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The effect of two different anesthesia regimens on annexin V levels and early postoperative complications in CABG

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Introduction. Annexins are a family of phospholipid-binding proteins that reversibly, specifically, and with high affinity bind to cells expressing phosphatidylserine during apoptosis. This phenomenon may be important in the pathogenesis of early postoperative cardiac complications.

The aim of the study was to analyse the effect of anaesthetic strategy on the dynamics of annexin V during coronary artery bypass graft (CABG) with cardiopulmonary bypass (CPB) as well as the dependence of direct clinical results on the expression of annexin V.

Materials and methods. The study included 30 patients with coronary artery disease (CAD) who underwent coronary artery bypass grafting with CPB. According to the anaesthetic management, all patients were divided into two groups: the study group (13 patients) – multimodal low-dose opioid anaesthesia; and the control group (17 patients) – high-dose opioid anaesthesia. The determination of the level of annexin V in the blood was performed before CPB and after sternum closure.

Results. The level of annexin V was 1.5 times (i.e., significantly) lower in the multimodal low-dose opioid anaesthesia group at the end of the surgery as compared to the high-dose opioid anaesthesia group. A negative correlation of weak strength ($r = -0.117$, $p = 0.523$) was found between the levels of annexin V and IL-6. One-way analysis of variance showed that patients who had low cardiac output syndrome in the postoperative period had a significantly higher level of annexin V after CPB ($p = 0.001$).

Conclusions. The use of multimodal low-dose opioid anaesthesia is characterized by a lower level of annexin V compared to high-dose opioid anaesthesia.

Key words: apoptosis, cardiopulmonary bypass, coronary artery bypass grafting, ischaemic-reperfusion syndrome.

Vliv dvou odlišných anestetických režimů na hladiny annexinu V a časné pooperační komplikace po CABG

Úvod. Annexiny patří do rodiny proteinů vázajících fosfolipidy, které se během apoptózy reverzibilně, specificky a s vysokou afinitou váží na buňky exprimující fosfatidylserin. Tento jev může mít význam v patogenezi časných pooperačních kardiálních komplikací.

Cílem studie bylo analyzovat vliv anestetické strategie na dynamiku annexinu V během aortokoronárního bypassu (CABG) s kardiopulmonálním bypassem (KPB), jakož i závislost přímých klinických výsledků na expresi annexinu V.

Materiál a metody. Do studie bylo zařazeno 30 pacientů s ischemickou srdeční chorobou, kteří podstoupili aortokoronární bypass s KPB. Podle anestetického režimu byli všichni pacienti rozděleni do dvou skupin: studijní skupina (13 pacientů) – multimodální anestezie s nízkou dávkou opioidů; a kontrolní skupina (17 pacientů) – anestezie s vysokou dávkou opioidů. Stanovení hladiny annexinu V v krvi bylo provedeno před KPB a po uzávěru sterna.

Výsledky. Hladina annexinu V byla na konci operace ve skupině multimodální anestezie s nízkou dávkou opioidů 1,5krát (tj. signifikantně) nižší než ve skupině anestezie s vysokou dávkou opioidů. Mezi hladinami annexinu V a IL-6A byla zjištěna

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negativní korelace slabé síly (r = –0,117, p = 0,523). Jednorozměrná analýza rozptylu ukázala, že pacienti, kteří měli v pooperačním období syndrom nízkého minutového výdeje, měli po KPB signifikantně vyšší hladinu annexinu V (p = 0,001).
Závěr. Použití multimodální anestezie s nízkou dávkou opioidů je charakterizováno nižší hladinou annexinu V ve srovnání s anestezií s vysokou dávkou opioidů.

Klíčová slova: apoptóza, kardiopulmonální bypass, aortokoronární bypass, ischemicko-reperfuzní syndrom.

Introduction

Today, many studies support the safety of the clinical use of low-dose opioids (either short-acting or long-acting) in cardiac surgery patients and highlight the possibility of more conservative opioid use in cardiac surgery, given the potential for faster recovery and lower cost, as well as considering the recent opioid crisis and rise in opioid addiction [1, 2].

Lidocaine is the most common component of most modern multimodal low-dose opioid regimens. Lidocaine is unique in that it has been shown to significantly improve important Enhanced Recovery After Surgery (ERAS) outcomes, namely early ambulation and feeding, early fitness for discharge, and increased patient satisfaction [3].

