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IMPORTANCE OF BIOMARKERS IN PREOPERATIVE EVALUATION OF CARDIOVASCULAR RISK

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Preoperative assessment of cardiovascular risk and timely diagnosis of myocardial damage are of great importance in the prevention of postoperative morbidity and mortality. The latest guidelines by the European Society of Cardiology (ESC) / European Society of Anesthesiology (ESA) emphasize the importance of the anesthesiologist in the multidisciplinary approach as well as the central role of biomarkers in the preoperative preparation of patients. In addition to the standard battery of biomarkers, which has been used for years to assess the cardiovascular risk, there are new biomarkers which promise more accurate and more specific preoperative assessment. Acta Medica Medianae 2016;55(1):70-75.

Key words: biological markers, risk assessment, H-FABP, human, MR-pro-ADM, human, miRNA

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Introduction

The fact that anesthesiologists are in daily contact with patients who are at increased cardiovascular risk has led to the necessity of the specific guidelines for preoperative determination of cardiovascular risk in everyday clinical practice. The risk of perioperative complications depends on patient's preoperative condition, the prevalence of comorbidity and urgency, extensiveness, type and duration of surgery (1, 2). Perioperative patient's risk can be estimated based on the severity of existing heart failure, presence of arrhythmia, the occurrence of recent myocardial infarction, patient's age, etc. More specifically, cardiovascular complications may arise in the patients who have verified or asymptomatic ischemic heart disease, left ventricular dysfunction, arrhythmias and valvular heart disease, and who are undergoing operations with prolonged hemodynamic and cardiac stress (2). Postoperative development of arterial hypertension, cardiac insufficiency and arrhythmia mainly occurs two days after the operation, while the risk of perioperative myocardial infarction persists for five or six postoperative days (3). The number of patients at risk of cardiovascular complications increases each year. Around the world, non-cardiovascular surgeries are associated with the complication rate of 7-11% and with mortality degree of 0.8-1.5% (4). As 42% of these cases are caused by cardiovascular complications, therefore timely diagnosis of myocardial damage is crucial (4, 5). One of the most important parameter for cardiovascular risk assessment is the use of adequate battery of biomarkers, whose significance is enhanced in the latest guidelines.

General regulations of preoperative cardiovascular risk assessment

Anesthesiologists can be led first by clinical signs and their experience in the preoperative assessment of cardiovascular risk. One of the main items in the first contact with the patient is to assess functional capacity and it represents an extremely important step in the preoperative assessment of cardiovascular risk. It is measured in metabolic equivalents (MET). Functional capacity below 4 METs indicates poor functional capacity and is considered to indicate a high risk of postoperative cardiac complications. If the functional capacity is low or unknown, the clinician is referred to the risk factors in combination with the type of the operation in order to determine the postoperative risk (2, 6).

In the past 30 years, a number of risk assessment scales have been developed, however, the most frequently used are those by the authors Goldman, Detsky, and Lee (2, 7-10). The so-called Lee score for cardiovascular risk assessment has emerged as a modification of the Goldman score. This evaluation places six independent predictors in focus, such as: high-risk operation, history of ischemic heart disease, history of congestive heart

failure, history of cerebrovascular disease, preoperative insulin therapy and preoperative serum creatinine> 2.0 mg / dL (11).

Although Lee score is the most commonly used today, other methods of assessment are developed. The use of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database has helped for a new model in the form of an interactive calculator to predict intraoperative / postoperative myocardial infarction and cardiac arrest to be developed (12, 13). Studies conducted in order to assess the quality of this interactive calculator indicated that hospitals that have introduced it in their practices had a smaller number of complications, as well as reduced treatment cost (14).

Biomarkers in cardiovascular risk assessment

The risk of developing cardiovascular complications after non-cardiac interventions has declined in the last 30 years as a result of the development of new anesthetic and surgical techniques. However, extensive analysis suggests that the clinical evaluation of patients is not enough because about 50% of deaths are caused by cardiovascular complications which occur in patients who have cardiovascular diseases in history (15). For this reason, the increasing importance in practice is given to cardiac specific biomarkers. Different biomarkers exhibit a variety of patho-physiological mechanisms of cardiovascular diseases, such as oxidative stress, myocardial stress, heart muscle damage, activation of neurohormonal pathways, apoptosis, etc. Due to this fact the modern currents in anesthesia practice support the so-called multimarker approach (16, 17).

