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Состояние системы гемостаза пациентов с брадикардиями после имплантации двухкамерных электрокардиостимуляторов

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АННОТАЦИЯ

Обоснование. Как и множество других оперативных вмешательств, имплантация электрокардиостимулятора (ЭКС) в ближайшем или отдаленном периоде может сопровождаться неблагоприятными исходами. Поиск возможных факторов риска неблагоприятных исходов может способствовать разработке эффективных и безопасных методов ведения пациентов с ЭКС в послеоперационном периоде. Одним из актуальных направлений в данной области является изучение влияния имплантации ЭКС на систему гемостаза пациентов.

Цель. Оценка влияния имплантации двухкамерного ЭКС на систему гемостаза у пациентов с различными видами брадиаритмий, а также определение возможных факторов риска неблагоприятных исходов в данной группе пациентов.

Материалы и методы. Исследование выполнено при финансовой поддержке РФФИ в рамках научного проекта № 19-315-90109. В проспективное исследование (ClinicalTrials.gov ID NCT04499612) был включен 61 пациент (мужчин — 45,9%) со средним возрастом 71,5 ± 8,8 лет. В оперативные группы вошли 23 пациента с атриовентрикулярной (АВ) блокадой и 25 пациентов с синдромом слабости синусового узла (СССУ), в консервативную — 13 пациентов с АВ блокадами и СССУ, но без показаний к имплантации ЭКС. Антикоагулянтную терапию получали 1 пациент с АВ блокадой, 12 пациентов с СССУ и 5 пациентов консервативной группы. Остальные пациенты находились на антиагрегантной терапии. Пациентам оперативных групп производились ультразвуковое исследование вен верхних и нижних конечностей и забор периферической венозной крови до и через 7 суток после имплантации ЭКС для определения уровня фибриногена (FI) и активности факторов свертывания VIII (FVIII) и IX (FIX), антитромбина III (AT III) и протеина С. В группе С аналогичное обследование производилось только при включении в исследование.

Результаты. У пациентов с АВ блокадами отмечено значимое увеличение уровня FI крови через 7 суток после операции (p = 0,042). При межгрупповом сравнении оказалось, что у пациентов оперативных групп после имплантации активность AT III была выше, чем у пациентов консервативной группы (p = 0,018 и p = 0,006, соответственно). После операции у пациентов с СССУ на фоне антикоагулянтной терапии активность FVIII и FIX была ниже, чем на фоне антиагрегантной терапии (p = 0,048 и p = 0,015). По данным ROC-анализа, факторами риска летального исхода у пациента с АВ блокадой является сниженная активность AT III, у пациента с СССУ — повышенная активность FIX.

Выводы. Баланс системы гемостаза пациентов с АВ блокадами на антиагрегантной терапии сдвинут в сторону гиперкоагуляции как минимум в течение 7 дней после имплантации ЭКС. Применение антикоагулянтов у пациентов с СССУ обеспечивает сдвиг в сторону гипокоагуляции. Сниженная активность AT III у пациента с АВ блокадой и повышенная активность FIX у пациента с СССУ являются прогностическими факторами летального исхода в течение года после операции.

Ключевые слова: *система гемостаза; электрокардиостимуляция; брадиаритмия; атриовентрикулярная блокада; синдром слабости синусового узла; фибрилляция предсердий*

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Hemostasis system in patients with bradycardias after the implantation of dual-chamber pacemakers

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ABSTRACT

INTRODUCTION: As with many other surgical interventions, the implantation of a pacemaker may be associated with adverse outcomes in the immediate or distant period. The search for probable risk factors of adverse outcomes may promote the development of effective and safe management methods of patients with pacemaker postoperatively. One of the important directions in this field is the investigation of the effect of pacemaker implantation on the hemostasis system of these patients.

AIM: To evaluate the effect of the implantation of dual-chamber pacemaker on the hemostasis system of patients with different kinds of bradyarrhythmias and to determine probable risk factors for unfavorable outcomes in this group of patients.

