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ON THE ISSUE OF SYSTEM OF BLOOD COAGULATION AND HIS COMPLICATIONS IN PATIENTS WITH LVAD IN THE POSTOPERATIVE PERIOD

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The work was carried out within the framework of a bilateral agreement on scientific cooperation between the department of Anesthesiology & Intensive Care in National Medical Academy of Post-Graduate Education Named After P.L. Shupik and the Silesian Center for Heart Diseases (Poland), as a final report.

Resume. The purpose of this scientific work is to analyze the state of the blood coagulation system and its response to therapy and complications in the early postoperative period in fifty patients with implanted devices for mechanical support of the left ventricle, left ventricle assist device, LVAD, in the Silesian Heart Disease Center (Śląski Centrum Chorób Serca – SCCS), Poland. Patients were divided into two groups, a control group receiving classical anticoagulation targeted therapy (ATT), which included the most controlled monotherapy with heparin, after reaching the target values of APTT, the addition and transition to monotherapy with warfarin until reaching the target INR and ASA, and the main, research group, who received an alternative ATT consisting of the previous one with the addition of P2Y12-receptor blockers and Xa-factors.

The result of the work demonstrated the benefit of the modified anticoagulant treatment scheme against the classical approach to reduce clinical complications with clear confirmation by correlation-regression indicators of a significant degree of reliability.

Key words: left ventricle assist device (LVAD), anticoagulant targeted therapy (ATT), perioperative complications.

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ПИТАННЯ СИСТЕМИ ЗГОРТАННЯ КРОВІ ТА ЇЇ УСКЛАДНЕННЯ У ХВОРИХ НА ДЛШ У ПІСЛЯОПЕРАЦІЙНОМУ ПЕРІОДІ

Мазуренко О.П.

Робота виконана в рамках двосторонньої угоди про наукове співробітництво між кафедрою анестезіології та інтенсивної терапії Національної медичної академії післядипломної освіти імені П.Л. Шупіка та Сілезького центру хвороб серця (Польща) як підсумковий звіт.

Резюме. Метою цієї наукової роботи є аналіз стану системи згортання крові та її відповіді на терапію та ускладнення в ранньому післяопераційному періоді у 50 пацієнтів з імплантованими пристроями механічної підтримки лівого шлуночка, допоміжним пристроєм лівого шлуночка (LVAD) у Сілезькому центрі серцевих захворювань (Śląski Centrum Chorób Serca – SCCS), Польща. Пацієнти були розподілені на дві групи: контрольна група отримувала класичну антикоагулянтну таргетну терапію (АТТ), яка включала максимально контрольовану монотерапію гепарином, після досягнення цільових значень АЧТЧ, доповнення та перехід на монотерапію варфарином до досягнення цільового значення МНВ та АСК, та основна, дослідницька група, яка отримувала альтернативний АТТ, що складається з попереднього з додаванням блокаторів P2Y12-рецепторів та Ха-факторів.

Результат роботи продемонстрував перевагу модифікованої схеми лікування антикоагулянтами проти класичного підходу щодо зниження клінічних ускладнень із чітким підтвердженням кореляційно-регресійними показниками значного ступеня достовірності.

Ключові слова: допоміжний апарат лівого шлуночка (LVAD), антикоагулянтна таргетна терапія (АТТ), періопераційні ускладнення.