Biomarker is a characteristic which can be objectively measured and which represents an indicator of a certain biological process. Characteristics of an ideal biomarker are: high levels in the heart tissues, absence in other tissues, absence in the serum of healthy people, quick release for early diagnosis, long half-life in order to have late diagnosis and positive results in clinical trials (1, 18, 19).

When the evaluation of perioperative risk is in question, biomarkers can be divided into markers which concern myocardial ischemia and damage, inflammation and left ventricular function. The most commonly used biomarkers in clinical practice are: aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), hydroxybutyrate dehydrogenase (HBDH), creatine kinase MB isoenzyme (CK-MB), CK-MB mass, myoglobin, carboxy anhydrase, glycogen phosphorylase BB, troponin T (TnT), troponin I (TnI), etc. (1).

Biomarkers in the guidelines of europaen society of cardiology (ESC)/ european society of anesthesiology (ESA)

The latest guidelines by the European Society of Cardiology (ESC) / European Society of Anesthesiology (ESA) point to the great importance of troponin (cTnI and cTnT), BNP and NT-proBNP in the assessment of myocardial damage.

Cardiac troponins T and I (cTnT and cTnI) are the most important markers for the diagnosis of myocardial infarction in the presence or absence of renal failure (20). Studies point out that even the smallest increase in cTnT in the perioperative period indicates a clinically significant myocardial damage that worsens postoperative prognosis (21, 22). Troponin is also considered to be an ideal biomarker for postoperative monitoring of cardiovascular complications (23).

Markers of inflammation preoperatively reveal patients with an increased risk for the development of the unstable coronary plaque. BNP and NT-proBNP are formed in cardiomyocytes as a response to the occurrence of the myocardial wall damage (24). Their preoperative determination indicates the possibility of development of cardiovascular complications after major non-cardiovascular surgery (1, 2). A number of studies point to the fact that BNP and NT-proBNP give a prognosis of cardiovascular risk in patients who suffer from some type of heart disease as well as in healthy individuals (21).

Blankenberg et al. have examined the effectiveness of 30 biomarkers in the MORGAM study. The results showed that the optimal combination of NT-proBNP, CRP and Troponin leads to the high specificity in the risk prediction (25).

Determination of serum biomarkers in patients undergoing a non-cardiovascular surgery is not used routinely, but is considered for patients at high risk (MET≤4) (2).

Novel biomarkers

The availability of new research methods and procedures for testing different biological pathways opens new possibilities for efficient and specific detection of biomarkers (25).

Development of novel biomarkers, such as: high-sensitive troponin (hsTnT), heart-type fatty acid binding protein (hFABP), survivin, mid-regional fragment of proadrenomedullin (MR -PAMP), micro RNA (miRNA) will improve the assessment of myocardial damage in the future (1, 21).

Weber et al. have pointed out that hsTnT adds to the significance in the prediction of cardiovascular risk of the patients in combination with Lee index and the use of NT-proBNP as highly specific biomarkers (21). As a result of this study, the use of NT-proBNP and hsTnT as the most specific combination of preoperative assessment of risk is suggested.

Cytoplasmic FABP represents a family of transport proteins which facilitate the transport of fatty acids through the membrane. H-FABP represents a tissue-specific protein for heart and brain tissue. It is present in the cardiac tissue in high concentrations and is released rapidly into the circulation following damage of the heart tissue (26-28).

Elevated levels of H-FABP are present in the circulation 2 to 3 hours after the damage and return to normal within 12 to 24 hours after the initial

event (26, 29). Studies have shown that H-FABP is more specific in the diagnosis of myocardial injury than cTnT in the patients with chronic heart failure (30), while it is the most specific biomarker besides hsTnT in the evaluation of patients with chest pain in primary care (31). These data make H-FABP highly reliable biomarker for the assessment of myocardial tissue damage in acute coronary syndrome and in assessing minor damage of myocardial tissue in the patients with heart failure and unstable angina pectoris (32). In the first 6 hours after the acute heart tissue damage H-FABP has proven to be more specific in relation to the TnT (33-35).

