KEY ASPECTS OF USING LOW-FREQUENCY PIEZOELECTRIC THROMBOELASTOGRAPHY AS A DYNAMIC METHOD OF ASSESSING THE STATE OF THE HEMOSTASIS SYSTEM IN REAL TIME

КЛЮЧОВІ АСПЕКТИ ВИКОРИСТАННЯ НИЗЬКОЧАСТОТНОЇ П'ЄЗОЕЛЕКТРИЧНОЇ ТРОМБОЕЛАСТОГРАФІЇ ЯК ДИНАМІЧНОГО МЕТОДУ ОЦІНКИ СТАНУ СИСТЕМИ ГЕМОСТАЗУ В РЕАЛЬНОМУ ЧАСІ

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Abstracts

A condition that leads to the development of venous or arterial thrombosis and its consequences is considered prothrombotic. In the biological regularity of the system of regulation of the aggregate state of blood (RASK) under thrombohazard, in the broad sense of this word, one should understand the incoherence of the PACK subsystems, which makes it impossible to ensure the discreteness of the hemostatic potential in different areas of the blood flow adequately to the conditions formed in them. Venous thromboembolism is the most common vascular disease after acute myocardial infarction and stroke. According to a number of authors, the frequency of objectively confirmed in-hospital deep vein thrombosis (DVT) reaches approximately 10 to 40% among patients undergoing general surgery and 40 to 60% after major orthopedic operations. In 25–30% of patients, the thrombosis affects the deep veins, causing DVT and can lead to pulmonary embolism (PE). In surgical and orthopedic patients, PE occurs in 10% of patients and is the main cause of hospital deaths. Despite conducting many studies of the blood coagulation system, cases of thromboembolic complications in patients who are at risk of thrombotic complications are becoming more and more frequent.

In cases where it is necessary to obtain a dynamic picture of the blood coagulation system, for example, cardiovascular surgery, obstetric bleeding, severe injuries, etc.

This article reflects the technique of low-frequency piezoelectric thromboelastography, its practical value and examples of using the NPTEG method.

In addition, the methods of using NPTEG to detect the degree of risk of thrombotic danger in patients included in the risk group are displayed.

Conclusion. Thromboelastography, in particular NPTEG, is an effective method of assessing hemostatic potential, which, unlike standard laboratory tests, provides a detailed picture of the hemostasis system in graphic and numerical form, and a larger number of indicators makes it possible to determine disorders in a specific link of the hemostasis system. Thus, NPTEG is an effective method of assessing hemostasis to determine therapeutic tactics and the risk of thrombo-hemorrhagic disorders in patients with changes in hemostatic potential.

Key words: hemostasis, thrombosis, bleeding, thromboelastography.

Протромботичним вважають стан, який призводить до розвитку венозного чи артеріального тромбозу та їхніх наслідків. У біологічній закономірності системи регуляції агрегатного стану крові (РАСК) під тромбонебезпечністю у широкому значенні цього слова слід розуміти неузгодженість підсистем РАСК, що робить неможливим забезпечення дискретності гемостатичного потенціалу в різних ділянках кровотоку адекватно сформованим у них умовам. Венозна тромбоемболія є найпоширенішим захворюванням судин після гострого інфаркту міокарда та інсульту. За даними низки авторів, частота об'єктивно підтвердженого госпітального тромбозу глибоких вен (ТГВ) досягає приблизно від 10 до 40% серед хворих, які проходять за загальною хірургією, і від 40 до 60% після великих ортопедичних операцій. У 25–30% пацієнтів тромбоз вражає глибокі вени, викликаючи ТГВ, і можуть призвести до тромбоемболії легеневої артерії (ТЕЛА). У хірургічних та ортопедич-

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них хворих ТЕЛА трапляється у 10% пацієнтів та є основною причиною стаціонарних летальних випадків. Незважаючи на проведення багатьох досліджень системи згортання крові, випадки тромбоемболічних ускладнень у пацієнтів, що входить до групи ризику тромботичних ускладнень, стають усе більш частими.

У випадках, коли необхідно отримати динамічну картину системи згортання крові, наприклад, кардіо-васкулярна хірургія, акушерські кровотечі, важкі травми тощо.

У цій статті відображена методика низькочастотної п'єзоелектричної тромбоеластографії, її практичне значення та приклади використання методу НПТЕГ.

