In Russia, according to the Ministry of Health, diseases of the circulatory system are leading among all causes of death, being ahead of diseases of the respiratory and digestive organs and neoplasms [1]. Over the past 20 years, mortality from diseases of the circulatory system accounted for an average of 55% of the total number of deaths.

The system of blood clotting (hemostasis) is a multifactorial mechanism aimed at maintaining optimal blood rheology. The system is represented by the platelet–vascular link (with the participation of platelets to form platelet aggregates) and the coagulation link (with the participation of plasma blood proteins to form fibrin polymers). Both links have complex mechanisms of implementation and regulation, and any violations of these can be the cause of diseases. Such violations include dysfunctions or abnormal platelet count, congenital or acquired deficiencies of coagulation factors, violations of fibrinogen synthesis, synthesis and expenditure imbalance of clotting factors, vascular disorders, etc. [2]. To detect these disorders of the blood clotting system, a range of different methods, described below, are now used in clinical practice.

Methods of Investigating Plasma Hemostasis State

The Morawitz method is the simplest: a drop of capillary blood of diameter 4–6 mm is applied to a glass. The surface of the droplet is stroked every 30 s by a thin glass capillary. The clotting time is determined by the time of appearance of the first fibrin strands extending behind the capillary.

The Lee–White method uses venous blood. A test tube containing 1 ml of venous blood is set in a water bath at 37°C and every 30 s is tilted at an angle of 45–60°. The time from taking the blood sample until the moment of clotting is the blood clotting time.

Obvious disadvantages of such methods are high impact of external factors on the result, as well as low sensitivity of these methods [3].

Optical and mechanical coagulometry. To assess the state of the plasma hemostasis indicators such as prothrombin time (PT), prothrombin index (PI) and activated partial thromboplastin time (aPTT) are widely used.

By PT, PI, or its standardized variation, international normalized ratio (INR), the state of the extrinsic pathway of blood coagulation is assessed, and by aPTT — the state of the intrinsic pathway of blood coagulation. PT and aPTT represent the time of formation of a fibrin clot in plasma after adding an appropriate coagulating agent. By the PT indicator, using formula (1), the value of INR is calculated, the introduction of which into laboratory and clinical practice is due to an attempt to standardize the values obtained between laboratories:

\[
\text{INR} = \left( \frac{\text{PT}_{\text{mes}}}{\text{PT}_{\text{norm}}} \right)^{\text{ISI}},
\]

where PT_{mes} — the patient’s prothrombin time; PT_{norm} — normal prothrombin time; ISI — International Sensitivity Index of thromboplastin.

By combining indicators of PT (PI, INR) and aPTT, hemostatic disorders can be suspected. Also, PT (INR) is used in the selection and dose adjustment of drugs affecting the plasma pathway of blood coagulation.

This article discusses methods of measurement used in clinical practice for diagnosis and treatment of patients with various blood clotting disorders.
Indicators of plasma hemostasis are determined by coagulation analyzers (coagulometers). The principle of operation of coagulometers is based on optical, mechanical, or optical—mechanical methods of measurement. Citrate-stabilized blood plasma was used as a sample for the study. In the optical mode, the moment of clot formation is recorded by interrupting or changing parameters of the light beam generated by the optical system of the device as the optical density of the sample changes.

To register coagulation in the mechanical mode, a method of detecting deceleration of a ball in the study sample is used when changing the rheological properties of blood during the coagulation process.

As the detecting element, a wheel or star may be used, e.g. as used in the apparatus “Coag-Sense” (CoaguSense, Inc.) (Fig. 1). Figure 1b shows how the gaps in a rotating star accumulate clotted blood. A laser beam passes through the periphery of the star, the interruption of which records the appearance of a fibrin clot.

As the sample, whole blood or plasma can be used, and only 10 μl is needed for the analysis. The main advantages of this system are weak dependence on hematocrit levels (15-60%), and the study time is less than 1 min (precise PT). Also, this method is unique in its simplicity of implementation, high accuracy, and low sensitivity to interference.

Hardware implementation allows study in specialized hematology clinics as well as at home and measure the value of PT and INR only, i.e. investigating only the performance of the extrinsic pathway of blood coagulation.

The methodology used in the apparatus “Coag-Sense” is recognized as the “gold standard” for the mechanical mode of studying blood clotting parameters.

Determining length of the path traveled by the blood sample in the presence of coagulation activators. Technology implemented in the microINR apparatus (iLine Microsystems) is applicable for the quantitative determination of blood coagulation parameters.

The microINR system is used to work with whole capillary blood and is designed for independent analysis of INR. The principle of measuring PT is based on the detection of the front edge of blood sample flow in microchannels. Figure 2 shows the structure of the disposable chip.

The chip consists of two channels: the first is used to analyze the sample, and the second to control the measurement. The sample of capillary blood enters the reaction chamber from the reagent deposited therein. After mixing, the blood flows in microchannels. The prothrombin time is defined by the moment when the flow of the sample stops. In the process of clotting, blood viscosity increases and the behavior of the flow changes. The device monitors the position of the front edge of the sample flow and mathematically converts it to velocity and deceleration. INR is calculated based on the characteristics of the curves.

Advantages of this system are high measuring accuracy, recording the history of measurement (250 studies), and ease of control and reading data using the USB interface.

**Impedance coagulometry.** Coagulometers are standard medical laboratory equipment, but there are versions of coagulometers for individual use with a limited set of measured parameters. Such devices include the INRatio (Alere) and CoaguCheck (Roche).

The principle of operation of the INRatio and CoaguCheck instruments is based on measuring the impedance of samples in control and test cells. For analysis, whole capillary blood of the patient is used. When clotting is activated due to plasma protein, on the electrodes in the region of the reaction layers of fibrin clots are deposited, thereby increasing the impedance of the sample. With the change in the impedance, the dynamics of the formation of a fibrin clot can be assessed.