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Perioperative changes of levels of Interleukin–6 and Endothelin–1 in elderly patients during anesthetic management of surgical interventions

Abstract: The work is devoted to the study of perioperative change of markers of damage to the cardiovascular system in elderly patients during anesthetic management of surgical interventions.

Keywords: elderly patients, ischemic heart disease, Interleukin–6, Endothelin–1.

The rapid development of medicine leads to an increase in life expectancy, leading to an ever-growing number of elderly. The increasing number of elderly patients is a major problem for Surgery and Anaesthesiology. It is expected that in Europe by 2020 older people may reach 30 %, of which 70 % will suffer from coronary heart disease, and the number of surgical non-cardiac interventions in this group can reach 25 % of the total. For these patients is characterized by a large number of comorbidities generalized decrease in vital body functions, which significantly increases the operational risk and the development of intra- and postoperative complications, such as neurological disorders, acute lung injury, myocardial dysfunction, acute renal and hepatic failure [1, 630].

Appropriate preoperative management of patients with concomitant somatic pathology leads to minimize operational risk and mortality during anesthesia and surgery. With operations in elderly and senile important point is the choice of the method of anesthesia, which is largely dependent on factors such as age and general condition of the patient, the presence of a severity and comorbidity, emotional status of the patient, the volume of future surgery planned.

At that advanced age is taken into account as a factor that increases the operational and anesthetic risk, even in the absence of comorbidities. Anesthetic risk is increased in the presence of: hypertension, coronary heart disease, chronic congestive heart failure, chronic nonspecific lung diseases, diabetes, peripheral vascular disease, kidneys, joints, changes in the central nervous system.

The main mechanisms leading to the development of acute coronary syndrome, unstable angina and acute myocardial infarction, are atherosclerosis and thrombosis.

Studied a variety of risk factors for development and progression of coronary artery disease, but has not yet been fully explained, that is the root cause and the main trigger of acute coronary events. In the widely discussed recently inflammatory theory of atherosclerosis.

Numerous clinical-pathological and experimental studies in recent years indicate that the arterial wall in atherosclerosis is affected with the participation of immune mechanisms. As a result of inflammation occur thickening of the inner layer of the artery, necrosis of the core layer, segmental proliferation of cells of the inner and middle layers, deposition of lipids and calcium, blood clots in the pathologically altered segmental

portion of the artery. Destabilization of atherosclerotic plaques is determined by the high activity of the chronic inflammatory process.

Endothelial dysfunction plays an important role in the development of coronary artery disease. In the endothelium produces a number of substances with vasoconstrictor and procoagulant activity, as well as factors that have an anticoagulant and vasodilator effects. Intact endothelium has anticoagulant, antithrombotic and antiplatelet activity and ensures the free flow of blood through the blood vessels. When the situation is the opposite of CHD, dominated by products of endothelial factors have procoagulant and proagregant effect [2, 233].

Synthesis of endothelin–1 determines endothelial dysfunction is a trigger in the pathogenesis of CVD, and well ahead of the appearance of clinical signs of disease. Endothelin-1 is a potent and long-acting vascular constrictor. Elevated levels of endothelin-1 observed in acute myocardial infarction and congestive heart failure. Endothelin–1 is not the only marker for vasoconstriction of coronary vessels, and coronary artery disease, but also has a deleterious effect on the cardiac muscle, which could lead to decomposition of cardiac complications in the perioperative period.

IL–6 — protein molecular weight of 26 kD, relates to a multifunctional cytokine and stimulates the proliferation of T-lymphocytes, macrophages, endothelial cells. Acts as a growth and differentiation of B-lymphocytes, hepatocytes and neurons, activated endothelial cells, monocytes and procoagulant reactions occur. IL–6 modulates immunological processes, inflammation, proliferation, and apoptosis [4, 293].

The goal was to examine and assess endothelial function and dynamics of the level of pro-inflammatory interleukin-6 in elderly patients with concomitant cardiovascular disease in the pre- and postoperative non-cardiac surgery.

Material and methods

Clinical studies performed in the clinic of the Department of Anesthesiology, Intensive Care and Emergency Medicine FPO SE «Dnepropetrovsk Medical Academy» Health of Ukraine (Head. Department. — Professor, MD O.M. Klyhunenko). Clinical base — KU «Sixth City Hospital», Department of Anesthesiology and Intensive Care. Inclusion criteria were: patients of both sexes; age from 60 to 85 years; the physical status of patients — ASA II-ASA III;

carrying out elective surgery expectancy abdominal under total intravenous anesthesia.