However, the scientific literature has not yet sufficiently described the effect of multimodal low-dose opioid anaesthesia on the activation of the inflammatory response and apoptotic reactions, as well as their relationship with the final clinical results.

Cardiopulmonary bypass (CPB) and aortic cross-clamping during cardiac surgery trigger internal and external pathways of apoptosis activation due to the production of pro-inflammatory cytokines and ischaemic reperfusion damage, which can lead to the development of early postoperative complications [4].

Thus, given the activation of the systemic inflammatory response during cardiac surgery, a number of inflammatory mediators can activate apoptotic processes, including reactive oxygen species (ROS), TNF-α, cytokine release, NO, Fas ligands, and neurohumoral factors such as angiotensin II and p53 protein [5]. These substances potentiate the cascade of cellular reactions of the entire body. As Meldrum D.R. et al. point out in their study, elevated levels of the 'death-ligand' TNF-α and Fas in blood serum, as well as induction of apoptosis after CPB, cause secondary myocardial damage [6]. Annexin V and phosphatidylserine (PS) play a significant role in cellular damage involving the above mechanisms.

In normal healthy cells, PS is located on the inner layer of the plasma membrane, but during early apoptosis and inflammatory activation of cells, it passes from the inner to the outer surface of the membrane as a result of the action of the activated proteolytic enzyme caspase-3, where it functions as an 'eat me' signal to ensure early recognition and phagocytosis [7]. At the same time, the body activates the 'protective' mechanisms of homeostasis. As reported by Matsuda R. et al., with the development of myocardial ischaemia, an increase in endogenous annexin V is observed in blood plasma, which is absorbed in the area of ischaemia [8]. This position is also confirmed in the paper of Kenis H. et al., who posit that annexin V binding to PS prevents cell uptake by macrophages and arrests the development of apoptosis [9].

Annexins are a family of phospholipid-binding proteins; annexin V reversibly, specifically, and with high affinity binds to cells expressing PS [10]. In addition to its detectable antithrombotic effects, annexin V is also known to have diagnostic properties in visualizing cell death [11, 12].

Ewing M. M. et al. observed a decrease in the inflammatory response after administration of annexin V, which had a potential therapeutic effect in preventing vascular intimal hyperplasia [13]. Moreover, in a mouse model of myocardial infarction, de Jong R. C. M. et al. showed that the administration of exogenous annexin V was characterized by a significant (27%) decrease in the area of myocardial infarction and a 29% increase in the left ventricular ejection fraction compared to the controls [14].

Furthermore, Ravassa S. et al. reported that, in patients with heart failure, higher baseline plasma levels of annexin V were associated with a lower left ventricular ejection fraction [15]. It is important to note that the levels of annexin V in plasma and myocardium strongly correlate and increase dose-dependently [16].

However, to date, no studies have examined the dynamics of endogenous annexin V in coronary artery bypass grafting (CABG) performed with CPB and its direct effect on clinical outcomes.

The aim of the study was to analyse the effect of high-dose versus multimodal low-dose opioid anaesthesia on the dynamics of annexin V and low cardiac output syndrome (LCOS) and postoperative atrial fibrillation (POAF) during CABG with CPB.

Materials and methods

The study was conducted in accordance with the seventh revision of the principles of the Declaration of Helsinki on Human Rights (2013). Informed consent was obtained from all patients. The study was approved by the appropriate Ethical Review Board of Shupyk National Medical Academy of Postgraduate Education № 10 as of 05/11/2020.

The study included 30 patients with coronary heart disease (CHD) who underwent CABG at the Heart Institute of the Ministry of Health of Ukraine with the application of 2–3 anastomoses with CPB from January 2020 to January 2021. The mean patient age was 59.0 years (55.0; 62.0) (54 to 63 years). The average body weight was 92.1 ± 17.2 kg (79 to 112 kg). The number of men was 23 (76.7%) and there were 7 women (23.3%). The median surgical risk according to EuroSCORE II was, on average, 3.45% (2.15%; 4.05%).