Окрім того, відображені методи використання НПТЕГ для виявлення ступеня ризику тромбонебезпеки у пацієнтів, що входять до групи ризику.

Висновок. Тромбоеластографія, зокрема НПТЕГ, є ефективним методом оцінки гемостатичного потенціалу, який, на відміну від стандартних лабораторних досліджень, надає розгорнуту картину системи гемостазу в графічній та чисельній формі, а більша кількість показників дає змогу визначити порушення в конкретній ланці системи гемостазу. Таким чином, НПТЕГ є ефективним методом оцінки гемостазу для визначення терапевтичної тактики та ризику тромбо-геморагічних розладів у пацієнтів зі змінами гемостатичного потенціалу.

Ключові слова: гемостаз, тромбоз, кровотеча, тромбоеластографія.

The prothrombotic phase may result in the formation of venous and arterial thrombosis, leading to various consequences. The biological mechanism governing the regulation of blood clotting, known as the Blood Aggregation Regulation System (RAS), during thromboembolism, is primarily attributed to the malfunction of the RAS subsystem [4]. This malfunction prevents the proper discretization of hemostatic potential in different segments of blood flow, hindering the formation of clots as needed. Arterial thrombosis typically occurs following the erosion or rupture of an atherosclerotic plaque, leading to platelet-mediated thrombi that can cause ischemic damage, particularly in tissues at the end of the vascular bed [3]. Acute coronary syndrome and ischemic stroke are severe and common consequences of atherothrombosis. These outcomes are primarily driven by tissue ischemia, which can develop gradually due to atherosclerotic disease progression or suddenly in cases of thrombus embolization in blood vessels or the heart. Venous thromboembolism (VTE) is a prevalent vascular disorder following acute myocardial infarction and stroke. Studies suggest that the incidence of in-hospital deep vein thrombosis (DVT) ranges from approximately 10% to 40% in patients undergoing general surgery and 40% to 60% after major orthopedic procedures. DVT affects deep veins in 25–30% of cases, leading to potential pulmonary embolism (PE). PE occurs in 10% of surgical and orthopedic patients and is a significant cause of hospital mortality [1; 2].

VTE clinically presents as deep vein thrombosis (DVT) or pulmonary embolism (PE), with PE often resulting from DVT. The formation and propagation of thrombi depend on vascular wall integrity, blood flow disruptions, and activation of coagulation factors, known as Virchow's triad. Blood flow disturbances or venous stasis may occur due to extended periods of immobility, prolonged bed rest, or patient positioning during surgery. Various perioperative risk factors for VTE include the type of surgery, postoperative anastomosis failure, smoking history, immobility, trauma, obesity, cardiovascular and respiratory conditions, estrogen use, oncological diseases, age over 40 years, acquired hypercoagulable conditions, and hereditary hypercoagulation states [4; 6; 7].

Despite extensive research on the blood coagulation system, the incidence of thromboembolic complications in high-risk patients is on the rise, particularly during surgical procedures and the postoperative period, where the intervention itself acts as a triggering factor for thromboembolism. However, thrombosis is a preventable complication through timely diagnosis, risk assessment, and appropriate preventive measures, including both pharmacological and mechanical interventions. In cases where planned surgical procedures are scheduled for at-risk patients, angiosurgical intervention may be considered based on clinical indications [3; 8].

When it comes to diagnosing prothrombotic and thrombotic conditions in surgical candidates,

assessments typically include Doppler imaging of lower limb vessels, echocardiography, routine laboratory tests, and, when feasible, thromboelastography. Thromboelastography, a technique that has gained popularity in cardiac and vascular surgery in recent years, allows for a detailed dynamic evaluation of all components of the hemostasis system. While current methods for evaluating the hemostasis system are informative, they have a notable limitation – conventional approaches only offer a snapshot of the system at the moment of blood sampling, without providing insights into the reserve capacities of platelet-vascular, coagulation, and fibrinolysis components. When managing patients at risk of thrombo-hemorrhagic disorders, it is essential not only to assess the levels of markers within the Blood Aggregation Regulation System (RAS) but also to understand their functional interplay in maintaining the optimal hemostatic potential within the vascular bed. This comprehensive evaluation enables the characterization of the RAS system's functional activity and its response to changes in hemostatic potential triggered by various factors, ultimately allowing for an assessment of the compensatory abilities of the blood coagulation and fibrinolysis systems [9; 10].

