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# Rapid test for the qualitative simultaneous determination of cardiac fatty acid-binding protein and cardiac troponin I in the diagnosis of acute coronary syndrome

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**Aim.** To study the diagnostic characteristics of the rapid test for qualitative simultaneous determination of cardiac fatty acid-binding protein (FABPs) and cardiac troponin I (cTnI) CARD-INFO 1+1 in patients with acute coronary syndrome (ACS).

**Material and methods.** The study included 168 patients undergoing inpatient treatment after ACS, with typical anginal pain lasting at least 20 minutes occurred in the previous 1-24 hours. In addition to routine diagnostic procedures, on admission, we determined FABPs and cTnI concentrations using the high-quality immunochromatographic rapid test CARD-INFO 1 1 (OOO CARDIO-Plus, Russia).

**Results.** The sensitivity of the CARD-INFO 1+1 rapid test was 88,1%, specificity — 89,8%, diagnostic accuracy — 88,7%. The indicators of the diagnostic effectiveness of CARD-INFO 1+1 test in patients with STE-ACS and NSTE-ACS did not significantly differ (p>0,05). The sensitivity of the rapid test reached a maximum in the period from 3 to 6 hours from the onset of pain. Compared with the determination of cTnI performed on admission to the hospital, a higher sensitivity of the CARD-INFO 1+1 test was revealed in patients with STE-ACS (87,7% vs 75,3%; p=0,044), in the first 1-3 hours after the beginning of clinical manifestations (86,8% vs 60,5%; p=0,041) and in the entire sample as a whole (88,1% vs 77,1%; p=0,033), with comparable specificity (89,8% and 93,2%, respectively; p=0,741).

**Conclusion.** Qualitative immunochromatographic CARD-INFO 1+1 rapid test for the simultaneous determination of the content of FABPs and cTnI I is highly effective in the diagnosis of various forms of ACS. The highest diagnostic characteristics of the test were observed in patients in the early stages of the disease (the first 1-6 hours after the onset of pain). Carrying out the CARD-INFO 1+1 test revealed 12 MI cases more (11%) than the first determination of cTnI. Further studies will clarify the place of this technique in the modern algorithm for the management of patients with ACS and evaluate the possibility of using the rapid test in predicting the course of the disease.

**Key words:** acute coronary syndrome, cardiac fatty acid-binding protein, cardiac troponins, rapid test, multi-marker approach.

**Conflicts of Interest:** nothing to declare.

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Despite significant progress in treatment of diseases and the reduction of statistical parameters of deaths, mortality from myocardial infarction (MI) in the Russian Federation remains higher than in most of the world's economically developed countries. According to Rosstat, in 2018, MI caused the death of 54427 Russians [1, 2]. Early diagnostics and timely start of treatment are key factors to reduce hospital and long-term mortality, as well as the incidence of disabling complications.

In accordance with modern recommendations, cardiac troponins (cTn) are considered to be the leading biomarkers for the diagnosis of myocardial damage, and it is preferable to use highly sensitive methods (hs-cTn) for their determination [3]. Despite the numerous advantages, hs-cTn is not free of disadvantages. In particular, their determination is not sufficiently informative in the first hours after myocardial damage. Hs-cTn tests of different manufacturers have different values of 99th percentile and diagnostic levels, as well as algorithms for evaluating the results, which makes it difficult to compare and standardize the data obtained. The need for serial determination of hs-cTn, the economic aspect and the absence of "bedstand" express tests limit the possibility of their widespread use. A number of major studies have shown that the hs-cTn use in clinical practice instead of "normal" sensitivity tests has increased the frequency of MI detection and the number of percutaneous coronary interventions (PCI) performed, but has not led to a decrease in the mortality and MI prevalence [4, 5].

One of the most promising early markers of myocardial damage is Heart-type fatty acid binding protein (hFABP). Its main advantage is its rapid entry into the systemic circulation in case of cardiomyocyte damage, which allows detecting an increase in diagnostic concentrations within 30-60 minutes after the appearance of clinical symptoms [6]. Experts' opinions on the role and place of hFABP detection in IM diagnostic algorithms are contradictory.