According to the scheme of anaesthetic support, all patients were randomly divided into two groups. The study group using multimodal low-dose opioid anaesthesia comprised 13 patients. Induction consisted of intravenous administration of propofol at a dose of 1.5 mg/kg of 40 mg at intervals of 15–20 seconds. Following the administration of hypnotics, all patients were administered intravenous fentanyl at a dose of 1–1.5 μg/kg. After achieving an adequate

level of anaesthesia, muscle relaxation was achieved by intravenous administration of pipecuronium bromide at a dose of 0.1 mg/kg, followed by tracheal intubation. To maintain anaesthesia, sevoflurane was inhaled along a semi-closed circuit with the target maintenance of its concentration according to the age indicator of the minimum alveolar concentration (MAC). The target concentration of sevoflurane was calculated by using the formula: $MAC_{awake} = 0.34 \times MAC_{table} \times 2$, where MAC_{awake} is the minimum alveolar concentration in the patient's exhaled air, and MAC_{table} – tabular value of the MAC according to age. Before starting surgery, a subnarcotic dose of ketamine (0.5 mg/kg) and lidocaine 1 mg/kg bolus were added intravenously, with simultaneous adjustment of a continuous infusion of the latter at a dose of 1.5–2 mg/kg/h and dexmedetomidine of 0.7 µg/kg/h. Lidocaine infusion was continued throughout the operation until the patient was admitted to the intensive care unit. Analgesia was maintained during surgery by the administration of fentanyl. The average dose of fentanyl used for the entire duration of anaesthesia was 1.0 µg/kg/hour.

The control group with high-opioid anaesthesia comprised 17 patients. Induction into anaesthesia in patients in this group consisted of intravenous administration of propofol at a dose of 1.5 mg/kg of 40 mg at intervals of 15–20 seconds. Following the administration of a hypnotic, all patients were administered intravenous fentanyl at a dose of 1–1.5 µg/kg. After achieving an adequate level of anaesthesia, muscle relaxation was achieved by intravenous administration of pipecuronium bromide at a dose of 0.1 mg/kg, followed by tracheal intubation. Maintenance of anaesthesia – sevoflurane 1.5–2 MAC, analgesia was provided with fentanyl (8–10 µg/kg/hour), and muscle relaxation was achieved with pipecuronium bromide at a dose of 0.1 mg/kg.

Exclusion criteria of patients: emergency surgery; redo surgery; patients with 1 aorto-coronary anastomosis and those with 4 or more aorto-coronary anastomoses; a EuroSCORE II value above 5%.

Mechanical ventilation of the lungs in the patients studied in both groups was performed with an air-oxygen mixture with 50% FiO_2 in the normal ventilation mode with monitoring of blood gas composition (the mean value of arterial blood pCO_2 was 35–40 mm Hg).

CPB was performed on a SYSTEM 1 (Terumo, USA) apparatus using AFFINITY disposable membrane oxygenators (Medtronic, USA) under conditions of moderate hypothermia (+32 °C). CPB blood flow was maintained at the level of 2.4–2.5 l/min/m^2. Normovolaemic haemodilution was used during CPB with an average haematocrit level of 25–30% and haemoglobin of 80–90 g/l. Blood clotting was evaluated by activated clotting time (ACT), maintaining it in the range of 500–600 seconds.

Biochemical blood samples were taken from the central venous access prior to the beginning of CPB and at the end of the operation (during sternum closure). Serum and plasma samples were stored at –20 °C.

Annexin V and IL-6 levels were the primary clinical outcome. Annexin V in plasma was measured using a commercially available Annexin V Elisa kit (Zymutest Annexin V, Hyphen BioMed, France) with a standard range of 0.5–10.7 pg/ml and a sensitivity of 0.1 pg/ml. During statistical processing, annexin V values under the lower sensitivity limit of the method were taken as 0.05 pg/ml. Determination of IL-6 level in the blood was performed with the ELISA method using an Immunotech set (Coulter Company) manufactured in France.

Early postoperative complications such as LCOS and POAF were the secondary clinical outcomes. LCOS includes decreases in the cardiac index (CI) to < 2.0 l/min/m^2 and a systolic blood pressure of < 90 mm Hg, in conjunction with signs of tissue hypoperfusion (i.e., cold periphery, clammy skin, confusion, oliguria, elevated lactate level) in the absence of hypovolaemia. Postoperative atrial fibrillation is defined as new-onset atrial fibrillation in the immediate postoperative period.

The results obtained were statistically evaluated according to Student's ***t***-criterion. The data are presented as the arithmetic mean (M) for the results of each study ± standard deviation (SD). If the results showed skewed distribution, they were summarized as median with 25% and 75% quartiles (Me ($Q_{25\%}$;$Q_{75\%}$)) and comparisons were performed using the Mann-Whitney ***U*** test**.** Differences at $p < 0.05$ (95.5%) were considered reliable. Variance analysis of the results obtained was performed using the SPSS Statistics computer program.