Introduction. The use of a device for mechanical support of the left ventricle, LVAD, as the only chance for patients with severe degrees of heart failure to live to heart transplantation on the waiting list, is recommended by the American and European Associations of Cardiology and Cardiac Surgery. Currently, the use of these devices in patients receiving donor heart transplantation is approximately 46%, according to literature data, and the median time of LVAD support in patients awaiting heart transplantation is an average of 300 days (147–537 days). The number of implanted LVADs in the United States is currently approaching the number of heart transplants [1]. The transition from pulsatile to continuous-flow, centrifugal LVADs is associated with significantly lower overall adverse event rates, longer stable device performance, and much better long-term patient survival rates. In the first year, the incidence of complications in patients implanted with an LVAD is up to 30%, within two years after implantation in 80% of patients there is at least one event [2], which is a complication that arose in connection with the operation of implanting the device LVAD. According to world experience, the average time of re-hospitalization due to events in patients was 35 days after device implantation, the average duration of patient follow-up was eleven months [3]. The main complications after LVAD implantation include: bleeding, thrombosis of the device, ischemic and hemorrhagic strokes, acute kidney damage, multiple organ failure, infections, etc. The timing of complications after LVAD placement is classified as early (up to 30 days after implantation) or late (after 30 days until 3 years). Carrying out optimal therapy aimed at correcting the hemostasis system in such patients is an important component of intensive therapy, especially in the early postoperative period. The state of the hemostasis system, the development of thromboembolic and hemorrhagic complications, and the effectiveness of the mechanical blood circulation support system depend on the correctly chosen tactics of anticoagulant therapy. The most common complications include surgical and non-surgical ones (infections, ischemic and hemorrhagic lesions of the brain, acute renal failure occurring in the postoperative period, etc.). Most complications manifest in the early postoperative period. An individualized approach with preventive strategies is crucial for improving treatment outcomes for patients in this category.

This work analyzed the frequency of early adverse non-surgical events and complications in the short postoperative period within 14 days after implantation of a left ventricular mechanical support device in fifty patients treated at SCCS over a three-year period from 2016 to 2018, inclusive, aged 55±13.5 years old, with a body mass index of 30.8±8.3 m2, with a left ventricular ejection fraction of 8–28%. Comparison of the analyzed survey results refers to qualitative and quantitative assessments of adverse events and complications in patients with different approaches to anticoagulation targeted therapy.

Materials and methods. The study included 50 patients with various degrees of heart failure, all of whom had a device for mechanical support of the left ventricle of the heart installed, either planned or emergency. The average age of the patients was 52.8±1.7 years, with a predominance of patients older than 50 years (asymmetric type of distribution). The youngest patient was 19 years old, the oldest was 69 years old, Me=56.0 (1q: 47.0 3q: 62.0). The studied sample was characterized by a negative value of the asymmetry coefficient (As=-1.0 σAs=±0.3), the kurtosis coefficient had a positive value (κ=0.4 σ_{κ}=±0.6), the average BMI values were at the level of 26,1±0.9 kg/m^2 (Me=25.0 (1q=21.7; 3q=30.7). Patients were divided into two groups (Table 1), the control group and the main study group. In the control group (21 patients) patients received monotherapy with heparin or warfarin or in combination with aspirin, due to the impossibility of switching to another stage of anticoagulant therapy. In the study group (29 patients), after controlled anticoagulant therapy with heparin, patients received warfarin up to a target value of 2.5 IU and then additionally received a blocker of blood coagulation Xa-factor and blockers of P2Y12 receptors. All patients were equally subjected to all possible analyzes of the blood coagulation system after taking the medication.

Table 1

Characterization of patient groups and targeted anticoagulation therapy

Medication of ATT:	Control group of patients with classic ATT (N= 21)			Examinate group of patients with modificate ATT (n= 29)		
	n=6	n=1	n=14	n=6	n=20	n=3
Heparyn	+	–	+	+	+	+
Varfaryn	–	+	+	+	+	+
ASA	–	–	+	–	–	+
P2Y12 blocker	–	–	–	+	–	+
anty-Xa factor	–	–	–	–	+	+

Note: Ts ACT is targeted anticoagulant therapy; anti-Xa – calcium nadroparin or fondaparinux; ASA – aspirin; P21Y12-bl. – clopidogrel.

In the control group of the study, 8 patients received heparin therapy in the first two weeks by continuous submission at the infusomat on rate until 6 to 11 Units/kg/h. (Me-9.05 Units/kg/hour), and 2 patients were on monotherapy with heparin until the end of their stay in the intensive care unit. Eleven patients during the first week and 7 patients during the second week received warfarin indirect anticoagulant in a dose of 1.5–7 mg/day (Me-3.45 mg/day).

As an alternative to the standard ATT, the following drugs were used: 5 patients received aspirin in doses of 1.4±0.7 mg/kg/day during the entire period; 3 patients during the first week and 5 patients during the second week received clopidogrel 1.3±0.8 mg/kg/day; nadroparin calcium (0.3–0.6 ml/ 2 times a day) and fondaparinux Na (2.5–5 mg/ 2 times a day).

