships observed for MMSE and word recall tests, and inverse relationships for the Schulte test. **Discussion:** These findings suggest that oxytocin may serve as a potential biomarker for vascular cognitive impairment in CAD patients, offering a rapid and objective diagnostic tool that could enhance clinical practice. **Conclusion:** Ultimately, this study contributes to the understanding of cognitive deficits in CAD and supports the exploration of oxytocin as a diagnostic biomarker.

Keywords: *cognitive impairment, coronary heart disease, oxytocin.*

1. INTRODUCTION

There is ample evidence indicating a relationship between coronary artery disease (CAD) and the development of cognitive impairment of varying severity. Studies show that myocardial ischemia can lead to deterioration in cognitive function. [1]. Current studies demonstrate significant diversity in the screening methods and diagnostic criteria used, which in turn leads to high variability in the prevalence of cognitive impairment in patients with CAD, ranging from 9% to 85% [2]. Moreover, cognitive assessment is also not part of the daily clinical practice of cardiologists. [3]. However, existing data suggest that CAD increases the risk of developing cognitive impairment, and acute coronary events are associated with accelerated progression of cognitive impairment [4]. Moreover, the presence of cognitive deficit has serious clinical implications. This is associated with a deterioration in adherence to medical recommendations, which may complicate the achievement of secondary prevention goals that are critical for preventing adverse coronary events [5]. However, it is worth noting that awareness of the relationship between cognitive impairment and cardiovascular disease is increasing among cardiologists, which is reflected in the latest recommendations for the prevention of cardiovascular diseases concerning this issue [6].

Of particular importance is the early detection of vascular cognitive impairment in patients, which allows for the timely development of prevention and treatment strategies.

In this regard, the search for biochemical biomarkers associated with cognitive impairment in patients with coronary artery disease is becoming an extremely important task.

At the moment, official biomarkers have not been established for vascular cognitive dysfunction [7]. According to the definition proposed by experts from the US National Institutes of Health, a biomarker is a quantitatively measurable indicator that serves as an indicator of various biological processes both under normal conditions and in the presence of pathology. In addition, biomarkers play an important role in assessing the effectiveness of therapy [8]. However, scientists from different countries are actively searching for potential biomarkers, which opens up new prospects for the diagnosis and treatment of this pathology.

According to research, it has been found that oxytocin (OT) affects cognitive functions. It is involved in learning and the formation of various types of memory, including social, working, spatial and episodic. The OT system actively interacts with the amygdala, hippocampus and prefrontal cortex, which is important for the normal functioning of mental processes. Despite this, the mechanisms by which OT affects cognitive functions are still poorly understood and require further research [9]. There are studies devoted to the study of the relationship between OT and various aspects of cognitive control. For example, OT plays a significant role in the cognitive regulation of cravings for food [10], and also takes part in cognitive control during acute and natural stress [11]. Cognitive control is particularly important during stress, when cognitive resources are increasingly depleted and adaptive responses are critical. Moreover, cognitive control plays a critical role in emotion regulation, which is important for adaptation, social behavior, and well-being [12].

The aim of this study is to determine whether there is a relationship between cognitive function and blood and saliva OT levels in patients with multivessel CAD.

2. MATERIALS AND METHODS

The study was conducted at the Federal Center for Cardiovascular Surgery in Krasnoyarsk of the Russian Ministry of Health. The study included 91 male patients with multivessel CAD who were hospitalized for planned coronary artery bypass grafting under artificial circulation.

Exclusion criteria from the study: the presence of concomitant diseases (respiratory system, digestive system, musculoskeletal system) in the decompensation stage; the presence of diabetes mellitus; a history of CNS diseases in patients (history of traumatic brain injury; degenerative, metabolic diseases, epilepsy, psychosis); the presence of significant vascular lesions of the brain according to magnetic resonance imaging (MRI) of the brain or according to multislice computed tomography (MSCT) of the brain; hemodynamically significant stenosis of extracranial arteries (more than 50%); the number of points on the Mini-Mental State Examination (MMSE) scale less than 24; the number of points on the Frontal Assessment Battery (FAB) scale less than 11; patient refusal to start or continue the study.

All patients were examined by a neurologist before the surgical examination. A neuropsychological examination of patients was conducted using questionnaires (MMSE, FAB, clock drawing test, Schulte test, 10-word memorization test, which is conducted in three stages - immediate memorization, general memorization for 5 regions and delayed memorization). Determination of the level of oxytocin in saliva and blood plasma was carried out using special 96-well palettes coated with antibodies to oxytocin (High Sensitive ELISA Kit for Oxytocin) using the enzyme-linked

immunosorbent assay method for the quantitative measurement of oxytocin in biological fluids (pg/ml).

Statistical processing of the data was performed using the free software IBM SPSS Statistics software (version 19.0). The distribution was evaluated using the Shapiro-Wilk criterion. Central tendencies were presented as arithmetic mean, standard deviation, median and interquartile ranges as M ± SD (Me; Q_1; Q_3). Categorical and rank variables were presented as number of cases - absolute number (n) and proportion - relative number (%). To assess the relationship between multiple vectors that do not obey the law of normal distribution, or rank vectors, the Spearman correlation coefficient was used ($p<0.05$). The gradation of the strength of the relationship was determined using the value of the correlation coefficient (r), i.e. the higher the modulus of the correlation coefficient value, the higher the strength of the relationship. If the correlation coefficient is positive, this means that there is a direct relationship, while a negative coefficient indicates an inverse relationship.

The study was approved by the Local Ethical Committee: (protocol No. 102/2020 of November 27, 2020) and complied with the Ethical Standards of the World Medical Association Declaration of Helsinki. All patients signed informed voluntary consent to participate in the study.