It is important to note that H-FABP is present in skeletal muscles at low concentrations; however, clinicians believe that damage of skeletal muscles during surgery can not lead to the occurrence of high levels of H-FABP in serum (30).

Mid-regional fragment of proadrenomedullin (MR-PAMP) is released at higher concentrations compared to the adrenomedullin, it is inactive, has a greater half life, and can be used as a routine biomarker (36-39). The level of MR-PAMP is elevated in patients with ischemic heart disease, congenital heart failure and atherosclerosis and is a significant predictor of mortality (40). Comparative analysis of 12 biomarkers demonstrated that MR-PAMP, NT-proBNP, GDF-15 and cystatin C are the most significant predictors of cardiovascular complications in patients with stable angina pectoris (41). The so-called BACH (Biomarkers in Acute Heart Failure) study showed that MR-PAMP has greater significance in the prognosis of mortality within 90 days for patients diagnosed as acute heart failure than BNP (42, 43).

Micro RNA (miRNA) is a recently discovered class of endogenous, small, non-coding RNA molecules that are extremely stable in the circulation (44-46). Studies indicate exceptional character of miRNA in the processes of differentiation, growth, proliferation and apoptosis of cells, and it is considered that free miRNA molecules can be found in patient's blood due to liberation from the cells after the process of necrosis (29, 47, 48). MiRNA expression in myocardial cells is extremely high. Some of the miRNA expressed in heart tissue are: miR-21, -29a, -129, -210, -211, -320, -423 and -let7c (49). The most important role in the development of myocardial hypertrophy have: miR-1, -21, -133, -195 and -208 (29). Elevated expression of miR-126, -145, -146, -155 and -210 indicates the presence of atherosclerosis (50-52).

Devaux et al. showed that the concentration of miR-208b, -499 and -320 is significantly increased in patients with acute myocardial infarction, as well as that they do not have a significant diagnostic value without the simultaneous evaluation of the concentration of cTnT or hsTnT (53). miR-208a can serve as a new biomarker for early detection of myocardial damage (54). Circulating miR-1, -133, and -499 -208b may be of an importance in the case of acute myocardial infarction; however, they do not have a greater significance than cTnT (55). Current research indicates the greatest significance of miR-499 as a novel biomarker for the identification of perioperative myocardial infarction in cardiac surgery (56).

MiRNA still has a small diagnostic potential if it is interpreted independently from troponin. Another negative side is that there are no commercial rapid tests and standardized protocols available, and testing the presence of miRNA in the patient's blood takes too much time (49).

Mapping of the human genome indicated the presence of single nucleotide polymorphisms (SNPs) which are associated with cardiovascular disease and risk phenotypes. Until today, more than 30 genetic loci are known. The fact is that the exact mechanisms that connect most of these SNPs with cardiovascular disease are not yet fully understood (25, 57, 58).

Conclusion

Primary prevention of cardiovascular complications after non-cardiac surgeries relies on the ability to identify the individuals with an increased risk before mentioned complications arise. The latest research in the field of circulating, genetic and biomarker imaging have indicated their increasing significance and specificity. The fact is that no biomarker can be used in the assessment of risks isolated, but can only indicate patients at high risk. The so-called multi-marker approach is considered to be the most appropriate for clinical evaluation. It is believed that the new set of biomarkers will lead to the opportunities for their individual use.

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ZNAČAJ BIOMARKERA U PREOPERATIVNOJ PROCENI KARDIOVASKULARNOG RIZIKA

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Preoperativna procena kardiovaskularnog rizika i pravovremena dijagnoza oštećenja miocita su od izuzetnog značaja u prevenciji postoperativnog morbiditeta i mortaliteta. Najnovije smernice propisane od strane European Society of Cardiology (ESC)/European Society of Anesthesiology (ESA) ističu značaj anesteziologa u multidisciplinarnom pristupu kao i centralnu ulogu biomarkera u preoperativnoj pripremi bolesnika. Pored standardne baterije biomarkera, koji se godinama unazad koriste za procenu kardiovaskularnog rizika, postoje novi biomarkeri koji obećavaju tačniju i specifičniju preoperativnu procenu. Acta Medica Medianae 2016;55(1):70-75.

Ključne reči: *biološki markeri, procena rizika, H-FABP, humani, MR-pro-ADM, humani, miRNK*