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THE SIGNIFICANCE OF HEART-TYPE FATTY ACID BINDING PROTEIN AMONG PATIENTS WITH ACUTE CORONARY SYNDROME

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With increasing numbers of patients with acute coronary syndrome (ACS) it is very important to have reliable biomarkers for early diagnostics and treatment. The role of heart-type fatty acid binding protein (H-FABP) is investigated to confirm patients with ACS and to evaluate the long-term prediction of complications and death. H-FABP allows to define myocardial infarction with changes on ECG and without ST elevation, it helps to differentiate unstable angina. H-FABP sensitivity is higher than troponin, myoglobin and other biomarkers, at the same time H-FABP has a high specificity. Increasing of the H-FABP level is an independent prognostic factor in the long-term prediction in patients with suspected ACS. H-FABP definition, especially in combination with other biomarkers, has the important value, when the diagnosis of ACS is difficult against the background of the atypical clinical picture, the absence of typical ECG changes.

KEY WORDS: acute coronary syndrome, heart-type fatty acid binding protein

ЗНАЧЕННЯ СЕРЦЕВОГО БІЛКА, ЩО ЗВ'ЯЗУЄ ЖИРНІ КИСЛОТИ У ПАЦІЄНТІВ З ГОСТРИМ КОРОНАРНИМ СИНДРОМОМ

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З урахуванням зростання кількості хворих з гострим коронарним синдромом (ГКС) дуже важливо мати для ранньої діагностики і тактики ведення надійні біомаркери. Для підтвердження у пацієнтів ГКС та оцінювання довгострокового прогнозу ускладнень і смерті вивчається роль серцевого білка, що зв'язує жирні кислоти (СБЗЖК). СБЗЖК дозволяє визначити інфаркт міокарда зі змінами на ЕКГ і без підйому ST, допомагає диференціювати нестабільну стенокардію. Чутливість СБЗЖК вище ніж у тропонінів, міоглобіну та інших біомаркерів, в той же час СБЗЖК має високу специфічність. Підвищення рівня СБСЖК є незалежним прогностичним фактором довгострокових прогнозів у пацієнтів з підозрою на ГКС. Визначення СБЗЖК, особливо в комбінації з іншими біомаркерами, має важливу цінність, коли діагностика ГКС ускладнена на тлі атипового клінічного перебігу, відсутності характерних змін на ЕКГ.

КЛЮЧОВІ СЛОВА: гострий коронарний синдром, серцевий білок, що зв'язує жирні кислоти

ЗНАЧЕНИЕ СЕРДЕЧНОГО БЕЛКА, СВЯЗЫВАЮЩЕГО ЖИРНЫЕ КИСЛОТЫ У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ

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С учётом роста количества больных с острым коронарным синдромом (ОКС) очень важно иметь для ранней диагностики и тактики ведения надежные биомаркеры. Для подтверждения у пациентов ОКС и оценивания долгосрочного прогноза осложнений и смерти изучается роль сердечного белка, связывающего жирные кислоты, (СБСЖК). СБСЖК позволяет определить инфаркт миокарда с изменениями на ЭКГ и без подъёма ST, помогает дифференцировать нестабильную стенокардию. Чувствительность СБСЖК выше чем у тропонинов, миоглобина и других биомаркеров, в то же время СБСЖК имеет высокую специфичность. Повышение уровня СБСЖК является независимым прогностическим фактором долгосрочных прогнозов у пациентов с подозрением на ОКС. Определение СБСЖК, особенно в комбинации с другими биомаркерами, имеет важную ценность,

когда диагностика ОКС затруднена на фоне атипичного клинического течения, отсутствия характерных изменений на ЭКГ.

КЛЮЧЕВЫЕ СЛОВА: острый коронарный синдром, сердечный белок, связывающий жирные кислоты

Mortality among patients with cardiovascular disease (CVD) is high and it tends to increase. One of the most important CVD is acute coronary syndrome (ACS), that may be divided into unstable angina (UA) and myocardial infarction (Ml) with the typical ECG progression with ST-elevation (STEMI) or non-ST-segment elevation (NSTEMI).