Thromboelastography (TEG) is an important method of diagnosing hemostasis, which determines blood coagulation parameters in real time. This method allows you to assess the quality of blood coagulation, the risk of bleeding and the possibility of thrombus formation. Thromboelastography allows for a quick and accurate assessment of the patient's hemostasis in real time, which is especially important in critical conditions such as injuries, bleeding, critical conditions accompanied by thrombo-hemorrhagic disorders. Also, this method can be useful in anticoagulant therapy, pregnancy and in patients with thrombotic diseases. Routine laboratory indicators can reflect a specific parameter of the hemostasis system at the specific moment of taking the analysis, but thromboelastography reflects a dynamic picture of blood coagulation, which allows for a comprehensive assessment of the process of thrombus formation and to determine in more detail the link of hemostasis that needs to be treated with medication in the future.

In recent times, significant emphasis has been placed on "global" tests for the operational and integrative evaluation of plasma and cellular elements in whole blood, particularly in light of the emerging trend of "Point of Care Testing". These components play a crucial role in the fibrinogenetic process. Hemostatic potential (HP), a key aspect of hemocoagulation, can be assessed through "global" thromboelastography tests. Notably, the thromboelastograph is particularly informative during the later stages of fibrinogenesis, encompassing events such as lateral fibrin folding, cross-linked fibrin (PSF) formation, clot stabilization, and subsequent lysis.

The method of low-frequency piezoelectric thromboelastography NPTEG consists in the analysis of changes in the viscoelastic properties of blood during hemocoagulation, when it changes from a liquid state to a solid-elastic state. The dynamics of this process is determined by changes in the aggregate state of the blood and is recorded in the form of an integrated curve, where each point (Ai) reflects the state of the system at a certain moment in time (Ti).

NPTEG evaluates the following parameters:

A0 is the initial value of the amplitude at time t0.

t1 reaction period (time in minutes from the beginning of the study to reaching the minimum amplitude of NPTEG – A1).

A1 max t1 – decrease in amplitude over time – "t1" (reaction period).

t2 is the time to reach amplitude A2

A2 increase in the amplitude of NPTEG by 100 v.o.

t3 blood coagulation time (CTT) – gelling point (TJ) per minute, determined automatically when tg (tangent) of the curve angle changes by 60%.

A3 amplitude value of NPTEG in TJ in relative units.

A4 amplitude value of NPTEG 10 minutes after reaching the maximum amplitude.

A5 maximum amplitude of NPTEG, within 10 minutes.

t5 time of reaching the maximum amplitude (MA) (A5) (time of formation of the fibrin-platelet structure of the clot).

A6 value 10 min after reaching MA.

Calculated indicators of NPTEG include: Intensity of contact coagulation (CC) is defined as separate from the division of the difference in amplitudes (A1–A0) by the reaction period "t1". This indicator mainly reflects the aggregation activity of formed elements of blood, the I and II phases of coagulation or its suspension stability (SSC). The intensity of the coagulation drive (ICD) is defined as separate from the division of the difference in amplitudes (A3–A1) by the blood coagulation time (t3). This indicator mainly characterizes the proteolytic stage of the III phase of hemocoagulation. And the part of the NPTEG curve near the gelation point (changes in the tg angle of the curve by ~ 60%) reflects the beginning of the polymerization process, which at the gelation point leads to the formation of fibrin gel - the main structural frame of the hemostatic clot.

The constant of thrombin activity (CTA) is defined as separate from the division of the amplitude of NPTEG A2=(100 const) by time (t2–t1). The use of this indicator in the analysis of NPTEG is due to the need to define a universal criterion for assessing the intensity of the proteolytic stage of fibrin formation.

The intensity of polymerization of the clot (IPC) is determined as a separate division of the difference in the amplitudes of NPTEG (A4–A3) by a constant time = 10 min. This indicator mainly characterizes the polymerization stage of the III phase of hemocoagulation. Due to the fact that the process of changing the viscoelastic properties of the clot during polymerization of fibrin and the formation of transverse intermolecular (covalent) bonds is quite long, and the moment of transition to the stabilization stage is quite conditional, for the unification of the NPTEG analysis, we will apply a constant time interval equal to 10 minutes of gelation point registration. This makes it possible to evaluate and compare the initial stage of clot polymerization – the formation of a viscoelastic gel (post-gel).