MATERIALS AND METHODS: The study was performed with the financial support of the Russian Foundation for Basic Research within the Scientific Project No. 19-315-90109. The prospective study (ClinicalTrials.gov ID, NCT04499612) enrolled 61 patients (men, 45.9%) with a mean age of 71.5 ± 8.8 years. The group who received surgical treatment included 23 patients with atrioventricular (AV) block and 25 patients with sick sinus syndrome (SSS), and the group with conservative treatment included 13 patients with AV blocks and SSS, but without indications for pacemaker implantation. Anticoagulant therapy was given to one patient with AV block, 12 patients with SSS, and five patients with conservative therapy. All the remaining patients received antiplatelet therapy. The surgical group underwent ultrasound examination of the veins of the upper and lower extremities and sampling of peripheral venous blood before and 7 days after pacemaker implantation to determine the level of fibrinogen (FI) and activity of blood coagulation factors VIII (FVIII) and IX (FIX), antithrombin III (AT III), and protein C. In the conservative group, a similar examination was conducted only on inclusion in the study.

RESULTS: In patients with AV block, a significant increase in blood fibrinogen was noted at 7 days after surgery ($p = 0.042$). In the intergroup comparison, the activity of AT III after the implantation was higher in the surgical group than in the conservative group ($p = 0.018$ and $p = 0.006$, respectively). After surgery, the activity of FVIII and FIX was lower in patients with SSS on anticoagulant therapy than in patients with antiplatelet therapy ($p = 0.048$ and $p = 0.015$, respectively). Based on the receiver operating characteristics analysis, the risk factors for lethal outcomes were reduced activity of AT III in patients with AV block and increased activity of FIX in patients with SSS.

CONCLUSIONS: The balance of the hemostasis system in patients with AV blocks on antiplatelet therapy was shifted toward hypercoagulation within at least 7 days after pacemaker implantation. The use of anticoagulants in patients with SSS caused a shift toward hypocoagulation. The reduced activity of AT III in patients with AV block and increased activity of FIX in patients with SSS are prognostic factors for lethal outcomes.

Keywords: *system of hemostasis; cardiac pacing; bradyarrhythmia; atrioventricular block; sick sinus node; atrial fibrillation*

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ECO•VECTOR

LIST OF ABBREVIATIONS

AT III — antithrombin III
AV — atrioventricular
CHF — chronic heart failure
CI — confidence interval
ECP — electronic cardiac pacemaker
FI — fibrinogen
FIX — IX blood coagulation factor
FVIII — VIII blood coagulation factor
PrC — protein C
SSS — sick sinus syndrome
VTEC — venous thromboembolic complication

BACKGROUND

At present, cardiac pacing is the most effective method of correction of bradyarrhythmias, particularly atrioventricular (AV) blocks and manifestations of the sick sinus syndrome (SSS). Before cardiac pacing was introduced in medical practice, the prognoses of patients with bradyarrhythmia were mostly unfavorable [1–3].

In the absolute majority of cases, the implantation of an electronic cardiac pacemaker (ECP) implies the use of the venous system to gain access to the patient's heart. Then, one or more leads are positioned in the vessels to conduct impulses from the ECP, and in case of a leadless ECP, the device is fixed to the cardiac wall [3].

Like many other surgical interventions, ECP implantation may have adverse outcomes in both near and distant periods. These may be both complications of the procedure itself, such as the development of pneumothorax or dislodgement of a lead, and different complications and conditions associated with cardiac pacing, such as thromboses and thromboembolism, newly developed tachyarrhythmias, and cerebrovascular disorders. Unfavorable outcomes of cardiac pacing often require repeated hospitalizations, or simply end in death.

The search for probable risk factors of adverse outcomes and their interrelations with various data obtained through laboratory and instrumental examination methods may contribute to the development of the effective and safe methods of management of patients with ECP in the early and late postoperative periods. One of the important directions in this field is the investigation of the effects of ECP implantation on the hemostasis system of patients. Many patients planned for ECP implantation initially have a tendency to be in a hypercoagulation state due to the presence of bradyarrhythmia and some concomitant diseases, such as chronic heart failure (CHF), arterial hypertension, and coronary heart disease [2, 5]. Perioperative stress, injury to veins during lead implantation, and turbulent blood flow along the leads promote a further shift toward hypercoagulation. All these alterations may trigger some unfavorable outcomes [4, 6].

Aim — to examine the effect of implantation of a dual-chamber ECP on the hemostasis system of patients with different kinds of bradyarrhythmias and to determine probable risk factors for unfavorable outcomes in the analyzed group of patients.

MATERIALS AND METHODS

The prospective study (ClinicalTrials.gov ID NCT04499612) involved 61 patients (28 men, 45.9%) with a mean age of 71.5 ± 8.8 (69.2–73.8) years. Patients were divided to three groups:

- ***Group A*** — patients with AV block and indications for ECP implantation
- ***Group B*** — patients with SSS and indications for ECP implantation
- ***Group C*** — patients with AV block and SSS, but with no indications for ECP implantation (conservative group).

