Thromboembolic Complications and Its Relationship with the State of the Blood Coagulation and Anticoagulation System in Acute Calculus Cholecystitis

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ABSTRACT: Postoperative thromboembolic complications worldwide tend to increase in frequency, which is the cause of disability and mortality. The authors note that the risk of developing feasibility study can vary significantly depending on the nature of the operation, its duration, the type of anesthesia and the general somatic background of the patient. There are no existing schemes for the use of drugs for this disease, and methods for the prevention of feasibility studies are carried out without taking into account the state of the blood coagulation and anti–coagulation system. Patients suffering from obesity are most prone to EFT. Among obese individuals, calculus cholecystitis is more common than in people with normal body weight. Therefore, there is an urgent need for further study of the state of the blood coagulation and anticoagulation system in obese patients with ACC.

KEYWORDS: pulmonary embolism, thromboembolic complications, cholelithiasis, acute calculus cholecystitis.

INTRODUCTION
Gallstone disease (GSD) is one of the most important medical and social problems of modern society, it appears along with a decrease in the quality of life of patients, the development of various complications that can be life–threatening, and an increase in the frequency of surgical interventions, which and it brings a huge financial burden to the world, it also destroys the health care system [5;30;34]. For example, in the United States, the annual cost of surgical treatment of patients with cholelithiasis is estimated at $6.5 billion [34].

Calculation cholecystitis (CC) is one of the most common diseases of the abdominal organs, ranking third in the overall structure of diseases after cardiovascular diseases and diabetes mellitus [4]. According to World Health Organization today, cholelithiasis among various diseases of the biliary system takes 50–65% [40]. According to statistical studies of recent years, 10–15% of people in the world suffer from cholelithiasis [3;5].

Diagnostic errors made in 12–38% of cases are accompanied by a consistently high mortality rate (2.5%), and with the development of severe complications, and even more so in the presence of cardiovascular diseases–from 14–27% to 40% of cases [2;10].

THE MAIN PART
Pulmonary embolism (PE) is a syndrome characterized by blockage of the branches of the pulmonary artery by thrombi formed in the veins of the systemic circulation and a number of pathological reactions, the severity of which directly depends on the size of the thrombus, the compensatory capabilities of the right ventricle and the severity of concomitant diseases. This is a serious emergency, requiring urgent action, a condition often accompanied by the development of shock and a drop in blood pressure. Thromboembolism is not a separate disease; this is only a consequence of various pathological processes, as a result of which blood clots form in the lumen of arteries or veins [6;15;21].

This is the third most common cardiovascular disease with an annual incidence of 100–200 per 100 thousand people. VTE can be fatal in the acute phase or lead to a chronic course and disability [27;36].

The prevalence of PE progressively increases with age, which significantly increases the likelihood of patients with chronic obstructive pulmonary disease, obesity, and atherosclerotic vascular disease [17;32].
In most cases, embolism is the result of deep vein thrombosis of the lower extremities. The main source of thrombi is the system of the inferior vena cava (up to 85%). Much less often, blood clots form in the system of the superior vena cava (1.3–1.7%) or in the right heart (10–12%). The most common site of thrombus formation is the veins of the legs. The most dangerous are the so-called floating blood clots. After separation, the thrombus with blood flow passes through the right heart and enters the pulmonary artery, leading to blockage of its branches. The size of the thrombus determines the caliber of the obturated vessel and, to a large extent, the severity of the clinical picture (shock, hemodynamic disturbances).

Allocate: massive thromboembolism—develops with blockage of 50–75% of the vascular bed, it is accompanied by a clinical picture of shock, hypotension, acute right ventricular failure; submassive thromboembolism—occurs when less than 30% of the vascular bed is blocked, accompanied by the development of pulmonary hypertension, dysfunction of the right heart chambers, but without their insufficiency; non–massive thromboembolism, or thromboembolism of small branches of the pulmonary artery, it is not accompanied by hemodynamic disorders [9;11;16].

The epidemiology of PE is difficult to determine because it can remain asymptomatic and its diagnosis is accidental. In some cases, the first manifestation of PE may be sudden death [21;35]. Overall, PE is one of the leading causes of death, morbidity and hospitalization in Europe. Since people over 40 years of age have a higher risk than younger people, and the risk doubles every decade of life, an increase in the incidence of PE in the future, including death from it, is expected [33;35].

