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Review

Coagulation monitoring devices: Past, present, and future at the point of care

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ABSTRACT

Automated technologies have revolutionised the monitoring of coagulation disorders in the central hospital laboratory setting, allowing for high throughput testing, improved accuracy and precision, accompanied by a marked reduction in human error. However, they still require trained operators and sample transportation. With the advent of point of care (POC) testing, the working principle of traditional coagulometers was used as the foundation for the development of miniaturised devices. A number of POC coagulation devices have been commercially available for many years now, allowing the patient to assume more control over the management of their own medication, e.g. warfarin. While POC devices for measuring anticoagulation have relied principally on clotting time tests, novel platelet function tests, and factor-specific assays based on enzymatic or immunoassay principles are becoming available, driven by the emergence of new anticoagulant drugs, in addition to the inability of clotting tests to accurately detect many thrombotic disorders. This review highlights recent progress in the development of POC coagulation monitoring technologies and examines their future potential in clinical diagnostics.

Contents

1. The development of central laboratory coagulation testing

The monitoring of bleeding disorders has existed for around 3000 years with the first bleeding time test described by the Chinese emperor Huang Ti, as the length of time that blood flows from the skin after rupture. The bleeding time was also described by Sydenham at the turn of the seventeenth century, but it was not until the 1900s that disorders of the clotting system were detected using bleeding time at the bedside [1].

While comparatively more sophisticated in their mode of operation, many coagulation tests still use the same principles since their discovery in the early nineteenth century, when it was found that blood coming into contact with glass containers or various biological tissues, such as placenta, accelerated its clotting [1,2]. The development in the understanding of the coagulation cascade and the interaction of various factors led to the development of the first clotting time tests (Fig. 1). These tests principally include:

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(1) the Prothrombin Time (PT) test, which measures the tissue factor-induced clotting time of plasma [3];
(2) the activated Partial Thromboplastin Time (aPTT), one of the most frequently requested screening tests for monitoring unfractionated heparin (UFH) therapy [4,5];
(3) the Activated Clotting Time (ACT), currently used to monitor anticoagulation in patients undergoing cardiopulmonary bypass (CPB) and are receiving high doses of UFH [5]; and,
(4) the Thrombin Time test (TT), a simple assay measuring the conversion rate of fibrinogen to insoluble fibrin after the addition of thrombin to plasma [6].

Changes from the normal clotting times of these assays may result from changes in active coagulation factor concentrations due to genetic factors, disease or injury, or through the administration of anticoagulant drugs.

Initially, assay methods were based on the visual detection of a clot, through observation of fibrin strands or detection of bulk changes in viscosity [2,3,7] (Fig. 2). The level of automation involved was typically around controlling the mixing and the interaction of the sample with the clotting reagents or the surface contact with glass. Progressively, visual detection of clot formation was replaced by optical detection technologies, using turbidimetric [1] and nephelometric [8] techniques, in which the change in optical density of the sample resulted from the formation of the fibrin network. Mechanical detection also replaced visual detection, in which the change in viscosity was detected (e.g., by the cessation of movement of a steel ball in the rotating sample tube, which could be detected optically) [9]. This level of automation led to many advantages over manual testing, such as high-volume testing, better reproducibility due to strict quality-control programs, increased user flexibility, and cost reductions.

Coagulation instruments based on optical detection of clot formation could also be made compatible with the need for other assays applicable to hemostasis. This was particularly useful for the measurement of the activity of coagulation factors. These factors are typically serine protease enzymes that transform an inactive zymogen into its active form. The development of chromogenic substrates that, when cleaved, would release a chromophore now allowed enzymatic factor assays to be performed alongside traditional coagulation tests on a single instrument platform [10].

Other systems developed modified latex agglutination assays to perform immunoassays, again exploiting principles such as turbidimetry [11,12]. This has been further refined through the use of particle proximity assays, in which the close proximity of two particles due to a binding interaction results in a signal from one of the particles. For example, in the Luminescent Oxygen Channeling Immunoassay (LOCI), the photoactivated formation of short-lived singlet oxygen on one particle is then capable of inducing chemiluminescence on a neighboring particle when bound together via an antibody-antigen interaction [13]. A number of popular commercial central hospital coagulometers and their characteristics are listed in Table 1.

2. The development of point-of-care coagulation testing

The need for point-of-care (POC) coagulation technologies became necessary as centralized laboratories became increasingly unable to provide results in the time frames required to allow rapid

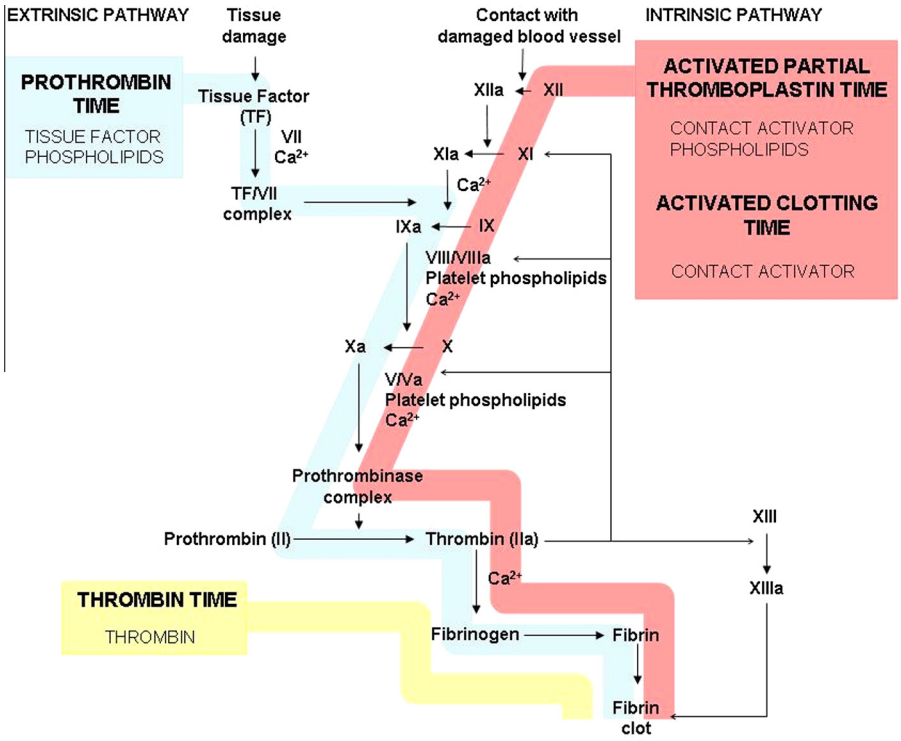

Fig. 1. The coagulation cascade and clotting time tests. The coagulation cascade has two primary, interconnected pathways – extrinsic and intrinsic. In the intrinsic pathway, damage to vessel walls reveals negatively-charged surface activators, which cause the sequential activation of coagulation factors (indicated by Roman numerals), which eventually lead to the formation of thrombin and the conversion of soluble fibrinogen to insoluble fibrin clot. The extrinsic pathway is activated via damage to the endothelium and the release of Tissue Factor (TF), which also leads to clot formation. The Prothrombin Time (PT) test mimics activation via the extrinsic pathway through the addition of tissue factor and phospholipids. The Activated Clotting Time (ACT) test uses the contact activator to measure high heparin dosage in whole blood. The Activated Partial Thromboplastin Time (aPTT) test uses contact activator and phospholipids in plasma to activate the contact pathway more rapidly. The Thrombin Time (TT) test adds thrombin to plasma to measure fibrinogen.