Exclusion criteria were: failure of a patient to participate in the study; the physical status ASA IV class, a history of polyvalent allergy, decompensated diabetes mellitus, acute stroke, epilepsy, organic damage to the central nervous system;

The study involved 55 patients aged 60 to 82 years who came to the hospital for elective surgery in the abdominal cavity. At the stage of anesthesia preparation for surgery all the studied parameters were taken into account together in a single group, patients were further divided into 2 subgroups based on sexgender — women (n = 22) and men (n = 23). Patients were representative for the main demographic indicators such as gender, age, severity of condition classification ASA, body mass index.

Table 1. – Clinical characteristics of patients

Number of patients	55
Gender male/female	23/22
The average age	of 72.5/73.62
Condition according to ASA II/III	32/23
Body mass index	28.1 ± 6.86
Condition for EuroScore	> 5 %
The level of cardiovascular risk	high

Used accounting demographic and metric parameters, comorbidities accounted for systems: cardiovascular, respiratory, urinary, endocrine system, taking into account prevailing hemostasis. Preoperative preparation of elderly patients with cardiovascular pathology was conducted according to the recommendations ESC Guidelines (2009) Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery [3].

Extended preoperative examination and treatment required patients with the following conditions: coronary artery disease, angioplasty and stenting of the coronary arteries in history, coronary bypass surgery history, cardiac arrhythmias and conduction, including presence of implanted devices, heart failure, essential hypertension, patients constantly receiving vitamin K antagonists (VKA), patients without clinical signs of heart disease, but with risk factors for coronary heart disease.

In addition to the ASA classification we deteriorated risk stratification of cardiac events with: evaluation of surgical risk (the risk of myocardial infarction or death from cardiac causes within 30 days after surgery) [ACC/AHA], risk stratification depending on the condition of the patient due to functional status of the patient, expressed in metabolic equivalents, scale EuroScore.

Preoperative examination consisted by identification and assessment of the severity of disease of the cardiovascular system: ischemic heart disease (acute coronary syndrome, myocardial infarction, angina pectoris, condition after surgery on the heart), CHF, life-threatening cardiac arrhythmias, presence of implanted devices (pacemaker/ICD/CPT), significant comorbidities, diabetes mellitus (DM), chronic

obstructive pulmonary disease (COPD), chronic renal failure (CRF), anemia, the defeat of the main vessels of the head and neck, and others.

Furthermore, the purpose of the examination was to assess efficacy of the therapy and the need for its correction before surgery.

Methods of preoperative evaluation of patients: complete blood count, including platelet count, urinalysis, X-ray (fluoroscopy) chest, blood glucose, evaluation of hemostasis (prothrombin time, activated partial thromboplastin time,) assessment of renal function (glomerular filtration rate, creatinine clearance, potassium, sodium, creatinine, urea (Cockcroft-Gault), resting ECG.

All patients received pharmacological treatment of myocardial infarction and hypertension to include nitrates, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, some patients — with the use of calcium antagonists and diuretics.

Laboratory studies with determination of endothelin-1 and IL-6 in EDTA-plasma by enzyme immunoassay (Biomedica and set “Elisa Diameb” (France) were carried out on the basis of “Diagnostic Centre Medical Academy.” Measurements of IL-6 levels were performed by means of commercially available enzyme-linked immunosorbent assays (Orgenium Laboratories, Vantaa, Finland). The appropriate volume of sample or standard was applied to a 96-well microtiter plate precoated with the corresponding monoclonal antibody. After the aspiration of the wells, plates were washed with a specific surfactant provided by the manufacturer. A solution of enzyme-linked polyclonal antibody and substrate was added to each well. The optical density of each well was read at the appropriate wavelength.

Study was conducted in accordance with the requirements of the Ethics Committee. Statistical processing of the results was performed using the package MS Excel 2007. Data are presented as $M \pm m$. Statistically significant value was considered $p < 0.05$.

Results and discussion

In conducting preoperative examination of patients with regard to operational risk for anesthesia — ASA was found that the severity of 58 % of patients meet the second degree of risk, 42 % of elderly patients — III degree for ASA.