Results

Patient characteristics before operation are given in Table I.

As can be seen in Table I, no significant changes in the baseline condition of patients were observed in either group ($p > 0.05$).

There were no significant differences between the groups in the duration of surgery ($p = 0.859$), anaesthesia ($p = 0.458$), CPB ($p = 0.458$), and the duration of aortic cross-clamping ($p = 0.061$). The number of

Table 1. *Characteristics of groups*

Characteristics	Study group (n=13)	Control group (n=17)	p-value
Age, years (Me(Q25,Q75)	62 (57;63)	58 (54;61)	0.239
Sex, n (%) ▪ male ▪ female	10 (76.92%) 3 (23.08%)	13 (76.47%) 4 (23.53%)	0.841
Body weight, mg (M±SD)	90.8 ± 9.7	95.9 ± 18.1	0.367
FC (NYHA), n (%) ▪ 2 ▪ 3	5 (38.46%) 8 (61.54%)	4 (23.53%) 13 (76.47%)	0.201
LV EF, % (M±SD)	46.92 ± 8.13	44.94 ± 9.61	0.555
EDV, ml (M±SD)	136.76 ± 18.93	151.58 ± 21.70	0.060
MI, n (%)	1 (7.69%)	2 (11.76%)	0.449
AH, n (%)	7 (53.84%)	8 (47.06%)	0.571
Hb, g/l (M±SD)	119.46 ± 11.92	123.06 ± 11.65	0.414

Notes: FC – functional class; LV EF – left ventricle ejection fraction; EDV - end-diastolic volume; MI - myocardial infarction; AH – arterial hypertension, Hb – hemoglobin

Table 2. *Comparison of perioperative data*

Characteristics	Study group (n=13)	Control group (n=17)	p-value
Duration of operation, min (M±SD)	204.15 ± 19.90	205.35 ± 16.85	0.859
Duration of anesthesia, min (M±SD)	220.62 ± 17.19	225.12 ± 15.47	0.458
Number of anastomoses: ▪ 2, n (%) ▪ 3, n (%)	 5 (38.46%) 8 (61.54%)	 7 (41.18%) 10 (58.82%)	0.631
Duration of CPB, min (M±SD)	85.77 ± 12.92	83.88 ± 10.99	0.669
Duration of aortic cross-clamping, min (M ± SD)	23.23 ± 3.78	26.00 ± 5.06	0.061
Requirement of RBCM, ▪ 1 unit ▪ > 1 unit	 9 (69.23%) 3 (23.07%)	 8 (47.06%) 5 (29.41%)	0.121

Notes: CPB – cardiopulmonary bypass, RBCM – red blood cell mass

Table 3. *Dynamics of Annexin V depending on the schemes of anesthesia*

Group	Annexin V, pg/ml		p-value
	before CPB	after CPB	
Study group (n=13)	0.74±0.53	0.85±0.52	0.736
Control group (n=17)	0.71±0.56	1.28±0.75	0.047
p-value	0.854	0.042	

Notes: CPB – cardiopulmonary bypass

Fig. 1. *Features of the dynamics of mean arterial pressure during coronary artery bypass grafting (Notes: * – in comparison with the previous value; MAP – mean arterial pressure (mmHg))*

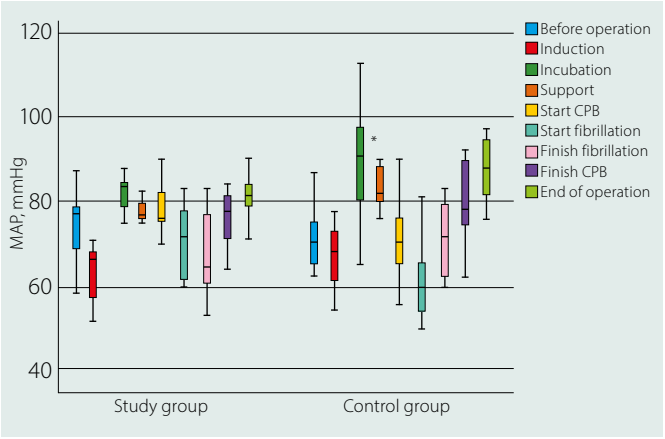


Fig. 2. *Features of heart rate dynamics (beats/min) during coronary artery bypass grafting*