In recent years, the possibilities of a "multi-marker approach" with simultaneous identification of several myocardial damage markers have been actively studied. Its potential advantages include faster and more reliable diagnosis verification and no need for routine determination of cTn, which may reduce the frequency and duration of hospitalizations and, consequently, economic costs [7, 8].

Studies have shown that the combined determination of hFABP and cTn makes it possible to confirm and exclude MI more correctly compared with the single determination of cTn, as well as combinations of cTn with myoglobin and/or creatine phosphokinase MB (CPK-MB), especially in the early (up to 6 hours) periods of the disease. The combination of hFABP and cTn I with copeptin has also been studied [9, 10]. Less single-valued results were obtained in the studies of the combined determination of FSLBC with hs-cTn [11-13].

It should be noted that in most of these studies the determination of the hFABP was carried out by a quantitative method, conducting of which has a number of limitations in real clinical practice. In 2017, the first report on the development of a rapid test for the combined qualitative immunochromatographic determination of hFABP and cTn I appeared, and in 2018 a similar test was created in our country. The CARD-INFO 1+1 diagnostic test (OOO Cardio-Plus, Obninsk) provides one-step express analysis for the detection of hFABP and cTn I in capillary or venous blood, as well as its serum. The results of the pilot study of this test showed good diagnostic parameters [14].

The aim of present research was to study the diagnostic characteristics of the CARD-INFO 1+1 rapid test for simultaneous qualitative determination of hFABP and cTn levels in ACS patients.

## Material and methods

One hundred eighty-four patients were screened and admitted to the Department of Anesthesiology and Intensive Care with ACS, characterized by typical anginal pain lasting at least 20 minutes and the time from their onset was 1-24 hours. The study did not include patients who had stroke, acute ischemia of limbs or other organs, severe injuries, burns and cardiac surgery during the previous 30 days.

In 16 (8,7%) patients, the diagnosis of ACS was not confirmed, and therefore they were excluded from the study. Thus, the final analysis included 168 patients with verified ACS, including 54 women (32,1%) and 114 men (67,9%). The average age of the patients was 63 [54-72] years.

Anamnestic characteristics of the studied patients are presented in Table 1.

The diagnosis of IM was established according to the Third Universal Definition of Myocardial Infarction (2012) [15]. The diagnosis of unstable angina was established in the presence of clinical signs of myocardial ischemia and absence of hypertensemia.

Hs-cTn I was used as marker which was determined serially (on admission to hospital and after 3-6 h), by quantitative method using Pathfast analyzer (Mitsubishi Chemical, Japan). The reference value of 99% percentile corresponded to a concentration of 0,02 ng/ml. Echocardiographic examination (EchoCG) was performed in 157 (93,5%) patients, coronary angiography — 122

(72,6%). In 10 (6,0%) patients who died during hospitalization, the diagnosis of IM was confirmed on autopsy.

In addition to routine diagnostic procedures, on admission, all patients were assessed for the hFABP and cTn I levels using the high-quality immunochromatographic rapid test "CARD-INFO 1 + 1" (OOO CARDIO-Plus, Russia), which has an analytical threshold for hFABP — 7 ng/ml, cTn I — 1,2 ng/ml. The test strip located in the plastic cassette contains monoclonal mouse antibodies to hFABP and ctn I. One antibody clone is conjugated with dye (colloidal gold), the other is plotted as lines in the test zone of the test strip. When a blood sample with a buffer solution is introduced, the liquid spreads along the test strip according to the thin layer chromatography principle. In the presence of antigens, they bind to monoclonal antibodies and form a specific immune complex with the appearance of stained lines in the test zone corresponding to each biomarker. The test was considered positive when two or three pink lines appeared — one or two in the test zones showing the presence of hFABP and/or cTn I, as well as the control zone. When a pink line appeared only in the control zone, the test was regarded as negative. The test was performed immediately after taking the blood. The result was evaluated visually 20 minutes after the introduction of the blood sample by an independent researcher who did not have information on anamnestic, ECG and laboratory data of patients.