The somatic condition of the patients corresponded to 6–14 points of the European System for assessing the risk of preoperative interventions, or 4–5/E. ASA. Depending on the status according to INTERMACS, Level 1 (cardiogenic shock) was observed in 15 patients, Level 2 (progressive circulatory failure) – in 6 patients, Level 3 – 17 patients, Level 4 – 10 patients, Level 5 – 2 patients. Severe pretransplantation pulmonary hypertension (transpulmonary gradient ≥15 mmHg. and/or pulmonary vascular resistance greater than 3 Wood's Units) was detected in 8 patients. Fifteen patients were operated on in a state of circulatory arrest with cardiopulmonary resuscitation, and ventricular fibrillation was noted in five patients.

Patients were implanted under artificial circulation (ECC) and without such, and moderate hypothermia with t = +31C°. The productivity of ECC device was 2.6 l/min/m^2. Schtoker alternating current systems (Germany) were used to protect the myocardium, which created artificial fibrillation at a frequency of 50Hz, 12V/25A.

Monitoring of systemic hemodynamics was carried out using the IntellsVue X2 Philips® systems (Netherlands), cardiac index indicators – using the A7 Vigileo Monitor-Acsesories EDWARDS® systems, cerebral oxygenation – using the INVOS Oximetr Somanetics® Inc. (USA) system.

The operation was performed under conditions of combined endotracheal anesthesia using a semi-closed circuit with targeted maintenance of the concentration of inhalation anesthetics according to the age-related indicators of the minimum alveolar concentration. Fentanyl was used for analgesia at a dose of 1.7±0.8 μg/kg/min. or sufentanil 0.015±0.03 μg/kg/min.

In patients with high pulmonary hypertension, inhaled NO was used under the control of electronic measurement device of molecules, in a dose of 30–200 p/m, this technique was also used for several days in the postoperative period.

After the end of the operation, artificial ventilation in the intensive care unit (IT) was carried out by the Drager Evita V300 device with an air-oxygen mixture with an oxygen concentration depending on the degree of need and pulmonary hypertension, under the control of blood gas analysis indicators, which were determined by the ABL800 device (France). The analysis of the dynamics of the myocardium was determined by the analysis of blood lactate, troponin I and MV fraction of creatine phosphokinase.

All the above-mentioned analyzes and studies of the blood coagulation system were carried out at the system laboratory station "Multiplate® Roche (France)". The average duration of blood circulation support with LVAD was 49.7±28.2 days. The duration of support for three patients with the pulsatile pneumatic system POLVAD ranged from 102 to 156 days, and for forty-seven patients with the centrifugal constant-flow LVAD ranged from 20 to 78 days.

Control of the drained fluid from the pericardial and thoracic cavities was carried out by a system of two-chamber active drainage systems connected to a constant negative pressure, which simplified the outflow of fluid and improved the hourly calculation of its amount.

Results. During the early postoperative period, in patients with different approaches to anticoagulant therapy, a rather diverse pattern of response to the therapy and, as a consequence, adverse events and complications was observed.

The existing differences in the distribution of hemostasis indicators in the comparison groups are of considerable interest (Table 2). As can be seen from the above, normalization of the hemostasiogram was observed in both the control and main research groups, which was more pronounced in the main group.

Attention is drawn to the multidirectionality of changes in the indicator of sensitivity to acetylsalicylic acid, which decreased by 10.3% in the control group, and increased by 5.6% in the main group at p>0.05.

The higher level of D-dimer in the control group in comparison with the main group requires explanation, also after the correction, their level was more pronounced in the control group (Δ=+12.5%) (Table 2).

Table 2

Dynamics of hemostasis indicators in comparison groups

	Control group		Investigate group	
	Before correcting	**After correcting**	**Before correcting**	**After correcting**
APTT, sec.	66.7±8.4	69.2±6.2	59.6±5.2	57.3±4.3
INR, unit	1.8±0.1	2.2±0.2	1.5±0.2	1.8±0.2*
ASPI, au\min.	495.5±62.2	444.8±57.3	625.4±64.2	662.2±58.4#
ADP, mcg\ml.	366.42±307.33	393.72±229.65	272.45±214.04	500.88±251.99
D-dimer, mcg\ml.	1.6±0.1	7.0±0.2*	1.5±0.2	6.2±0.2*#
Fibrinogen, mg\dl.	269.9±22.4	348.6±26.8*	283.3±23.3	497.7±48.3*#

Note: * – data after correction are statistically significantly different from the original, p<0.05.
– differences between groups are statistically significant, p<0.05.