The maximum amplitude (MA) of the clot. It is defined as the difference in values (A5–A1) in o.e. an indicator that characterizes the maximum density of the clot caused by the activity of platelets and the quantitative/qualitative characteristic of PSF. The indicator characterizes the end of the process of formation of a cross-linked fibrin clot that has undergone retraction.

Intensity of total coagulation (ITC). It is defined as separate from the division of the maximum amplitude (MA) by the time of its achievement (t5). The indicator makes it possible to evaluate the intensity of fibrinogenesis.

Intensity of clot retraction and lysis (IRLZ). It is determined as a percentage by which the amplitude of the clot decreases within 10 minutes after reaching MA: (A5–A6)/A5×100%. plasmin, leukocyte protease (granulocyte elastase, cathepsin G, monocytic cathepsin D, complement), erythrocyte kinases, which is in this volume of blood (0.5 ml). Therefore, the time of analysis to increase the accuracy of the research can be multiplied to 20, 30 minutes.

The coefficient of total anticoagulation activity (CTAA) is determined in relative units, as separate from the division of ICD by IPP. This blood activity is a key link in the regulation of the coagulation process and is due to the functioning of several groups of inhibitors: disaggregants (NO2; PGI2; c-AMP/cGMP), specific (serine) and non-specific inhibitors of serine proteases (α2-macroglobulin), tissue factor – TFPI), coenzyme inhibitors (proteins C and S, thrombomodulin) and fibrin degradation products. This indicator is proposed due to the fact that the peak values of the system functioning are manifested mainly in the I and II phases of coagulation, as well as at the stage of proteolysis of the III phase before the start of the process of active polymerization of the clot (TC).

To standardize the pre-analytical stage of research, venous blood sampling is performed with a three-component silicone syringe with a rubber cuff of one volume – 1.0 ml, without applying a tourniquet. The interval between blood sampling and placing it in a disposable cuvette should not exceed 20 seconds. The plastic cuvette located in the thermostat of the

device is filled to the measuring risk (~0.45 ml) and the study begins. Below (Figures 1 and 2) is a graph of changes in the aggregate state of blood during its coagulation (healthy volunteer). The amplitude of the studied process is estimated along the ordinate axis – (A1), in relative units. Along the abscissa axis is the research time (T1), in minutes.

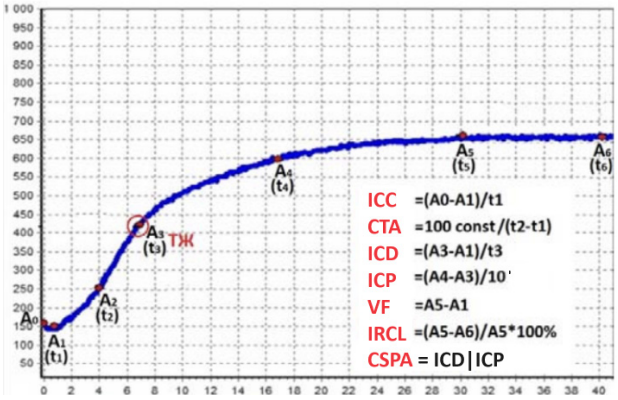

Fig. 1. NPTEG of whole blood of a healthy volunteer

(A0–A6) – amplitude of NPTEG in o. at the stages of PSF formation, retraction and lysis; t1–t5 – time intervals of fibrinogenesis stages in minutes: JP (t3) – gelation points in minutes; MA – the maximum density of the clot

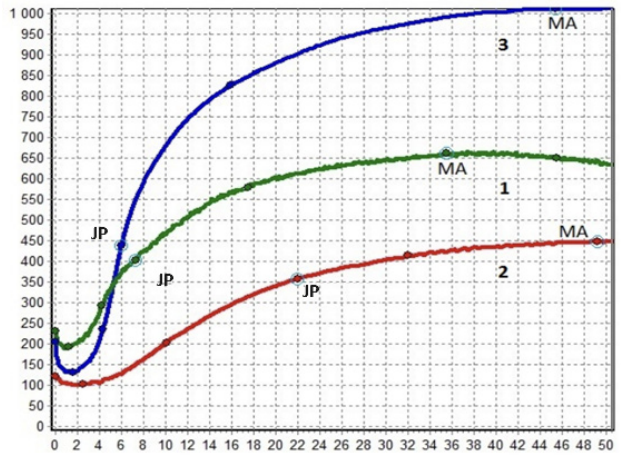

Fig. 2. The analysis of NPTEG in case of hypo- and hypercoagulable changes in the state of the RASK system is based on the comparison of registered NPTEG with reference indicators of the normocoagulation state

NPTEG in normo-(1), hypo-(2) and hypercoagulable (3) conditions.