The true frequency of PE is unknown. According to pathoanatomical studies, it remains unrecognized in 50–80% of cases. Most often, a presumptive diagnosis is made. In France, 100 thousand cases of PE are registered annually, in the UK—65 thousand, in Italy—60 thousand, in Ukraine up to 40 thousand cases [7]. In the Russian Federation, the prevalence of VTE is 50–70 new cases per 100 thousand population, and there is an exponential increase in the number of VTE with age—more than 200 cases per 100 thousand population. In the US, PE occurs in approximately 650,000 people and causes 350,000 deaths per year. In European countries, the prevalence of PE varies from 0.5 to 2.0 cases per thousand population per year. PE occurs more often in the elderly. Data on the relationship of gender with PE vary, however, an analysis of the US national database revealed that mortality is 20–30% higher in men than in women [22;25;37].

PE in 20% of cases leads to death, more than half of them in the first 2 hours after its occurrence. In 1/3 of cases it is the cause of all sudden deaths. 1 out of 1000 people die each year from PE. Mortality among untreated patients is 30–40%, and among patients who started receiving treatment in a timely manner 8–10%. In most cases, embolism is the result of deep vein thrombosis of the lower extremities. The main risk factors are: advanced age; thromboembolism and deep vein thrombosis in history; pregnancy; obesity; oncological disease; heart or respiratory failure; surgical intervention; smoking, etc. In 90% of cases, PE develops in patients with deep vein thrombosis (DVT) of the lower extremities [8].

For its diagnosis, ultrasound examination of the veins of the lower extremities with a compression test is used. The clinical picture of PE is non-specific, which makes its diagnosis difficult. The main symptoms of this condition are shortness of breath, cough, general weakness, in some cases chest pain and hemoptysis. Embolism with a large fragment of a thrombus can result in a rapid lethal outcome [19;31].

At the same time, early diagnosis of PE is of fundamental importance, since timely therapy restores blood flow and prevents recurrence of thrombosis. Mortality among untreated patients is 30–40%, and among patients who started receiving treatment in a timely manner 8–10%. Modern principles for diagnosing and managing patients with PE include the stages of assessing the clinical probability of the presence of the disease (Wells scale, Geneva scale), as well as determining the risk of early (30–day) death due to PE. The main method for diagnosing this condition is computed tomography of the veins of the lower extremities [28;38].

With small emboli, there are no symptoms. Large emboli worsen the perfusion of segments or even entire lobes of the lung, which leads to disruption of gas exchange and the development of hypoxia. In response to this, the lumen of the vessels of the pulmonary circulation narrows reflexively, and the pressure in the pulmonary arteries increases.

The right ventricular load increases due to high pulmonary vascular resistance caused by obstruction and vasoconstriction. Thromboembolism of small branches of the pulmonary artery is not accompanied by hemodynamic disorders and in 10% of cases pulmonary infarction and secondary infarct pneumonia develop [12;29;39].

Clinical evaluation 3–6 months after the acute event is now recommended for all patients with prior PE. This recommendation is primarily aimed at identifying patients with developed chronic post–thromboembolic pulmonary hypertension. Thus, symptomatic patients with perfusion defects during ventilation–perfusion scintigraphy 3 months after PE are recommended to contact a tertiary
center for further examination and treatment [1;29]. Anticoagulant therapy is an integral component of the treatment of patients with PE. The decision to prolong anticoagulant therapy for the purpose of secondary prevention of PE is made taking into account the individual characteristics of a particular patient, by analyzing the risk of recurrence of the disease, the development of bleeding. The introduction of parenteral anticoagulants (unfractionated heparin or low molecular weight heparins or fondaparinux) is carried out from the first day of the disease and lasts an average of 5–10 days [28].

Currently, low molecular weight heparins or fondaparinux have a number of valuable advantages (less risk of bleeding, heparin–induced thrombocytopenia) and are preferred in the treatment of PE. The management of unfractionated heparin is relevant for patients who are indicated for reperfusion therapy, as well as in the presence of severe obesity and decreased renal function (creatinine clearance < 30 ml / min), is carried out under the control of activated partial thromboplastin time (APTT). Intravenous unfractionated heparin is started as a bolus of 80 U/kg followed by an infusion of 18 U/kg per hour. Dose adjustment is carried out depending on the APTT values (Table 1), APTT determination is necessary 4–6 hours after the bolus, 3 hours after each dose adjustment, then, when the target APTT values are reached once a day [21;27].