As demonstrated in the above data, both the control and experimental groups differed in significant heterogeneity not only in the nature of the applied therapy and the duration of the surgical intervention, but also in the range of physiological responses to the intervention. A significant increase in the lactate content at the end of the operation in patients of the control group who received only heparin for coagulation control, as well as less frequent use of hemotransfusion among patients in the main group, who received complex anticoagulation therapy regimens involving, along with heparins, warfarin, clopidogrel, and ASA, require explanation.

The analysis of the daily fluid balance showed that during the stay in the ICU there was a decrease in the average daily balance from 9–11 ml/kg/day to 3–5 ml/kg/day. There is also an increase in the frequency of complications and the level of mortality in patients in whom the support of intra-aortic balloon counter pulsation (IABP) and extracorporeal membrane oxygenation (ECMO) was longer than the first two days of postoperative stay in the ICU (correlation +0.76, p<0 .05) (Table 3).

As the study showed, in the first days of heparin therapy, one patient developed pronounced heparin-induced thrombocytopenia, which led to a change of strategy to alternative therapy with the use of nadroparin calcium. Subsequently, this patient was diagnosed with infection of the outlet of the LVAD power cable and subsequently developed nosocomial pneumonia.

Table 3

Comparison of groups of 50 patients with LVAD on management in the ICU (N= 50)

Indicators of the period of intensive care and resuscitation	Control group of patients (n=21)			Examined group of patients (n=29)		
	n=6	n=1	n=14	n=6	n=20	n=3
Length of stay, days	13±9.33	14	14.92±9.91	13.3± 12.11	14.2±7.4	7.66± 5.55
Daily balance, ml.	747.33± 440.55	690	782.28± 368.28	84.66± 187.33	334± 281.78	386.66± 257.77
The days of use simultaneous use of inotrops in ICU is ≥2.	12.16±9.16	8	5.92±3.62	3± 2.4	7.61±3.61	7.33±8.44
Duration of mechanical ventilation, hours.	240±230.4	120	103.2± 120.5	25.44±18.6	40.32± 28.08	31.92±26.6
Pulse Index LVAD	2.65±1.33	3.5	3.86±0.78	3.56±0.9	3.45±0.73	2.56±1.71
IABP support, day.	2.5±1.83	4	–	1.66±2.44	0.16±0.31	–
ECMO support, day.	4.4±5.84	–	0.11±0.19	–	–	–

The data after correction are statistically significantly different from the original ones, p<0.05.

In five patients who received heparin monotherapy, there was a need for repeated surgical intervention in order to drain a large amount of exudate on the 2–3rd day of the postoperative period, as well as infection of the outlet of the LVAD power cable (Table 4).

Table 4

Characteristics of complications in LVAD patients with different types of ACCT

ACTT / Complication	Heparyn	Varfarin	Heparyn + Varfarin+ ASA	H/V/ A+P2Y12-bl.	H/V/A + anty-Xa.	H/V/A + P2Y12+ anty-Xa.
Quantity of patients	12%	2%	28%	12%	40%	12%
Death case	12%	2%	10%	2%	2%	0
Kind of LVAD:	1POLVAD / 5 LVAD	BiVENTR. POLVAD	LVAD	1POLVAD/ 5LVAD	LVAD	LVAD
Percutaneous Interventions	10%	0	6%	0	2%	0
SIRS & sepsis case	4%	2%	6%	0	2%	0
AKI with CRRT:						
HD-	10%	2%	4%	–	4%	0
HDF-	2%	–	4%	–	4%	4%
Stroke:						
– Ischemic	6%	2%	4%	1%	1,5%	–
Hemorrhagic	–	–	–	–	0,5%	–
Nosocomial pneumonia	4%	2%	6%	4%	10%	2%
Acute liver failure	10%	0	1,5%	0	2%	0
Right ventricle failure	4%	0	2%	0	4%	0
Ao-valve regurgitation	2%	0	0	0	2%	2%

The data are statistically significantly different from the original, p<0.05.