Thus, the application of this technology creates real prerequisites not only for evaluating the temporal slice of HP, but also for monitoring the effectiveness of antithrombotic therapy.

To confirm the possibility of the technology for evaluating the antiplatelet effect of the COX-1 inhibitor in a smaller dose (75 mg of aspirin) in Figure 3 shows the data obtained from 10 healthy volunteers, which clearly demonstrates the trend of a significant increase in t1 when taking this medicinal product.

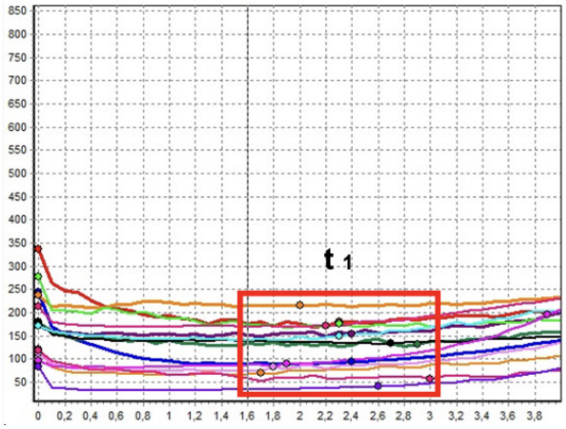

Fig. 3. Scaled baseline NPTEG plots of 10 healthy volunteers before (left) and 12 hours (right) after taking 75 mg of aspirin

The display of the effect of Heparin on the hemostasis system using low-frequency piezoelectric thromboelastography is quite indicative. The next study, performed with the participation of 10 conditionally healthy volunteers (Figure 4), demonstrates a comparable reaction of DP to the maximum effect of the drug. At the same time, the assessment of the intensity of the proteolytic stage of fibrinogenesis is carried out by comparing t1, t2 and CTA – a universal criterion for this stage of hemocoagulation.

The technique of instrumental research of low-frequency piezoelectric thromboelastography is used not only for the purpose of detecting pathology during an incident, but also as a method of identifying the risk of thromboembolism. For this, it is necessary to apply the functional stress

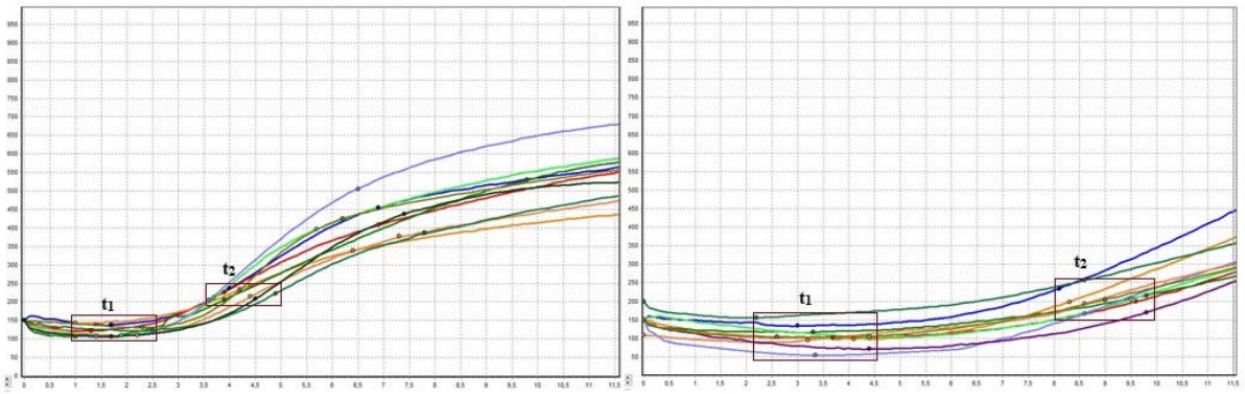

Fig. 4. Scaled plots of NPTEG recorded in 10 healthy volunteers before (left) and 10 minutes (right) after administration of 5000 units heparin

test "test with double local hypoxia of the upper limb". This test is especially useful in cases where patients with existing predictors and risk factors for thrombo-hemorrhagic complications are subject to planned surgical interventions. Determining the level of thrombogenicity and assessing violations of specific links of the hemostasis system make it possible to adequately choose preventive therapy, reducing the risk of complications in the perioperative period.