3. RESULTS

The average age of the study group of patients was 62.6 ± 4.87 years. In order to assess the degree of cognitive deficit, each patient underwent neuropsychological testing using screening scales. The testing results demonstrated the following indicators: the median on the MMSE was 25.0 [23.0; 27.0] points; when conducting the functional activity of the brain (FAB) test, the median was 16.0 [14.0; 16.0] points; the results of the clock drawing test showed a median of 9.0 [8.0; 10.0] points. When assessing the immediate memorization of 10 words, the median was 4.0 [4.0; 5.0] points, while for the sum of five attempts to memorize 10 words, the median reached 36.0 [32.0; 39.0] points. With delayed recall, a median of 4.0 [3.0; 5.0] points were recorded. The average time to complete the Schulte test was 34.04 ± 4.2 seconds.

All patients underwent venous blood and saliva sampling to measure oxytocin levels. The median OT level in venous blood plasma in patients was 897.70 [714.15; 1134.27] pg/ml, and the median OT level in saliva was 7.16 [5.65; 10.41] pg/ml. Next, an analysis was conducted of the relationship between cognitive functions and the level of OT in venous blood plasma and saliva.

When assessing the relationship between the cognitive status of patients and the level of OT in venous blood plasma and saliva, a statistically significant correlation was found with all screening tests used to determine cognitive functions and the level of OT in blood plasma and saliva. Thus, we found a statistically significant direct strong relationship between the blood OT level and the MMSE tests and the 10-word recall test (all three stages). And also, a statistically significant inverse strong relationship between the blood OT level and the Schulte scores. A direct statistically significant relationship of medium strength was found between the blood OT level and the clock drawing and FAB tests (Table 1).

Also, a statistically significant direct correlation of medium strength was found between the level of OT in saliva and the MMSE, FAB, clock drawing test and 10-word memory test (all three stages). And a statistically significant inverse correlation of medium strength was found between the level of OT in saliva and the Schulte scale scores (Table 2).

Table 1. Correlation between plasma oxytocin levels and cognitive function test

Neuropsychological test	**Oxytocin level in venous blood plasma**	
	p	**r**
MMSE, points	<0,001	0,722
FAB, points	<0,001	0,645
Clock Drawing Test, points	<0,001	0,684
Test 10 words - direct reproduction, points	<0,001	0,734
Test 10 words - general reproduction, points	<0,001	0,836
Test 10 words - delayed recall, Points	<0,001	0,816
Schulte test, sec	<0,001	-0,861

Table 2. Correlation between salivary oxytocin levels and cognitive function test

Neuropsychological test	**Oxytocin level in salivary**	
	p	**r**
MMSE, points	<0,001	0,578
FAB, points	<0,001	0,513
Clock Drawing Test, points	<0,001	0,503
Test 10 words - direct reproduction, points	<0,001	0,524
Test 10 words - general reproduction, points	<0,001	0,663
Test 10 words - delayed recall, Points	<0,001	0,541
Schulte test, sec	<0,001	-0,631

4. DISCUSSION

Screening tests are used to diagnose cognitive impairment in clinical practice. Although these tests are easy to use, they require a fairly long time to complete and do not allow the tests to detect mild cognitive impairment. That is why researchers are faced with the task of determining a biomarker that can be used for laboratory screening diagnostics of cognitive abilities. Since the use of biomarkers in routine practice allows to reduce the time of patient examination and exclude subjective assessment of a specialist as the only diagnostic method in making a final diagnosis.

Taking into account the obtained data on the relationship between the severity of cognitive deficit and the level of OT in biological fluids, we propose to consider oxytocin as a biomarker of vascular cognitive disorders. The data obtained as a result of our study can be used as a basis for developing a method for diagnosing the presence of cognitive impairment based on the level of OT in blood plasma and saliva, which, in turn, will significantly improve the quality of diagnostics and allow it to be carried out quickly. Since the proposed method is simple and quick to implement, it does not require the participation of specially trained personnel (neuropsychologists), it excludes contact between the subject and the doctor, and therefore the moment of subjective assessment of the patient.

5. LIMITATION

The limitations of our study are the relatively small sample size of patients and the inclusion of only male patients in the analysis. Despite these limitations, our study requires further study of the level of relationship between OT level and cognitive status

of patients. Future studies should include larger patient samples, including female patients. This can be based on the recognition of oxytocin as a biomarker of cognitive states in patients with CAD and the use of the theory of determining OT levels in blood and saliva to diagnose cognitive deficits in patients.

6. CONCLUSION

The results of our study confirm the existence of a connection between the level of OT in biological fluids and the state of cognitive functions of patients with multivessel CAD. The proposed study is new and has both practical and theoretical significance, since the obtained results allow us to consider OT as a biomarker of cognitive impairment in patients with CAD.

Author Contributions: Conceptualization, M.M.P.; methodology, O.L.L.; validation, O.V.M.; formal analysis, O.V.M.; investigation, O.V.M.; resources, O.L.L.; data curation, O.V.M.; writing, O.V.M.; editing, M.M.P.; supervision, M.M.P.; project administration, M.M.P. All authors have read and agreed to the published version of the manuscript.
Funding: The study was supported by the state assignment of the Ministry of Health of the Russian Federation No. 123022800057-6.
Institutional Review Board Statement: The study was approved by the Ethics Committee of V.F. Voino-Yasenetsky Krasnoyarsk State Medical University.
Informed Consent Statement: All study participants signed a voluntary informed consent.
Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data, in the writing of the manuscript.

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