100% of patients who received heparin monotherapy developed acute renal failure in the postoperative period, which required the use of renal replacement therapy. In 2% of patients with heparin monotherapy, the postoperative period was complicated by the development of hemorrhagic stroke, liver failure, aortic and right ventricular failure.

A patient treated with warfarin monotherapy postoperatively developed a BiPOLVAD exit site infection, resulting in sepsis, nosocomial pneumonia, renal failure, and right ventricular failure, leading to death.

100% of patients who received targeted anticoagulant therapy based on a combination of heparin, warfarin, and aspirin developed acute renal failure in the postoperative period, and 2% developed ischemic cerebral blood flow, which complicated the course of postoperative rehabilitation.

In patients who received fondaparinux sodium in combination with aspirin, clopidogrel and warfarin during the first seven days of the postoperative period, there were phenomena of renal failure, which required continued renal replacement therapy, as well as ischemic lesions of the brain, which, in combination with the generalization of the infectious process of the site the power cable coming out resulted in death.

In patients who received combined ATT, which consisted of warfarin, aspirin, clopidogrel, in 30% of cases has infection of the outlet of the power cable developed, and in 20% of cases – the development of acute renal failure with continuous renal replacement therapy (Table 5).

Table 5

Peculiarities of the course of infectious complications in patients with LVAD

Infection complication of LVAD patients	Control group of patients (N= 21)			Examinate group of patients (n= 29)		
	n=6	n=1	n=14	n=6	n=20	n=3
– primary postoperation – secondary of power cable	6% 2%	2%	16% 10%	4%	6% 12%	4%
Infectious pericarditis	2%	–	2%	2%	2%	–
Develop of sepsis	4%	2%	6%	–	2%	–

The data are statistically significantly different from the original, $p<0.05$.

The development of sepsis with a fatal outcome was noted in 20% of cases. Infectious pericarditis developed in 40% of patients. The main causative agents of infectious complications were Staphylococcus aureus, Klebsiella, Burkholderia, and Pseudomonas aeruginosa.

As shown in Table 7, timely acute renal replacement therapy (CRRT) in a short period of time helps to restore kidney function and further limit the manifestations of renal dysfunction. According to the obtained data, in all patients, the level of creatinine in the blood decreased in comparison with the previous values, also, against the background of renal replacement therapy, an increase in the rate of glomerular filtration was noted. Continuous renal replacement therapy has 43% patient from control group and 10% from main research group.

Discussion. As for the activity of the coagulation system according to ACT, it showed significant variability in both clinical groups. So, in the main group, the test cor-

responded to an average value of 123.8±3.7 units, and in the control group – 132.9±15.0 units. (p>0.05).

A similar situation was observed with regard to the final lactate level in the observation groups. So, in the main group, the lactate content did not exceed 4.6±0.8, and in the control group it reached 6.6±1.5 units. (p>0.05), which can be associated with a higher percentage of mortality.

At the same time, the risk of a fatal outcome in the control group was 3.5 times higher than in the main group (p<0.05).

Attention is drawn to the multidirectionality of changes in the sensitivity index to acetylsalicylic acid, which decreased in the control group from 495.5±62.2 to 444.8±57.3 units, and in the main group increased from 625.4±64.2 to 662.2±58.4 units. The higher level of D-dimer in the main group in comparison with the control requires an explanation, despite the fact that the increase in the indicator after the correction was more pronounced in the main group (Δ=+400% vs +148%).

The analysis of the daily fluid balance showed that during the stay in the ICU there was a decrease in the average daily balance from 9–11 ml/kg/day to 3–5 ml/kg/day. There is also an increase in the frequency of complications and the level of mortality in patients in whom the support of IABP and ECMO was more intensive during the first two days of the postoperative stay in the ICU (Δ=+105% vs +19%).

Further analysis showed that, depending on the applied anesthetic support, the duration of the surgical intervention, the volume of transfusion, the patients registered postoperative complications of different structure and frequency. The same factors caused postoperative mortality. When searching for the most significant predictors of survival, activated clotting time and lactate level at the end of surgery were identified as such.