The clinical characteristics of the analyzed groups of patients are given in Table 1.

According to modern clinical recommendations, anticoagulant therapy was given only to patients with atrial fibrillation. In group A, 1 (4.3%) patient received dabigatran. In group B, 8 (32.0%) patients received rivaroxaban; 2 (8.0%), apixaban; and 1 (4.0%), warfarin. In group C, 4 (30.8%) patients took rivaroxaban and 1 (7.7%) received apixaban.

In groups A and B, peripheral venous blood samples were collected before and 7 days after ECP implantation to determine the level of fibrinogen (FI), activity of coagulation factors VIII (FVIII) and IX (FIX), and activity of natural anticoagulants, namely, antithrombin III (AT III) and protein C (PrC). SYSMEX CA 660 automatic coagulometer (Japan) and SIEMENS reagents (Germany) were used. In the same period, patients underwent ultrasound examination of the veins of the upper and lower extremities to assess their patency. In group C, a similar examination was performed only on inclusion in the study.

Statistical analysis was performed using IBM SPSS 26 (Statistical Product and Service Solutions). Qualitative parameters are represented by frequencies; for analysis, the $\chi 2$ test and Fisher's exact test were used. Quantitative parameters with a normal distribution according to the Shapiro–Wilk test were represented by an arithmetic

Table 1. Clinical characteristics of the analyzed groups of patients

Characteristics	Group A (n = 23)	Group B (n = 25)	Group C (n = 13)	p
Age, years	69.2 ± 7.6 (65.9–72.5)	73.1 ± 8.5 (69.6–76.6)	72.5 ± 11.0 (65.5–79.5)	0.281
Gender, n (%)				
- male	13 (56.5)	8 (32.0)	7 (53.8)	0.152
Body mass index, kg/m^2	27.9 ± 5.3 (25.6–30.2)	26.8 ± 2.8 (25.7–28.0)	27.7 ± 4.8 (24.6–30.8)	0.691
Main disease, n (%)				
- atrioventricular block	23 (100)	–	4 (30.8)	–
- sick sinus node	–	25 (100)	9 (69.2)	–
Concomitant diseases and conditions, n (%)				
- essential hypertension	22 (95.7)	25 (100)	12 (92.3)	0.393
- exertional angina	6 (26.0)	7 (28.0)	4 (30.8)	0.902
- atrial fibrillation	1 (4.3)	12 (48.0)	5 (38.5)	0.003
- chronic heart failure	23 (100)	25 (100)	13 (100)	–
of functional classes:				
I	3 (13.0)	1 (4.0)	1 (7.7)	
II	9 (39.0)	11 (44.0)	7 (53.8)	0.813
III	11 (48.0)	13 (52.0)	5 (38.5)	
IV	0	0	0	–
- history of myocardial infarction	4 (17.4)	5 (20.0)	0	0.258
- history of acute cardiovascular accident	0	2 (8.0)	3 (23.1)	0.04
- diabetes mellitus	7 (30.4)	7 (28.0)	4 (30.8)	0.945
- varicosity of the subcutaneous veins of the lower extremities	5 (21.7)	8 (32.0)	2 (15.4)	0.541
Antithrombotic therapy, n (%)				
- antiplatelet	22 (95.7)	13 (52.0)	8 (61.5)	0.003
- anticoagulant	1 (4.3)	12 (48.0)	5 (38.5)	

mean with mean square deviation and 95% confidence interval (CI) of the mean and other parameters by median and interquartile interval. In the comparison of two related aggregates, the Student or Wilcoxon tests was used, whereas the Student or Mann–Whitney tests was used in unrelated ones. For multiple comparisons, the one-factor analysis of variance or the Kruskall–Wallis test was used. In the evaluation of unrelated aggregates, the equality of variances was further checked according to the Levin test. Predictive models were constructed using ROC analysis and binary logistic regression method. The critical significance level was $p < 0.05$ (bilateral p).

RESULTS

The average follow-up period was 10 (5–17) months. The surgical groups were implanted with dual-chamber ECPs. The vascular access in all patients was made through the cephalic vein. All ventricular leads had passive fixation, while all atrial ones had active fixation. Anticoagulant therapy was cancelled one day before the implantation and was resumed on the next day after it. Antiplatelet therapy was not cancelled.