A randomized prospective study was conducted. Patients were divided into two groups depending on the presence of risk factors for thrombosis. Group 1 consisted of healthy volunteers (n = 40) who are not at risk of thrombosis. Group 2 includes patients with existing factors of thrombotic risk (n = 120) who are preparing for scheduled surgical interventions. The criteria for inclusion in Group 2 were: anamnesis of smoking, history of venous thromboembolism, paralysis of the lower limbs, trauma (fracture of the bones of the lower limbs, etc.); morbid obesity (body mass index more than 35 kg/m^2); concomitant pathology of the cardiovascular system and respiratory system, including acute myocardial infarction, atrial fibrillation, congestive heart failure, ischemic stroke in anamnesis, obliterating atherosclerosis, chronic respiratory failure, chronic obstructive pulmonary disease, use of estrogens in pharmacological doses – for example, oral contraceptives, hormone replacement therapy, oncology, age >40 years, acquired hypercoagulation conditions, including autoimmune diseases. Exclusion factors were: taking antiplatelet and/or anticoagulant therapy.

The patients underwent a functional test known as "double local hypoxia of the upper limb" (DLHUL), utilizing thromboelastographic (TEG) methods to examine the hemocoagulation system. This method is based on inducing Virchow's triad in a specific area of the vascular bed, involving vascular wall damage, blood flow obstruction, and alterations in blood rheology. The primary objective of this functional test is to trigger a response that delineates the hemostatic limits, as well as to observe the onset and duration of adaptive and compensatory reactions within the hemostasis system. Double local hypoxia of the upper limb is achieved by temporarily occluding arterial and venous vessels in the limb for approximately 5–6 minutes, with a 20–25-minute interval between occlusions using a tourniquet. Thromboelastograph readings are taken before and after the test to assess various aspects of hemostasis, including the aggregate blood state (A0), contact coagulation intensity (CCI), coagulation drive intensity (ICD), maximum clot density (MA), and fibrinolytic activity represented by clot retraction and lysis index (IRCL).

Analyzing the data of thromboelastography after performing DLHUL, two types of reaction of the hemostasis system were found among patients of Group 1 in patients without predictors of thrombotic risk: the first type is compensated