The diagnostic effectiveness of the CARD-INFO 1 + 1 test and hs-cTn I test were evaluated by sensitivity parameters (the proportion of positive test results in patients with MI), specificity (the proportion of negative test results in patients without MI) and accuracy (the proportion of right positive and right negative results among the total number of test results). The indicated parameters were evaluated in the entire sample, as well as depending on the type of ECG changes and the time from the onset of clinical manifestations to the test. The diagnostic characteristics of the rapid test were also compared with the results of the first determination of hs-cTn performed at admission to the hospital. For this, a quantitative parameter of the hs-cTn I concentration was converted to binary, depending on whether it reached the level of 99% percentile or not.

The monitoring of patients continued until they were discharged from hospital.

**Table 1**

**History characteristics of studied patients**

| Characteristics | N | % |
|---|---|---|
| Stable angina | 54 | 32,1 |
| Postinfarction cardiosclerosis | 49 | 29,2 |
| Arterial hypertension | 144 | 85,7 |
| Chronic heart failure | 25 | 14,9 |
| Prior percutaneous coronary interventions or coronary artery bypass grafting | 36 | 21,4 |
| Hypercholesterolemia | 39 | 23,2 |
| Atrial fibrillation | 29 | 17,3 |
| Smoking | 61 | 36,3 |
| Obesity Class I<br>Class II<br>Class III | 58<br>9<br>1 | 34,5<br>5,4<br>0,6 |
| Type 2 diabetes mellitus | 35 | 20,8 |
| Lower extremity arterial disease | 4 | 2,4 |
| Stroke or transient ischemic attack | 21 | 12,5 |
| Chronic bronchopulmonary diseases | 12 | 7,1 |
| Gastrointestinal diseases | 32 | 19,0 |
| Chronic kidney diseases | 21 | 12,5 |
| Anemia | 7 | 4,2 |

**Table 2**

**Diagnostic efficiency of «CARD-INFO 1+1» and markers singly depending on ACS form**

| Diagnostic characteristic | Test interpretation | STEACS | NSTEACS | p |
|---|---|---|---|---|
| Sensitivity | hFABP test zone | 86,4 (77,1-92,4) | 85,7 (67,9-94,9) | 0,823 |
| | cTn I test zone | 49,4 (38,8-60,1) | 60,7 (42,4-76,5) | 0,301 |
| | Common test interpretation | 87,7 (78,6-93,3) | 89,3 (72,0-97,1) | 0,914 |
| Specificity | hFABP test zone | 88,9 (54,3-99,9) | 90,0 (78,2-96,1) | 0,619 |
| | cTn I test zone | 88,9 (54,3-99,9) | 94,0 (83,2-98,6) | 0,874 |
| | Common test interpretation | 88,9 (54,3-99,9) | 90,0 (78,2-96,1) | 0,619 |
| Accuracy | hFABP test zone | 86,7 (78,0-92,4) | 88,5 (79,3-94,0) | 0,907 |
| | cTn I test zone | 53,3 (43,1-63,3) | 82,1 (72,0-89,1) | <0,001 |
| | Common test interpretation | 87,8 (79,3-93,2) | 89,7 (80,8-95,0) | 0,876 |

**Note:** data is presented in % format (95% CI).

**Table 3**

**Diagnostic efficiency of «CARD-INFO 1+1» and markers singly depending on the time from onset of pain**

| Diagnostic characteristic | Test interpretation | 1-3 h | 3,1-6 h | > 6 h |
|---|---|---|---|---|
| Sensitivity | hFABP test zone | 84,2 (69,2-92,9) | 92,3 (79,0-98,1) | 81,3 (64,3-91,5) |
| | cTn I test zone | 44,7 (30,1-60,3) | 46,2 (31,6-61,4) | 68,8 (51,3-82,2) |
| | Common test interpretation | 86,8 (72,2-94,7) | 92,3 (79,0-98,1) | 84,4 (67,2-94,7) |
| Specificity | hFABP test zone | 100,0 (81,0-100,0) | 90,0 (68,7-98,4) | 79,0 (56,1-92,1) |
| | cTn I test zone | 100,0 (81,0-100,0) | 100,0 (81,0-100,0) | 79,0 (56,1-92,1) |
| | Common test interpretation | 100,0 (81,0-100,0) | 90,0 (68,7-98,4) | 79,0 (56,1-92,1) |
| Accuracy | hFABP test zone | 89,7 (78,9-95,5) | 91,5 (81,3-96,7) | 80,4 (67,4-89,2) |
| | cTn I test zone | 63,8 (50,9-75,0) | 64,4 (51,6-75,4) | 72,6 (59,0-83,0) |
| | Common test interpretation | 91,4 (81,0-96,7) | 91,5 (81,3-96,7) | 82,4 (69,5-90,7) |