The dynamics of the parameters of the hemostasis system in the surgical groups and the values of the conservative groups are shown in Table 2.

In group A, a significant increase in the Fl level of blood was noted ($p = 0.042$). In the intergroup comparison, the AT III activity after implantation was higher in patients of the surgical groups than in patients of the conservative group ($p = 0.018$ and $p = 0.006$, respectively). Besides, the AT III activity was higher in group B before surgery ($p = 0.03$), and the FVIII activity was significantly lower after surgery ($p = 0.012$) in group C.

To evaluate the effect of anticoagulant therapy on the analyzed parameters, additional statistical analyses were conducted. After the operation, the activity of FVIII and FIX in patients with SSS who received anticoagulant therapy was lower than in those with antiplatelet therapy ($p = 0.048$ and $p = 0.015$, Table 3). Besides, the activity of FIX in patients receiving anticoagulants showed a significant change after 7 days ($p = 0.022$), but not in patients receiving antiplatelet drugs ($p = 0.574$). In the multiple comparison, the activities of FVIII and FIX in group B receiving anticoagulant therapy were lower in 7 days after the implantation than in group A in the same period ($p = 0.037$ and $p = 0.014$) as well as in group C ($p = 0.002$ and $p = 0.029$). In group C, parameters of patients receiving different types of antithrombotic therapy were not different ($p > 0.05$).

Upon inclusion in the study, increased activities of FVIII ($p = 0.049$) and FIX ($p = 0.002$) were noted in patients with exertional angina and that of FIX was observed in patients with a history of myocardial infarction ($p = 0.007$). In CHF of functional class III according to the New York Heart Association, the initial activity of FIX was higher than that in CHF of functional class II ($p = 0.016$). The initial activity of PrC and AT III was higher in women ($p = 0.011$ and $p = 0.027$).

During the follow-up period, 2 (8.6%) cases of venous thromboembolic complications (VTEC) were detected in group A: one thrombosis of the left subclavian vein and one thrombosis of the left large saphenous vein. Thrombosis of the subclavian vein was diagnosed in a patient 2 weeks

Table 2. Dynamics of the analyzed parameters in the early postoperative period

Group	Parameter	Before surgery	7 days after surgery	p
A	FI, g/l	2.48 ± 0.76 (2.05–2.9)	2.98 ± 0.77 (2.56–3.41)	0.042
	FVIII, %	78.27 ± 35.49 (58.61–97.92)	82.18 ± 24.71 (68.50–95.87)	0.625
	FIX, %	83.77 ± 20.83 (72.24–95.30)	86.79 ± 26.59 (72.07–101.50)	0.504
	PrC, %	104.63 ± 16.31 (95.60–113.66)	103.29 ± 16.04 (94.41–112.17)	0.6
	AT III, %	105.00 (100.00–108.40)	109.40 (93.00–113.50)	0.363
B	FI, g/l	2.70 ± 0.55 (2.45–2.96)	2.99 ± 0.65 (2.05–2.90)	0.066
	FVIII, %	88.54 ± 28.85 (75.40–101.68)	77.26 ± 25.77 (65.53–88.99)	0.101
	FIX, %	88.59 ± 23.16 (78.04–99.13)	79.90 ± 25.13 (68.46–91.34)	0.054
	PrC, %	110.14 ± 15.10 (103.26–117.02)	104.63 ± 22.13 (94.08–114.22)	0.084
	AT III, %	107.00 (90.60–112.45)	106.80 (92.25–113.90)	0.289
C	FI, g/l	2.88 ± 1.00 (2.24–3.50)		0.597* 0.896**
	FVIII, %	104.73 ± 22.38 (90.51–118.95)		0.434* 0.014**
	FIX, %	96.32 ± 26.74 (79.33–113.31)		0.35* 0.217**
	PrC, %	94.39 ± 23.18 (79.66–109.12)		0.064* 0.432**
	AT III, %	88.15 (81.03–103.28)		0.06* 0.006**

Notes: * — multiple comparisons of parameters of the conservative group and surgical groups before surgery, ** — multiple comparisons of parameters of the conservative group and surgical groups in 7 days surgery

after ECP implantation and that of the large saphenous vein was identified in a female patient 1 year after the implantation. Both patients were on antiplatelet therapy. In 1 (4.3%) patient of group A, newly developed atrial fibrillation was recorded. In group B, relapses of atrial fibrillation paroxysms were registered in 7 (28.0%) patients during the follow-up period, and two of them (8.0%) required hospitalization for CHF decompensation. No differences were noted in the analyzed parameters or risk factors in relation to these outcomes (p > 0.05).