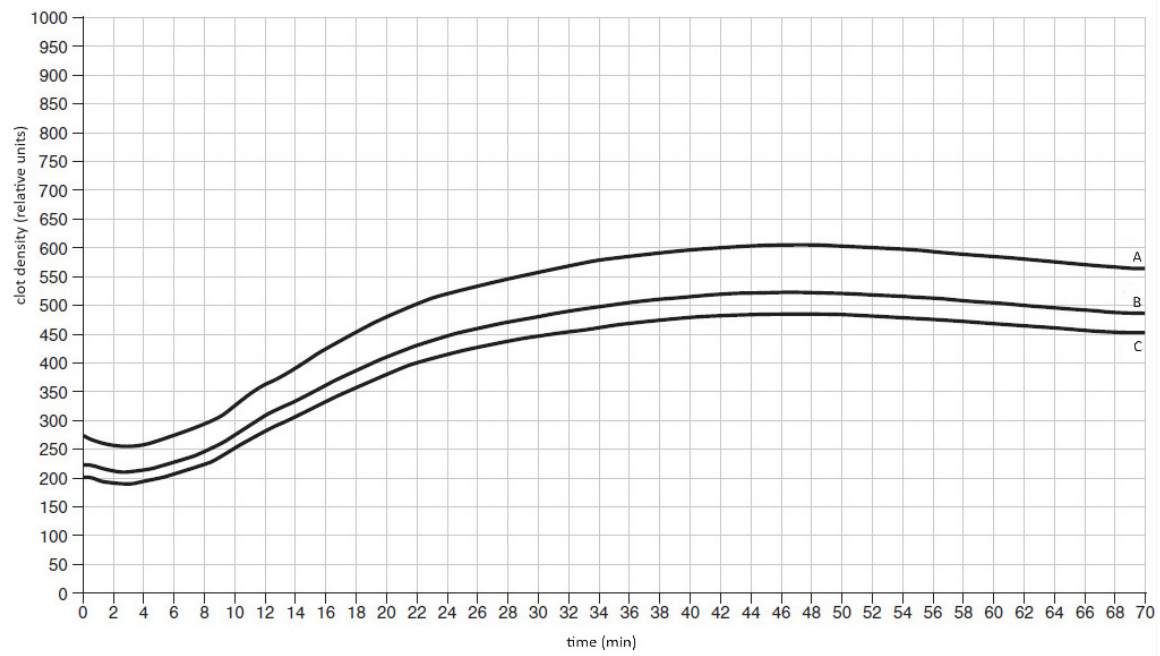

Fig. 5. Changes in the state of the hemocoagulation system in Group 1 before and after a functional test with double local hypoxia of the upper limb: A – subcompensated type; B – compensated type; C – before carrying out a functional test with double local hypoxia of the upper limb

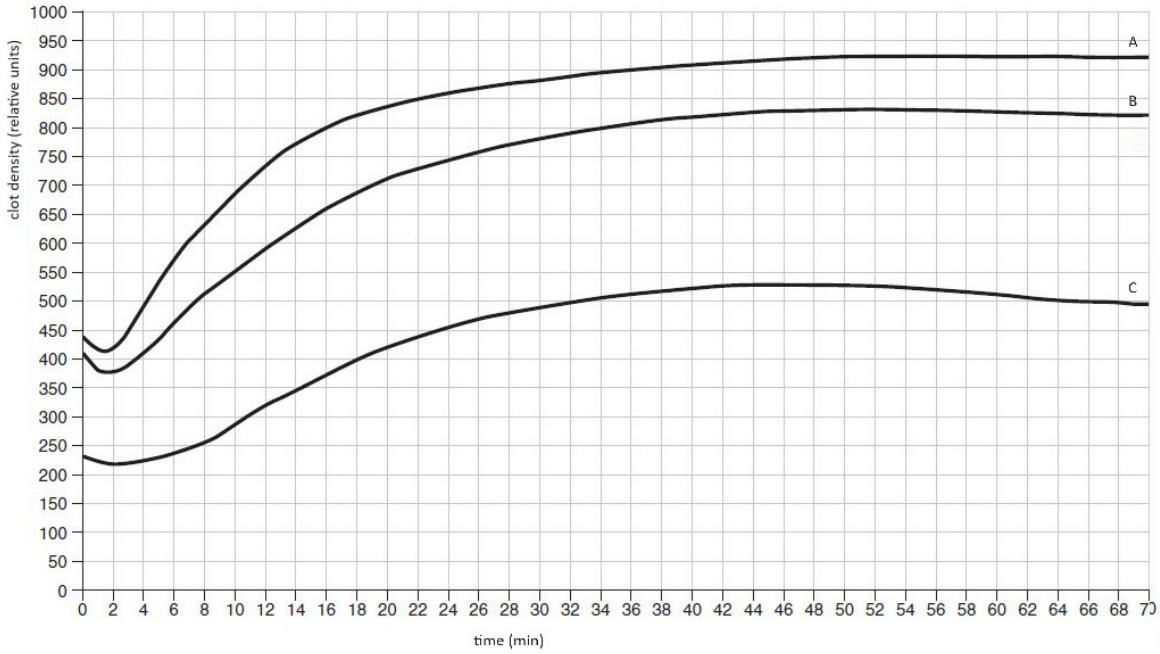

Fig. 6. Thromboelastogram of changes in hemostatic potential in patients with risk factors for thrombosis (Group 2) before and after performing a functional test with double local hypoxia of the upper limb: C – averaged thromboelastogram of group 1; averaged thromboelastogram of Group 2 before B and after A performing the DLHUL test

(characterized by a decrease in the indicators of the vascular-platelet component; the second type is subcompensated (characterized by an increase in the indicators of the vascular-platelet component). These two types have different TEG indicators corresponding to the compensated and subcompensated type and statistically occur with the same frequency (n1 = 20); (n2 = 20) (Table 1).

In the subjects of Group 1, who had a subcompensated type of reaction, an increase in CCI and a decrease in blood clotting time were found after the stress test. This indicates an increase in the external mechanism of prothrombinase formation. Evaluating all the TEG indicators obtained during the study, it was found that the reaction of the procoagulant link of the blood coagulation system in group 1 in response to the influence of the trigger (DLHUL test) indicates a change in the directionality of the hemostatic potential in the direction of hypercoagulation (Figure 1). In the subjects of group 1 with the compensated type, there is an increase in the components of fibrinolysis. There was a decrease in ICC compared to the subcompensated type, after the DLHUL test and an increase in blood clotting time, indicating a decrease in the external mechanism of prothrombinase synthesis. Considering the data in Table 1 and comparing the graphs in Figure 1, a hemostatic potential towards hypocoagulation is observed.