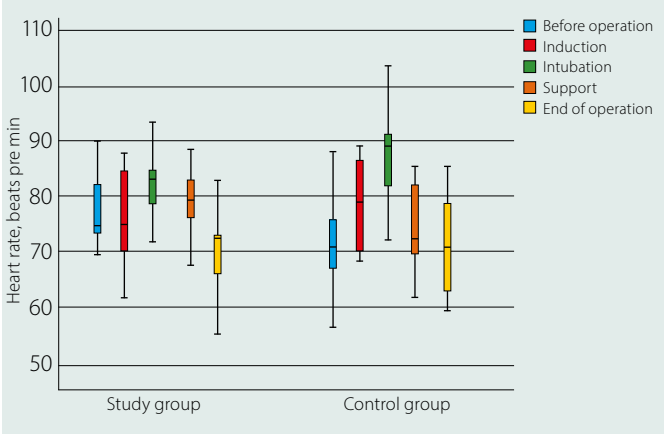


Table 4. *The incidence of low cardiac output syndrome in the early postoperative period*

Groups	Low cardiac output syndrome		Number of patients	chi-squared	p-value
	Yes	No			
Study group	1 (7.6%)	12 (92.4%)	13	0.632	0.427
Control group	3 (17.6%)	14 (82.4%)	17		

Tab. 5. *The incidence of atrial fibrillation in the early postoperative period*

Groups	Atrial fibrillation		Number of patients	chi-squared	p-value
	Yes	No			
Study group	2 (15.4%)	11 (84.6%)	13	0.810	0.368
Control group	5 (29.4%)	12 (69.7%)	17		

anastomoses (p = 0.631), as well as the intraoperative need for red blood cell mass (p = 0.121) did not differ significantly between the groups (Table II).

Changes in blood pressure during surgery did not exceed 20% of the initial level in the study and control groups (Fig. 1). However, it is worth noting that, at the intubation stage, patients in the control group showed a significant (32.81%) increase in mean arterial pressure (MAP) compared to the induction stage (p = 0.041) (Fig. 1).

Also, in study-group patients, the value of heart rate (HR) did not differ significantly compared to the initial level (Fig. 2).

The results of determining annexin V showed an increase in this indicator at the end of surgery compared to the initial values (Table III).

Thus, in the control group, a significant 1.8-fold (p = 0.047) increase in the level of annexin V was observed compared to the initial level (Table III). At the same time, patients in the study group showed an increase in annexin V compared to the initial values (p = 0.736) (Table III). An analysis of this indicator between the groups showed no significant difference between the initial results (p = 0.854). However, the level of anti-apoptotic annexin V was significantly (1.5 times) lower at the end of surgery in the study-group patients than in the control group (Table III).

In addition to perioperative factors, it was also important to evaluate associative relationships between IL-6 and annexin V immediately after surgery.

In general, patients in both groups showed a significant increase in IL-6 levels immediately at the end of surgery: 5.2 times (p < 0.0001) in the study group and 7.8 times (p < 0.0001) in the control group (Fig. 3).

In addition, among patients in the study group, the IL-6 value at the end of surgery was significantly (28.38%) lower (p = 0.020) compared to the control group (Fig. 3).

Interestingly, when analysing associative relationships between the value of annexin V and the level of IL-6, a negative weak correlation was found (r = –0.117, p = 0.523) (Fig. 4).

Regarding clinical results, patients in the study group were significantly less likely to have low cardiac output syndrome (7.6% vs. 17.6%, p = 0.427); however, the results obtained were not significant (Table IV).

Fig. 3. *Dynamics of changes in the levels of IL-6 (pg/ml) during coronary artery bypass grafting (n = 30) (Notes: * – in comparison with the initial value; ^ – in comparison between the study groups; CPB – cardiopulmonary bypass; IL-6 – interleukin-6)*