In group A, 4 (17.3%) lethal outcomes occurred, while 2 (8.0%) were noted in group B. Based on the results of the receiving operating characteristics analysis (Figure 1), prognostic factors for lethal outcomes in both groups were identified.

In group A, the probability for lethal outcomes increased with low AT III activity (area under the curve [AUC] 0.824 ± 0.096, 95% CI 0.635–1, p = 0.049), and the threshold value of AT III activity was 98.30%. In group B, the probability for lethal outcomes increased with high FIX activity (AUC 0.955 ± 0.044, 95%CI 0.868–1, p = 0.037), and the threshold value of FIX activity was 129.15%.2 (8.0%).

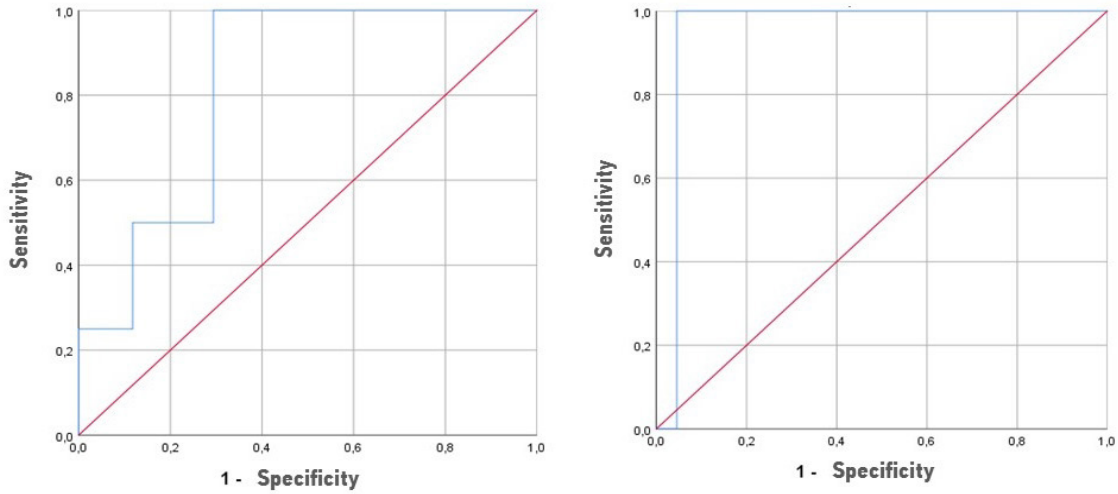

Fig. 1. Results of the ROC analysis. A prognostic model of the fatal outcome of a patient with atrioventricular block (left) and of a patient with sick sinus syndrome (right).

Table 3. Comparison of the analyzed parameters in patients of group B depending on type of antithrombotic therapy

Parameters		Patients receiving antiaggregants (n = 13)	Patients receiving anticoagulants (n = 12)	p
Fl, g/l	Before surgery	2,70 ± 0,52 (2,35–3,04)	2,71 ± 0,62 (2,27–3,16)	0,71
	After surgery	2,90 ± 0,47 (2,59–3,22)	3,10 ± 0,82 (2,51–3,68)	0,526
FVIII, %	Before surgery	95,11 ± 31,82 (73,73-116,49)	81,32 ± 24,78 (63,59–99,05)	0,398
	After surgery	87,27 ± 29,59 (67,40–107,15)	66,24 ± 15,67 (55,03–77,45)	0,048
FIX, %	Before surgery	95,86 ± 21,79 (81,21–110,50)	80,59 ± 23,00 (64,14–97,04)	0,071
	After surgery	92,11 ± 25,21 (75,17–109,05)	66,11 ± 17,74 (53,77–79,15)	0,015
PrC, %	Before surgery	116,55 ± 11,81 (108,60–124,48)	103,09 ± 15,71 (91,85–114,33)	0,038
	After surgery	107,97 ± 21,97 (93,21–122,74)	99,94 ± 22,68 (93,72–116,16)	0,42
AT III, %	Before surgery	104,60 (89,90–112,20)	107,00 (90,60–113,45)	0,865
	After surgery	103,50 (98,80–112,70)	107,10 (92,28–116,43)	0,863

DISCUSSION

At present, implantation of a dual-chamber ECP is mainly performed in patients with AV block and SSS. In patients with SSS, cardiac pacing of only the atrium is possible with implantation of a single-chamber ECP, but with further progression of the AV conduction disorder with a high risk for development of atrial fibrillation, the system in these patients shortly requires upgrading to the dual-chamber type. Because of this, in patients with SSS, a dual-chamber ECP is more often implanted immediately for medical and economic considerations [7, 8].