**Note:** data is presented in % format (95% CI).

**Abbreviations:** hFABP — heart-type fatty acid binding protein, cTn I — cardiac troponin I.

Statistical analysis of the data was carried out using Microsoft Excel (2013) and SPSS Statistics 22.0. The number and percentage of observations are given in the description of parameters presented as alternative variables. The distribution of parameters was assessed using the Kolmogorov-Smirnov test. In the case of normal distribution, the data are presented in the form of M±m, with a different from normal — in the form of median and interquartile range (Me [Q1-Q3]). Calculation of 95% confidence interval (CI) by means of the modified Wald method was carried out. Pearson's chi-squared test was used to compare diagnostic characteristics. For small samples, Yates' correction or Fisher's exact test was applied. Differences were considered valid at $p<0,05$.

The study was carried out in accordance with the principles of the Helsinki Declaration and Good Clinical Practice (GCP) standards. All patients signed an informed consent to participate in the study. The study was approved by the independent ethics committee of N. I. Pirogov Russian National Research University.

## Results

The average duration of clinical manifestations at the time of the test was 4,0 [2,7–7,2] hours (including from 1 to 3 hours in 58 (34,5%) patients, from 3 to 6 hours — 59 (35,1%) and >6 hours — 51 (30,4%)). According to the results of the survey, MI diagnosis was established in 109 (64,9%) cases, unstable angina — in 59 (35,1%).

**Table 4**

**Comparison of the diagnostic characteristics of the "CARD-INFO 1 + 1" test and the first estimation of hs-cTn I**

| Characteristic | Sensitivity (n=109) | | Specificity (n=59) | | Accuracy (n=168) | |
|---|---|---|---|---|---|---|
| | CARD-INFO 1+1 | hs-cTn I | CARD-INFO 1+1 | hs-cTn I | CARD-INFO 1+1 | hs-cTn I |
| STEACS | 87,7* (78,6-93,3) | 75,3 (64,9-83,5) | 88,9 (54,3-99,9) | 88,9 (54,3-99,9) | 87,8* (79,3-93,2) | 76,7 (66,9-84,3) |
| NSTEACS | 89,3 (72,0-97,1) | 82,1 (63,9-92,6) | 90,0 (78,2-96,1) | 94,0 (83,2-98,6) | 89,7 (80,8-95,0) | 89,7 (80,8-95,0) |
| 1-3 h | 86,8* (72,2-94,7) | 60,5 (44,7-74,4) | 100,0 (81,0-100) | 95,0 (74,6-99,9) | 89,7* (78,9-95,5) | 72,4 (59,7-82,3) |
| 3,1-6 h | 92,3 (79,0-98,1) | 79,5 (64,2-89,5) | 90,0 (68,7-98,4) | 100,0 (81,0-100) | 91,5 (81,3-96,7) | 86,4 (75,2–93,2) |
| Over 6 h | 84,4 (67,2-94,7) | 93,8 (78,8-99,3) | 79,0 (56,1-92,1) | 84,2 (61,6-95,3) | 80,4 (67,4-89,2) | 90,2 (78,6-96,2) |
| Whole sample | 88,1* (80,5-93,0) | 77,1 (68,3-84,0) | 89,8 (79,2-95,6) | 93,2 (83,4-97,8) | 88,7 (82,9-92,7) | 82,7 (76,3-87,8) |