In parallel with the appointment of parenteral anticoagulants, it is necessary to initiate the selection of the dose of warfarin or consider the possibility of prescribing new oral anticoagulants: rivaroxaban, apixaban, dabigatran, edoxaban [12;14;28].

It should be noted that, according to the latest recommendations, an alternative to the appointment of a parenteral anticoagulant with parallel selection of the dose of warfarin in low–risk patients in the acute period of PE can be the appointment of new oral anticoagulants: rivaroxaban at a dose of 15 mg 2 times a day for the first three weeks with a subsequent transition at 20 mg once a day (IB), apixaban at a dose of 10 mg 2 times a day for the first week, followed by a transition to 5 mg 3 times a day (IB) [26;28].

Thrombolytic therapy is indicated for patients at high risk of early death in PE. An obligatory and determining component of the clinical picture of this category of patients is hemodynamic instability with the presence of shock or arterial hypotension. Thrombolytic therapy is most effective within the first 48 hours after the onset of the clinical picture of PE, but may be effective when symptoms last 6–14 days [28]. Thrombolytic therapy in patients with PE has been approved with streptokinase (250,000 IU IV over 30 minutes followed by 100,000 IU per hour for 12–24 hours or accelerated regimen: 1.5 million IU over 2 hours), urokinase (4400 U/kg for 10 min, then 4400 U/kg per hour for 12–24 hours or fast: 3 million U for 2 hours) or tissue plasminogen activator (alteplase) (100 mg for 2 hours or fast): 0.6 mg per kg for 15 minutes (maximum dose 50 mg) [23;28].

Silina E.V. et al. [20] note the expediency of using direct methods for studying hemodynamics and an individualized approach to preventive and therapeutic anticoagulant therapy.

The first attempt at surgical treatment of PE dates back to 1908 and is known as the Trendelenburg operation. Only in 1924, the German surgeon Martin Kirchner achieved a successful outcome of this intervention. For a long time, surgical embolectomy was rarely performed, and its efficacy and safety could not be assessed [27]. At present, surgical embolectomy is rarely used and can be indicated in patients with high–risk PE with extremely severe pulmonary perfusion disorders, severe hemodynamic disorders, ineffectiveness or contraindications of thrombolytic therapy, as well as in patients with right atrial thrombi stuck in the foramen ovale of the interatrial septum [24;28].

It is known that the main components of the hemostasis system are the coagulation, anticoagulation and fibrinolytic systems. Damage to the vascular wall ensures the contact of a specific integral protein–tissue factor with blood factor VII (first phase), which leads to the transformation of factors IX and X into the active form IXa and Xa and the formation of a small amount of thrombin. In the second phase of blood coagulation–increased coagulation–the formed micromolar amounts of thrombin activate factors V, VIII and XI. Their activation is facilitated by the glycoprotein complex Ib–V–IX of platelets. In the third phase of blood coagulation–the spread of the coagulation process–the formation of tenase and prothrombinase complexes occurs on the platelet surface with the production of a large amount of thrombin, which leads to the transformation of fibrinogen into fibrin. The process of blood coagulation is associated with adhesion and aggregation of platelets. The coagulation process under physiological conditions is localized by the area of the vessel defect. Its non-proliferation is facilitated by the anticoagulant system and normally functioning endotheliocytes. An important role in limiting the spread of coagulation is played by an inhibitor of the tissue factor pathway, whose antithrombin III activity significantly increases when interacting with heparin–like glycosaminoglycans [13;18].
CONCLUSION

Thus, postoperative thromboembolic complications worldwide tend to increase in frequency, which is the cause of disability and mortality. The risk of developing feasibility study can vary significantly depending on the nature of the operation, its duration, the type of anesthesia and the general somatic background of the patient. There are no existing schemes for the use of drugs for this disease, and methods for the prevention of feasibility studies are carried out without taking into account the state of the blood coagulation and anti–coagulation system. Patients suffering from obesity are most prone to EFT. Among obese individuals, calculous cholecystitis is more common than in people with normal body weight. Therefore, there is an urgent need for further study of the state of the blood coagulation and anticoagulation system in obese patients with ACC.

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