When conducting a DLHUL test in subjects of Group 2, the reaction of the hemostasis system to the trigger stimulus was determined (Table 1). The state of the hemostasis system in Group 2 patients is characterized by marked changes in the hemostatic potential in all links of the hemostasis system. In the vascular-platelet link, a violation of platelet aggregation was noted, with an increase in indicators in response to a stimulus. According to TEG data (Table 1), a statistically probable deviation from the norm of A0 and CCI indicators, which characterize the aggregation properties of platelets, was found. The CCI after performing the functional test exceeds the indicator before performing the functional test by 21.07%. The initial indicator of the aggregate state of blood (A0) increased by 5.87%. An increase in the index of coagulation drive (ICD) by 8.51%, an increase in the maximum density of the MA clot by 8.17%, indicate the activation of the coagulation layer. Fibrinolytic activity, which reflects the indicator of IRCL, after performing the DLHUL test

Table 1

Results of TEG during DLHUL

Indicator	GROUP 1				GROUP 2			
	Before		After		Before		After	
	M	±σ	Compensated type	Subcompensated type	M	±σ	M	±σ
Aggregate state of blood (A0)	225.22	13.32	211.31 ± 20.64*	269.56 ± 17.15*	435.02	22.44	462.13	30.01
Intensity of contact coagulation (CCI)	86.32	1.01	75.54 ± 1.12*	91.01 ± 1.01*	142.17	2.44	180.12	3.46*
Intensity of coagulation drive (ICD)	21.15	0.62	20.65 ± 0.46*	21.37 ± 0.41*	41.07	1.12	44.89	1.66*
Maximum clot density (MA)	513.51	31.44	490.11 ± 31.01*	600.03 ± 33.42*	878.01	60.99	956.13	42.44
IRCL	15.55	0.42	21.04 ± 0.42*	15.66 ± 0.44*	7.47	0.77	6.04	0.45*

Notes: * – $p < 0.05$ – statistically significant difference between the background and sample in the group; * – $p < 0.05$ – a statistically significant difference between studies after conducting a test with double local hypoxia

significantly decreased (by 23.67%), which indicates the inhibition of fibrinolytic activity in patients of group 2 after the functional test (Figure 2). When conducting the DLHUL test in the subjects of group 2, a decompensated (n1 = 98) and exhausted (n2 = 22) type of reaction to the test with local hypoxia of the upper limb was determined, for the most part. That is, with increased platelet aggregation, hypercoagulation, inhibition of the anticoagulant system and fibrinolysis before the action of the trigger factor, after performing the DLHUL test, these disorders in the hemostasis system progress towards hypercoagulation, which is indicated by the increase in platelet aggregation, the strengthening of the coagulation link of the hemostatic system, the depression of fibrinolysis increases. However, the intensity of these changes is not as high as in patients of group 1 after the DLHUL test. Depending on the type of reaction of the platelet-vascular, coagulation components of hemostasis and fibrinolysis to the influence of the trigger, two types of reaction of the blood aggregate state regulation system are possible in people who do not have an anamnesis of factors provoking a hypercoagulable state: compensated and subcompensated. Therefore, when planning surgical intervention in this cohort of patients, the risk of thrombotic complications is low. Depending on the type of reaction of the platelet-vascular, coagulation components of hemostasis and fibrinolysis to the influence of the trigger, two types of reaction of the blood aggregate regulation system are possible in people with an anamnesis of factors provoking a hypercoagulable state: decompensated (more often) and depleted (less often). Patients with an anamnesis of factors provoking a hypercoagulable state have a high risk of perioperative thrombotic complications and a possible risk of thrombo-hemorrhagic complications, including the syndrome of disseminated intravascular coagulation.

Conclusion. Thromboelastography, in particular NPTEG, is an effective method of assessing hemostatic potential, which, unlike standard laboratory tests, provides a detailed picture of the hemostasis system in graphic and numerical form, and a larger number of indicators makes it possible to determine disorders in a specific link of the hemostasis system. Thus, NPTEG is an effective method of assessing hemostasis to determine therapeutic tactics and the risk of thrombo-hemorrhagic disorders in patients with changes in hemostatic potential.

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