CVD is the reason of over 4 300 000 deaths a year in Europe, and it is 48 % of all cases of death. According to American College of Cardiology (ACC) there is about 1100000 MI per year in USA, and about 40 % of patients die [1, 2, 3].

There are a lot of patients with CVD in Ukraine. It is about 47,8 % of the population of the country. And CVD is the reason about 62,5 % of all cases of death. There was more then 50 000 cases of MI per year in Ukraine in 2010, and 10031 patients died [4].

CVD and ACS are caused more frequently by atherosclerosis of coronary arteries. So it is very important to identify healthy people and people with high risk, to influence modified risk factors, and to conduct primary and secondary prevention [4, 5].

With increasing numbers of patients with ACS it is very important to have reliable biomarkers for early diagnosis, to identify ACS and to optimize further tactics of patients management and prediction of the risk of recurrent ischemic damage and mortality.

Acute myocardial infarction (AMI) leads to cardiomyocytes necrosis because of lengthy ischemia, unlike UA. One of the main reason of high AMI mortality is untimely diagnostics [6-9].

The most frequent complaint in patients with ACS is chest pain. Chest pain is pressing or squeezing, it does not stop after taking nitrates (sublingually) or renew for a short time.

However, ACS patients may have atypical clinic and ACS may be present with nonspecific symptoms, such as weakness, dizziness, shortness of breath, or altered mental status or pain may be in neck, the lower jaw, shoulder, under the left shoulder-blade or in the epigastric region. Sometimes, it may be with the lack of air; heart palpitation; a feeling of discomfort in the left half of the chest; shortness of breath, generalized weakness, nausea, anxiety/fear. 20-30 % of patients with ACS have no pain, especially the elderly, patients with diabetics or hypertension [4-10]. At least every third patient has nonspecific complaints, such as weakness, dizziness, shortness of breath, or altered mental status. Factors, against that atypical manifestations of ACS are often observed, are older age, female gender, diabetes mellitus, arterial hypertension, and heart failure in history [8].

Furthermore, chest pain may also be observed in diseases of the cardiovascular system (pulmonary embolism, pericarditis, myocarditis, hypertension, etc.), stomach (GERD, stomach ulcer and 12 duodenal ulcer, acute pancreatitis, etc.), respiratory system (pneumonia, pleurisy, pneumothorax, etc.), nervous system (neurosis, neuralgia), musculoskeletal disorders (osteochondrosis of cervical and thoracic spine, Tietze syndrome), oncological diseases, that also requires timely differential diagnosis [8, 11, 12].

Diagnosis of ACS may be hampered by the presence of ECG changes (Bundle Branch Block, cardiosclerosis), or non-ST segment elevation [7, 8, 10].

According to ACCF/AHA recommendations, features of UA low probability are: age less than 70 years, the duration of pain less then 20 minutes, slow increasing of the pain, normal or unchanged ECG, no cardiac markers elevation [1].

Clinical examination provides minimal information for the evaluation of the ACS and it is often no diagnostic. Risk factors of ACS are old age, male sex, diabetes, MI, a history of previous episodes of stable angina and smoking. However, neither presence of them, nor absence of them does not exclude the possibility of ACS [8].

Standards of myocardial damage diagnosis and the main criterion for NSTEMI diagnosis are biochemical markers, which are very important for early verification, for risk stratification, for the selection of treatment and for the control of the disease progression

and for the treatment efficacy in patients with ACS.

Now the most widely used biomarkers in the diagnosis of ACS are cardiac troponins, that have high sensitivity with a slight myocardial injury and almost absolute specificity for myocardial damage.

Cardiac troponins are more specific and sensitive than traditional cardiac enzymes, such as creatine kinase (CK), its MB isoenzyme (CK-MB), and myoglobin [6-9, 13, 14]. However, cardiac troponin I (cTnI) can be discovered at least in 4-6 hours after the beginning of AMI; moreover, its level is not increased after 12 hours after the start, it is not optimal for the identification of patients with ACS without ST raising on ECG (NSTEMI) [6, 15-17]. 2 hours after AMI more highly sensitive cTnT compared with cTnI. However, cTnT analysis reflects the cell membrane permeability, not clinical threat of AMI [16].