The dependence of the risk of thrombosis or bleeding is significant, but not absolute. As studies have shown, even in the case of monotherapy, it has a non-linear nature and is obviously caused not only by the pharmacodynamics of the drug, but also by the presence of complications, both infectious and inflammatory and caused by dysfunctional relationships in the systems of the cardio-hepato-renal continuum.

It is noteworthy that the risk of an adverse clinical outcome increases significantly when the values of various coagulogram indicators are out of the target range at the same time. At the same time, the risk of a fatal outcome in the control group was 3.5 times higher than in the main group (p<0.05) on Table 6.

Table 6

Values of various score indicators range of bleeding& thrombosis

Group/ Case	Thrombosis	Bleeding	Pulmonary embolism
Control group	0.003357	-0.280719	-0.012796
Exame group		0.048388	0.297030

As can be seen from the above, this approach allows assessing the risk of bleeding, but not of thrombotic complications.

Thus, regardless of the applied monitoring methods, the possibility of prediction of coagulation drive and serious complications related to blood coagulation function seems questionable. Obviously, there are advantages to multimodal anticoagulation

therapy schemes, which require as frequent as possible full monitoring of the main indicators of the coagulogram.

In the first days of heparin therapy, three patients who received classical anticoagulation target therapy developed pronounced heparin-induced thrombocytopenia, which led to the appointment of alternative therapy using nadroparin calcium. Subsequently, one patient had gastrointestinal bleeding (GI) of unknown location.

In five patients who received heparin monotherapy, reoperation was performed for drainage of a large amount of exudate on the third day of the postoperative period. In two patients, the postoperative period was complicated by the development of renal failure. One patient developed extensive hemorrhagic stroke and liver failure.

In the group where patients received an infusion of heparin during the first three days, with subsequent transfer to the indirect anticoagulant warfarin and aspirin, half of the cases (six patients) developed acute renal failure. In three patients of this group, cerebral circulation disorders of the ischemic type developed, which complicated the course of postoperative rehabilitation. One patient developed thrombosis of the device's pump rotor with subsequent LVAD system replacement, with only temporary benefit. Also, one patient developed gastro intestinal bleeding (GIB) without a specific localization, but without a fatal outcome.

A patient receiving warfarin monotherapy underwent reoperation for chest bleeding in the first week postoperatively, which was subsequently complicated postoperatively by thrombosis of the device pump with subsequent replacement of the LVAD system, combined with the development of renal and pulmonary insufficiency, which resulted in a fatality.

One patient, in the group where targeted anticoagulant therapy included fondaparinux sodium in combination with aspirin and warfarin, developed renal dysfunction and gastrointestinal bleeding -GIB of unknown etiology and location in the first week.

The patient, who after three days of heparin therapy was switched to clopidogrel therapy, developed an ischemic brain injury during the second week of treatment.

In five patients receiving combined ATT, which included warfarin, aspirin, and clopidogrel, 30% of cases developed GIB of unknown etiology, and 20% of that cases – renal dysfunction.

The most common complication after LVAD implantation is bleeding. Such patients require antiplatelet and anticoagulant therapy, which increases the risk of bleeding. Bleeding that occurs in the first 14 days after implantation is mainly associated with surgical intervention. The causes of late bleeding are: the development of arteriovenous malformations, liver dysfunction due to right ventricular failure and acquired von Willebrand syndrome. [4]. Identifying potential causes and risk factors for bleeding is important to improve treatment outcomes and quality of life in LVAD patients. The cumulative risk of CHD for patients receiving such types of left ventricular mechanical support devices as HeartMate II and HeartWare is 21%, 27%, and 31%, at the first, third, and fifth years, respectively [5; 6]. At the same time, previous studies have found that the upper gastrointestinal tract is the most common site of bleeding in patients implanted with an LVAD [5; 7].

A recent, small, retrospective study showed that videocapsule endoscopy, which captures the mucosa of the entire gastrointestinal tract using images of a disposable oral microcamera [6], is a safe and effective method for the detection of unexplained gastrointestinal tracts. Mostly, only videocapsule endoscopy detected bleeding from the

small intestine and angiodysplastic changes of the small intestine, which are difficult to diagnose by a generally accepted method.