**Note:** data is presented in % format (95% CI). * — p <0,05.

ECG shows diagnostically significant elevation of the ST segment in 84 (50,0%) cases, in 41 (24,4%) — depression of the ST segment, in 35 (20,8%) — there were no changes or were non-specific, in 5 ( 3,0%) — a total block of the left bundle branch (LBB) or, and in 3 (1,8%) cases a pathological Q wave was detected for the first time without deviations of the ST segment. The result of the CARD-INFO 1 + 1 test was regarded as positive in 102 (60,7%) cases (including a positive test reaction for hFABP in 100 (59,5%) patients, and in cTn I — 61 (36,3%), both markers characterized by a positive reaction in 59 (35,1%) cases), as negative — in 66 (39,3%) patients. In 1 case (0,6%), the reaction was absent, which required repeated testing.

According to established diagnoses, 96 (57,1%) of the test results are interpreted as true positive, 6 (3,6%) as false positive, 53 (31,5%) true negative and 13 (7,7%) false negative. Thus, the sensitivity of the test with the determination of both markers was 88,1% (95% CI: 80,5-93,0), specificity 89,8% (95% CI: 79,2-95,6), diagnostic accuracy — 88,7% (95% CI: 82,9-92,7).

Parameters of the diagnostic effectiveness of each of the biomarkers, as well as their combined determination using the CARD-INFO 1+1 test, depending on the ACS variant and the time elapsed since the onset of the pain syndrome, are presented in Tables 2 and 3.

No significant differences in the sensitivity, specificity and diagnostic accuracy parameters of the CARD-INFO 1+1 test were found in patients with STE-ACS and NSTE-ACS (p>0,05). When comparing the parameters obtained for each of the biomarkers used in the rapid test, there was a higher sensitivity of hFABP to cTn I in STE-ACS (p<0,001) and a similar tendency with NSTE-ACS (p=0,071), with comparable specificity (p>0,05). The sensitivity of the CARD-INFO 1+1 test reached a maximum in the time interval of 3-6 hours from the onset of pain. The specificity parameter tended to decrease, which, apparently, is associated with small samples of patients without MI. There were significantly higher sensitivity and diagnostic accuracy of hFABP compared with cTn I in the intervals of 1-3 hours and 3-6 hours (p <0,001 for both parameters) from the onset of clinical manifestations to testing, in the absence of specificity differences (p>0,05).

Of the 6 cases considered as false positives, a positive response to hFABP was noted in all cases, and to cTn I — in 4 (66,7%).

The level of hs-cTn I determined on admission to the hospital simultaneously with the CARD-INFO 1+1 test exceeded the reference value in 88 cases (52,4%). The sensitivity of hs-cTn I test was 77,1%. The results of efficacy comparing of rapid test with hs-cTn I test are presented in Table 4. The higher sensitivity of the CARD-INFO 1+1 test was revealed in comparison with hs-cTn I in patients with STE-ACS (87,7% vs. 75,3%, p=0,044), in the first 3 hours since the development of clinical manifestations (86,8% vs. 60,5%, p=0,041) and in the whole sample (88,1% vs. 77,1%, p=0,033). A higher diagnostic accuracy of the rapid test was noted than in the case of hs-cTn I in STE-ACS (p=0,05) and in the terms of 1-3 hours from the moment of the disease development (p=0,034). Specificity parameters of hs-cTn I and CARD-INFO 1+1 tests did not differ significantly (93,2% vs. 89,8%, p=0,741).

## Conclusion

Thus, immunochromatographic rapid test CARD-INFO 1+1 for the simultaneous determination of hFABP and cTn I levels is highly effective in the diagnosis of various forms of ACS. The highest diagnostic characteristics of the test

were observed in patients in the early stages of the disease (the first 1-6 hours after the onset of pain). Carrying out the CARD-INFO 1+1 test made it possible to identify 12 cases (11% in absolute value) of MI more than the first hs-cTn I determination (8 of them — in the first 6 hours of the disease).

Further studies will define the place of this technique in the modern algorithm for the management of patients with ACS and assess the possibility of rapid test using in predicting of the disease course.

**Conflicts of Interest:** nothing to declare.

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