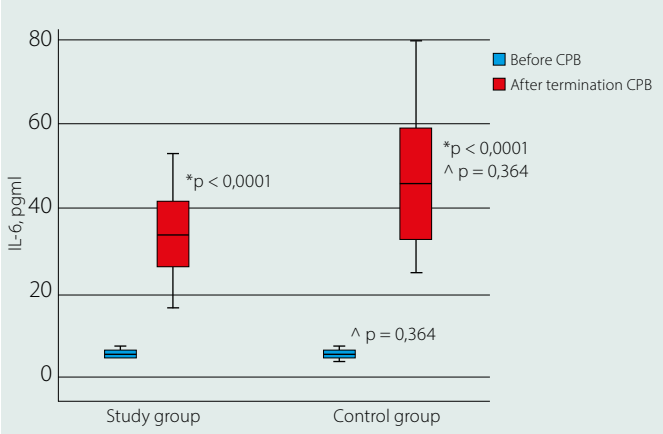


Fig. 5. *The value of annexin V (pg/ml) depending on the presence of low cardiac output syndrome*

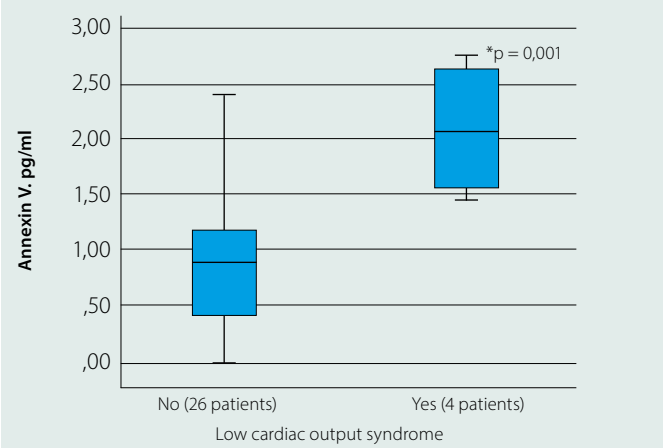


Fig. 4. *Regression of annexin V (pg/ml) from the value of IL-6 (pg/ml) after CPB (n = 30) (Notes: CPB – cardiopulmonary bypass; IL-6 – interleukin-6)*

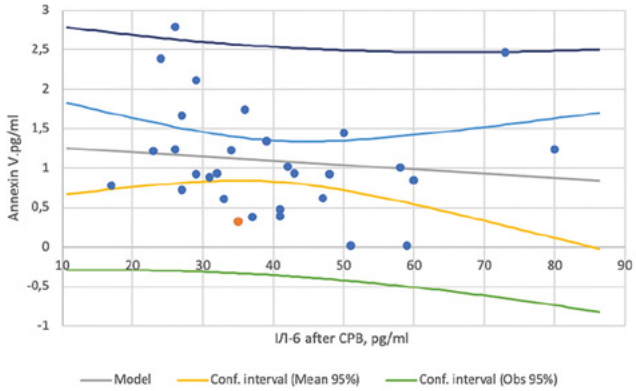
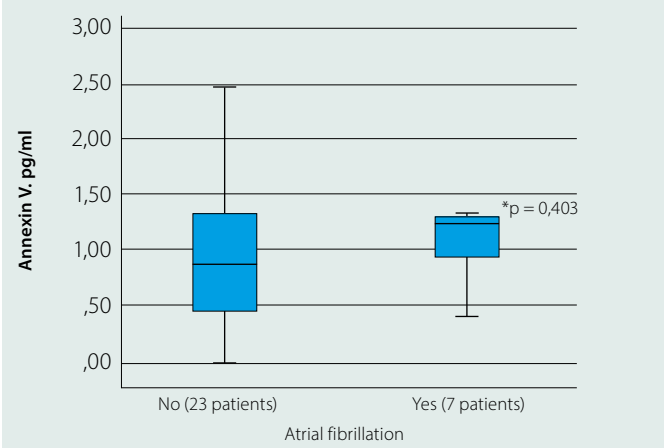


Fig. 6. *The value of annexin V (pg/ml) depending on the presence of postoperative atrial fibrillation*



At the same time, a univariate analysis of variance showed that patients who had LCOS in the postoperative period had significantly higher levels of annexin V after CPB (p = 0.001) (Fig. 5).

Patients in the study group were also significantly less likely to develop atrial fibrillation compared to the control group (15.4% vs. 29.4%, p = 0.368), but without a significant difference (Table V).

Univariate analysis of variance did not establish a significant association between annexin V levels and the frequency of postoperative atrial fibrillation (p = 0.403) (Fig. 6).

Discussion. As the results of our study showed, the study group was characterized by significantly lower levels of annexin V at the end of surgery compared to the control group.