In the analysis of comorbidity coronary heart disease in the form of diffusion and atherosclerotic cardiosclerosis met in 30.6 and 58.3 % of cases, respectively; Hypertensive heart was available in 4.37 % of patients, arrhythmias — in 11.6 %. Additional pathology of the respiratory system as concomitant highlighted in 27.4 % of patients, disorders of the endocrine system — 3 %, urinary — 8.51 % in elderly patients. Varicose veins of the lower limbs suffered 11.4% of patients. Almost 25 % of elderly patients with abdominal pathology was observed joint presence of comorbidity on several systems.

It is known that the synthesis of endothelin-1 largely determines endothelial dysfunction, which is a trigger in the pathogenesis of cardiovascular disease (atherosclerosis,

hypertension, thrombosis), and well ahead of the onset of clinical signs of disease. Endothelin-1 is a potent and sustained vascular constrictor of efficiency, which is much higher than the potential vasoconstrictor angiotensin II (A II) (Randall M., 2001), for which he received a fair description of "the most powerful of all known short-lived, but long-term mediators." Cardiac effects of endothelin-1 (vasoconstriction and ischemia) realized through receptor system (receptor subtype A), localized mainly in the smooth muscles of coronary arteries. A number of receptors sensitive to endothelin-1 was found in the membranes of cardiomyocytes and their number increases along with increased levels of endothelin-1 levels in terms of experimental and clinical myocardial infarction, which gives reason to assume a direct effect of the peptide on the myocardium. Increased endothelin-1 content in peripheral blood observed in acute myocardial infarction and heart failure. The concentration of immunoreactive endothelin-1 significantly increased in patients with essential hypertension stage II–III hypertension and symptomatic. There is evidence of predominantly local production of endothelin-1 in heart failure and cardiac arrhythmia.

Table 2. – The value of endothelin-1 and interleukin-6 in the stages of research

	1 stage	2 stage	3 stage
The level of endothelin-1 marker, fmol/ml	0.556 ± 0.02	0.627 ± 0.01*	0,582 ± 0.013*
The level of interleukin-6 marker, pmol/ml	4.81 ± 0.9	35.39 ± 13.4*	10,47 ± 1.2*

Note: * – $p < 0.05$.

In the preoperative period, the level of interleukin-6 in all patients exceeded the reference values of 2 times. At 1 day after the operation level of the marker, which we explored, increased compared with preoperative values up to 10 times. By the fifth days of positive dynamics in the form of a reduction of interleukin-6 is almost 3.5 times as compared with the early postoperative period, but did not reach the values before surgery.

Conclusions

In elderly patients with concomitant cardiovascular disease, which is planned to conduct non-cardiac surgery showed a significant increase in the levels of endothelin-1

Thus, we can assume that endothelin-1 is not only a marker and the expression of vasoconstriction of coronary vessels and coronary heart disease, but also has some damaging effects on the heart muscle itself, which can lead to the development of cardiac complications in the perioperative period.

We have compared the levels of endothelin-1 in elderly patients with concomitant cardiovascular pathology in pre- and postoperative 1 day after surgery and for 5 days. In the preoperative period, the level of endothelin-1 in all patients was significantly increased by 45 % compared with the reference values (values of endothelin-1 in plasma obtained during the examination of healthy persons according to the literature, were 0.1–0.35 fmol/ml) (Table. 2). Thus, we have received confirmation of laboratory manifestations of cardiovascular disease with signs of endothelial dysfunction in patients who planned noncardiac surgery. At 1 day after the operation level marker that we studied, increased significantly compared with the preoperative values. By the fifth day postoperative levels of endothelin — 1 in both study subgroups was significantly decreased to preoperative baseline, but did not reach the reference values.

and proinflammatory interleukin-6 in plasma, indicating the presence of endothelial dysfunction and activation of pro-inflammatory system.

In the early postoperative period, the vascular endothelium responds to the release of vasoconstrictor and pro-inflammatory markers in the surgical trauma,

By the fifth day of the postoperative period with signs of endothelial dysfunction and inflammation in elderly patients decrease, but not disappear completely.

In order to clarify the mechanisms of influence and effects of existing endothelial dysfunction and inflammatory further research is needed.

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