Alternative markers are elaborated for patients with possible ACS. New biochemical markers reflect the different phases of the pathophysiological abnormalities in patients with ACS and, therefore, they can identify particular pathological processes to determine the specific therapy. Also more and more evidence of the multimarker approaches benefits are elaborated in patients with ACS [18].

The alternative marker is heart-type fatty acid binding protein (H-FABP), the role of which is actively investigated to confirm patients with ACS and to evaluate of the long-term prediction. H-FABP can predict a 6-year mortality after acute coronary syndrome [9, 18, 19].

H-FABP confirms the acute cardiomyocytes necrosis and also myocardium ischemia. H-FABP allows to define STEMI and NSTEMI, helps to differentiate unstable angina.

H-FABP is small size molecule (14 kDa) (in comparison with troponins, with the size 21-27 kDa and myoglobin with the size 17.2 kDa), that promotes more rapid exit of H-FABP than troponins from the cells. H-FABP is involved in fatty acids transport [4, 11, 20].

H-FABP is water-soluble protein. It contains in the cytoplasm of the cardiac myocyte. H-FABP is found in abundance in cardiomyocytes but is also expressed (to a lesser extent) in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary glands and placenta. H-FABP is approximately ten times more abundant in the cardiac myocyte than skeletal muscle [6, 8].

The main biological function of H-FABP is to facilitate intracellular translocation of long-chain fatty acids, which is usually hampered by the very low solubility of these compounds in aqueous solutions [21]. Mechanisms, that initiate and maintain increase free fatty acids (FFA) concentration after ischemia, are not clear. Some reasons are suggested: increased blood catecholamines in association with ischemia cause increasing FFA concentrations and then increased FFA release through adipose lipolysis, and although ischemia activates lipid hydrolysis within the heart [22].

After dissociation from plasma albumin, fatty acids are translocated through the lipid bilayer via passive diffusion, membrane-associated proteins, or a combination of both. The membrane-associated fatty acid transporters: fatty acid-binding protein (FABPpm), fatty acid translocase (CD36), and fatty acid transport protein (FATP) are involved. Intracellular fatty acids are bound to cytoplasmic H-FABP (FABPc) and, after activation to fatty acyl-CoA, to acyl-CoA–binding protein (ACBP). After dissociation from plasma albumin, fatty acids are translocated through the lipid bilayer via passive diffusion, membrane-associated proteins, or a combination of both. The membrane-associated fatty acid transporters fatty acid-binding protein (FABPpm), fatty acid translocase (CD36), and fatty acid transport protein (FATP) are involved. Intracellular fatty acids are bound to cytoplasmic H-FABP (FABPc) and, after activation to fatty acyl-CoA, to acyl-CoA–binding protein (ACBP) [21].

Although H-FABP include participation in signal transduction pathways, such as regulation of gene expression by mediating fatty acid signal translocation to peroxisome proliferator–activated receptors, and putative protection of cardiac myocytes against the detergent-like effects of locally high concentrations of long-chain fatty acids, particularly during ischemia [21].

H-FABP release into the blood as early as 30 minutes after cardiomyocytes injury, detectable in the circulation as early as 1-3 hours and return to baseline within 12-24 hours [14, 20]. The greatest significance of H-FABP

determination is within 12 hours. H-FABP is also found in urine as early as 1-2 hours following an ischemic damage [6, 8].

Normally H-FABP level is 0-6 μg/l, with myocardial ischemia 6-20 μg/l, with necrosis of cardiomyocytes 6-2000 μg/l [21].

The sensitivity of H-FABP testing is higher then troponin testing every time period after beginning of ACS [23].

First hours H-FABP sensitivity was higher then troponin at 18-32 %, and H-FABP specificity was almost the same, but if there was no ECG changes or Bundle Branch Block, H-FABP has higher sensitivity and specificity compared with troponins [14, 19, 23, 24].