Surgical intervention leads to the development of the hypercoagulation syndrome in the early postoperative period [6, 9]. In our study, this syndrome was manifested by a high Fl activity in patients with AV block on postoperative day 7. In the study by Zhang et al., increased Fl activity was observed in patients in similar periods irrespective of the ECP model. Besides, increased activities of natural anticoagulants between the surgical groups and conservative group also serve as markers of a hypercoagulation state. The activities of AT III and PrC usually increase in response to high levels of the produced thrombin. For example, in the study by Zhang, et al., the activity of AT III was significantly higher in patients with ECP than in those in the control group [10].

More substantial data were obtained in the analysis of patients according to the type of antithrombotic therapy. The analyzed parameters of patients with SSS receiving antiplatelet therapy did not change within 7 days after surgery; besides, no differences were found between parameters of patients with SSS and AV block receiving antiplatelet drugs. On the contrary, patients with SSS receiving anticoagulants showed reduced FVIII and FIX activities in the early postoperative period, which was also significant in comparison with patients receiving antiplatelet drugs. This allows us to suggest that the differences in the analyzed markers of the hemostasis system in the early postoperative period after the implantation of dual-chamber ECP depend not on the level of a conducting system disorder but on the type of antithrombotic therapy used.

During the observation period, two VTEC cases were recorded. This number of outcomes was too small to search for probable risk factors. Nevertheless, VTECs were identified in patients with AV block receiving antiplatelet therapy. Van Rooden et al. and Mandal et al. noted that antiplatelet therapy does not prevent the development of VTEC [11, 12]. In the study by Korkeila et al., anticoagulant therapy prevented the development of thrombotic complications [13]. Our previous studies have revealed that thrombosis of the veins of the upper extremities was mostly observed in patients receiving antiplatelet agents, but cases of thrombosis were also recorded in patients receiving warfarin and dabigatran [6].

Lethal outcomes in patients with AV blocks were associated with low AT III activity and in patients with SSS with increased FIX activity. In the international literature, the interrelation of 30-day lethal outcomes in patients with past cardiac asystole or atrial fibrillation was reported with increased activities of the FIX–antithrombin complex and coagulation factor XI–antithrombin complex. A multivariate analysis revealed significant correlation only with the coagulation factor XI–antithrombin complex, although a significant correlation between both complexes was noted [14]. A high FIX activity along with increased aggregation activity of platelets was noted in patients with acute coronary

syndrome. To reduce the mortality and improve the results of surgical interventions, FIX inhibitor has been actively developed in recent years [15].

The limitations of the study at this stage are the small sample of patients and the number of unfavorable outcomes. It is also not possible to evaluate the dynamics of the analyzed parameters in patients with AV block receiving anticoagulant therapy. The presence of an AV block is not an indication for the administration of anticoagulants, and a combination of AV block with paroxysmal or persisting form of atrial fibrillation, in which anticoagulant therapy is possible, is rare in the population and more often reflects simultaneous damage to the conduction system at the level of the AV and sinoatrial node. The continuation of the study will allow more effective evaluation of the dynamics of parameters of the hemostasis system and to identify a sufficient amount of unfavorable outcomes for the exact identification of their risk factors.

CONCLUSIONS

1. The balance in the hemostasis system of patients with atrioventricular block receiving antiplatelet therapy is shifted toward a hypercoagulation state for a minimum 7 days after implantation of a dual-chamber ECP. The use of anticoagulants in patients with SSS causes a shift toward hypocoagulation.

2. The activity of antithrombin III below 98.3% before implantation of a dual-chamber ECP in a patient with AV block is a prognostic factor of lethal outcomes within 1 year after surgery.

3. The activity of FIX above 129.15% before implantation of a dual-chamber ECP in a patient with SSS is a prognostic factor of lethal outcomes within 1 year after surgery.

ADDITIONAL INFORMATION

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