Another possible explanation for the high risk of GIB among laminar LVAD recipients is acquired Willebrand syndrome secondary to hemolysis [7]. Recent studies have shown that all patients were diagnosed with typical laboratory findings of acquired von Willerbrand syndrome (WS) after LVAD implantation, but not all experienced bleeding [8; 9]. These data suggest that WS alone is not sufficient for the development of bleeding complications after LVAD implantation.

Another serious complication is hemorrhage in the central nervous system, which occurs in the remote period. In a study with HeartMate II, it was shown that targeted anticoagulant therapy in the first two years after LVAD implantation was accompanied in 11% of cases by the development of hemorrhagic stroke as the main factor in delayed mortality [10]. A recent retrospective review showed that of 114 HeartMate II patients, 5% had intracranial hemorrhage [11]. The frequency of development of hemorrhagic-type cerebrovascular disorders was higher in the group of patients who took aspirin at a dose of 325 mg compared to the group of patients who took aspirin at a dose of 81 mg in combination with dipyridamole, or just aspirin at a dose of 81 mg [11].

An important reason for early re-hospitalization after LVAD implantation is anemia without an established source of bleeding, which requires red blood cell transfusion [12].

Optimal treatment of patients at increased risk of bleeding remains a challenge. The patient's clinical condition often requires a temporary change in the international normalized ratio, often by reducing it or temporarily withdrawing anticoagulation treatment to stop significant or even life-threatening bleeding. Boyle A.J. those et al., investigating the safety “corridor” of the international normalized ratio for LVAD patients, concluded that a target international normalized ratio of 1.5 to 2.5 may be safe in patients at increased risk of bleeding [14]. However, this advantage comes at the expense of a much higher risk of developing thrombotic complications [15].

Despite antithrombotic treatment, thromboembolic complications after LVAD implantation are common. These include: cerebrovascular ischemic injury, transient ischemic attack, CNS arterial embolism, or device motor thrombosis.

Conclusions

1. A monotherapeutic approach to anticoagulant therapy in patients with LVAD is clearly dangerous for patients due to the increased percentage of mortality and complications of various genesis. Combination strategies of heparin with warfarin and aspirin did not have a statistically significant difference in mortality and the number of complications with the strategy of a monotherapeutic approach. In contrast, the polytherapeutic approach with the addition of P1Y12-blockers and factor Xa blockers of blood coagulation had significantly lower 80%, statistically significant ($p<0.05$), levels of mortality and complications.

2. The dosage level of anticoagulants did not have a correlation of the dose from the instructions for the drug to the obtained level of the corridor value of the corresponding analyzed factor on the next day: ASA – ASPI, heparin – APTT, warfarin – INR, P2Y12 – ADP. This was due to the significant influence of concomitant comorbidity factors.

3. The highest percentage of complications, in the form of bleeding and thromboembolic events, was observed in the control group of patients who received monotherapy with heparin or warfarin or their combination and correlated with right ventricular

failure in 20% of cases and an increase in the diameter of the portal vein, which, when using modified ACTT, allowed reduce this indicator by 50%.

4. Alternative ACCT with the use of thrombin inhibitors, P1Y12-blockers and aspirin in the study group of patients was accompanied by a 70% decrease in the frequency of development of hemorrhagic and thromboembolic complications, statistically significant ($p<0.05$).

5. Infectious complications developed in 80% of cases, in 40% of patients the infection was complicated by the development of sepsis. In 20% of patients, antibacterial therapy did not have a positive effect and sepsis had fatal consequences. As our study showed, the use of targeted anticoagulant therapy does not have a significant impact on the strategy of treatment of infectious complications.

6. Acute renal failure develops in patients with implanted LVADs in 40% of cases and requires GNST due to thrombosis of the proximal part of the tubules of the kidneys and a decrease in the perfusion pressure on the laminar blood flow of the mechanical circulatory support device. The use of an alternative ACCT scheme developed by us allows to reduce the frequency of development of this complication by 90%.

7. Regardless of the applied monitoring methods, the possibility of prediction of coagulation drive and serious complications related to blood coagulation function seems doubtful. Obviously, there are advantages to multimodal anticoagulation therapy regimens, which require full monitoring of the main parameters of the coagulogram as often as possible.

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