H-FABP is not only independent prognostic marker, but it identifies high-risk patients who are troponin negative. H-FABP predicts long-term mortality and recurrent MI at troponin-negative patients with suspected acute coronary syndrome.

The peak of H-FABP is associated with increased risk of death and major negative cardiac events in patients with ACS and is not dependent for other installed clinical risk prediction and biomarkers.

Furthermore, elevated H-FABP levels were associated with increased risk of MI or recurrent ischemia within 30 days, especially in unstable angina patients, when they were determined the negative troponin I.

H-FABP for confirming AMI has a higher significance and sensitivity, compared with myoglobin, troponin, CK-MB elevation, and at the same time H-FABP has a high specificity [11].

H-FABP definition for the diagnosis of myocardial damage was effective without depending on sex, age and localization of myocardial injury. Thus, localization of MI does not affect the validity of the results, H-FABP sensitivity was higher for Q-positive MI than for Q-negative MI [10].

For practical using H-FABP determination express-methods are significant, they are based on immunochromatographic method that helps carry out a qualitative or quantitative assessment of the level of H-FABP, but not immunoassay, that allows conducting quantitative determination of H-FABP. Advantages of rapid tests are easy for techniques, compactness, efficiency of obtaining results [23].

When H-FABP, troponin I, myoglobin and B-type natriuretic peptide were estimated simultaneously, the degree of increased H-FABP worsen the prediction regardless of biomarkers values. The more H-FABP increasing was, the higher risk of cardiovascular complications was. Moreover, the level of H-FABP had the greatest predictive value within 48 hours after the onset of chest pain [18, 25-27].

Furthermore, predicting of mortality depends from increased levels of H-FABP, but it does not depend on the level of troponin [19].

Multimodal regression approach confirmed that the age, prior MI, heart rhythm disorder and the concentration of H-FABP remained statistically significant, as independent factors of development-term complications [18].

Also high H-FABP concentration is associated with a risk of cardiovascular complications, including heart failure, recurrent myocardial infarction, sudden cardiac death.

Furthermore, high H-FABP concentration worsen ventricular contractility, by disordering the splitting of mitochondrial proteins that impairs the production of energy by the mitochondria [19].

There is a gradient of increasing risk with elevated H-FABP concentration ($p < 0.001$). During the study of O'Donoghue M. et al. was confirmed that there was the correlation between the level of H-FABP and the risk of subsequent adverse clinical events, according to which the patients are divided into three groups, depending on the level of H-FABP: low risk (< 8 ng/mL), medium (from 8 to 16 ng/mL), and high (> 16 ng/mL). The relationship was established between the level of H-FABP and risk of death, recurrent MI, chronic heart failure, and these values [18].

Moreover, the elevated H-FABP level within 30 days also was associated with the risk of recurrent ischemia [18]. Normal levels of troponin and H-FABP were associated with very low risk of death [19].

During the study of Kilcullen N. et al. mortality within 1 year in patients with unstable angina in patients with H-FABP level < 5,8 micrograms/l was 2,1 %, and in patients with higher H-FABP levels was 22,9 % [19].

Determination of biochemical markers is not only the method, that complement methods of verification of the diagnosis of ACS, but it is an independent criterion in making a decision about invasive treatment strategy in the early

hours of NSTEMI. Combining of highly sensitive cardiac troponin and H-FABP significantly increases diagnostic accuracy of ACS, with greater sensitivity and specificity [11, 26].

CONCLUSIONS

Thus, H-FABP allows to differentiate ACS in the early period and also to assess prognostic significance for patients with ACS and further adverse complications. H-FABP has sensitivity higher than troponins and other biomarkers, furthermore it has high specificity. Definition H-FABP, especially in combination with other biomarkers, has the important value, when the diagnosis of ACS is difficult against the background of the atypical clinic, the absence of typical ECG changes, or presence of myocardial disorders. Increased H-FABP level is an independent prognostic factor in the long-term prognosis in patients with suspected ACS, especially among troponin-negative patients, even in combination with high sensitivity troponin tests.

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