Annexin V is one of the factors that counteract the development of excessive activation of apoptotic responses [17]. However, we could see that when multimodal low-dose opioid anaesthesia was administered, this indicator was significantly lower compared to the control group; we posit that this is due to a positive feedback with pro-apoptotic factors – with a low level of activation of apoptotic reactions, the production of annexin V is lower – and vice versa.

It is also worth noting that, in our study, there was a significant negative correlation between the level of annexin V and IL-6, which may indicate the anti-inflammatory activity of this factor. The results are consistent with a number of studies that suggest anti-inflammatory properties of annexin V.

In their study on mice, de Jong R.C.M. et al. found that the administration of exogenous annexin V significantly reduced the production of IL-6 by macrophages [14]. However, the exact mechanism by which annexin V regulates IL-6 production in this situation remains unknown and should therefore be the focus of further study. The use of multimodal low-dose opioid anaesthesia in the study group was characterized by lower levels of both annexin V and IL-6 compared with the control group.

Each of the elements of multimodal low-dose opioid anaesthesia can affect the level of inflammatory response and, accordingly, the development of apoptosis during cardiac surgery. Lugga T.S. et al. found that the use of subnarcotic doses of ketamine (0.5 mg/kg) in cardiac surgery was characterized by significantly lower levels of IL-6 in the serum in the early postoperative period compared with placebo [18]. As for dexmedetomidine, as reported in the meta-analysis of Li B. et al., the use of this agonist of α2-adrenergic receptors during general anaesthesia significantly reduced the levels of interleukin-6 (IL-6), while there was an increase in anti-inflammatory IL-10 [19]. Moreover, in the work of de Oliveira M. et al. (2015), the use of lidocaine at doses of 2 mg/kg/h was characterized by a significant reduction in postoperative stress response, including lower levels of IL-6 compared with placebo groups [20].

Another important finding in our study was the identification, by analysis of variance, of a significant relationship between the level of annexin V at the end of surgery and the frequency of LCOS. Similar results regarding the role of annexin V in the development of cardiac dysfunction were obtained by Ravassa S. et al. Specifically, the researchers found that plasma levels of annexin V reflect increased production of annexin V in the myocardium. Moreover, this paper showed that the level of annexin V in plasma can act as a marker of myocardial systolic dysfunction [15].

However, according to Matsuda R. et al., high levels of serum annexin V in patients with acute myocardial infarction, cardiac arrest, and severe trauma may reflect the severity of myocardial and/or other visceral organ damage, and measurements of the concentration of annexin V in the plasma can aid in assessing patient prognosis [8]. At the same time, the authors emphasize that reliable clinical trials are needed before reaching conclusions about the predictive value of annexin V as a serum biomarker.

The use of multimodal low-dose opioid anaesthesia was also characterized by a tendency to reduce the frequency of POAF. Because the occurrence of POAF and the activation of the complement system with the release of anti-inflammatory cytokines coincide over time, this may indicate an inflammatory component in the mechanism that triggers POAF [21]. Thus, an example of the role of inflammation in the development of AF is the study by Frustaci A. et al., which found lymph node infiltrates in atrial tissues among 66% of patients with isolated AF [22]. In addition, a direct causal relationship between inflammation and postoperative AF was shown in a model of sterile pericarditis in dogs, with prednisolone use reducing postoperative C-reactive protein and AF frequency [23].

Furthermore, the lower frequency of POAF may be due to the antiarrhythmic properties of lidocaine, which – by blocking sodium channels in the conduction system as well as the muscle cells of the heart – raises the depolarization threshold, thereby making the heart less likely to initiate or conduct early action potentials [24]. Another mechanism may be the antiarrhythmic effect of dexmedetomidine: by activating G-protein transmembrane alpha-2 receptors in the brain, dexmedetomidine can theoretically influence the transmission of sympathetic activity from the central to the peripheral nervous system and elicit an antiarrhythmic effect [25].

The main limitation in our study is that it uses a small sample of patients that may not be sufficiently representative. Another limitation is that the occurrence of LCOS was relatively low, as could be supposed when taking into account favourable LVEF of the patients. Lastly, we only studied anti-apoptotic factors without taking into account pro-apoptotic ones.

Conclusions. The study group was characterized by a significant (1.5-fold) reduction in annexin V at the end of surgery compared to the control group. Univariate analysis of variance showed that patients with LCOS in the postoperative period had significantly higher levels of annexin V after CPB ($p = 0.001$).

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