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Advances in Methodologies for Point-of-Care Testing of Coagulation Parameters

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Abstract. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are utilized to assess the time required for the extrinsic and intrinsic pathways of blood coagulation, respectively, and are commonly used to monitor dosages of anticoagulant medications. Point-of-care testing (POCT) methodologies for coagulation primarily include electrochemical, flow-based, viscoelastic, and optical methods. This paper compares these methods from the perspectives of principle, application, and user experience, elucidating their respective advantages and disadvantages. The conclusion indicates that different methodologies possess distinct characteristics. POCT methods offer greater convenience and simplicity; however, they also suffer from drawbacks such as poor anti-interference capability and insufficient accuracy. Furthermore, performance varies among different POCT methods. From an accuracy standpoint, the electrochemical method demonstrates the highest accuracy, followed by flow-based, viscoelastic, and finally impedance and optical methods. Regarding user convenience, most methodologies (platforms) require fingertip blood sampling. Except for the optical method, which requires quantitative blood sampling, other methodologies do not impose specific requirements in this aspect.

Keywords: PT/INR, POCT, Electrochemical, Flow-based, Viscoelastic

1. Introduction

Blood coagulation refers to the process by which blood transitions from a liquid state to a gel. External cues ignite a rapid clotting cascade, transforming fibrinogen into a fibrous mesh that snares blood cells to seal the breach [1]. Conventional coagulation pathways include the extrinsic, intrinsic, and common pathways. This paper focuses on the first two: the extrinsic pathway, also known as Prothrombin Time (PT) [2], and the intrinsic pathway, also known as Activated Partial Thromboplastin Time (APTT) [3].

PT refers to the time required for clot formation after blood vessel wall injury, initiated by contact between blood and tissue factor. APTT activators are typically negatively charged substances. Unlike PT, APTT results from different platforms are not directly comparable.

This paper primarily describes advances and research related to POCT methodologies for PT and APTT coagulation testing, particularly the development and iteration of new technologies in recent years. A detailed investigation and comparison of the advantages and disadvantages of various detection methods are presented.

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2. Common methodologies in Point-of-Care Testing

Point-of-Care Testing (POCT) refers to testing performed at or near the patient's location [4]. Detection methods include electrochemical, flow-based, and optical, among others, each with its own strengths and weaknesses.

2.1. Electrochemical test strips

Electrochemical methods include impedance and amperometric detection. Amperometric detection utilizes thrombin generated during coagulation to cleave a substrate. This cleavage process produces an electrical current, allowing the determination of the coagulation endpoint by detecting the generated current. The reaction principle is illustrated in Figure 1 [5, 6].

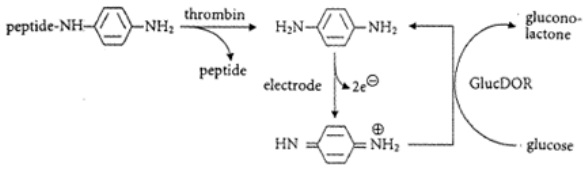

Figure 1. Schematic diagram of electrochemical PT detection principle

A peptide (modified with p-phenylenediamine) serves as the substrate. In the presence of thrombin in the blood, thrombin cleaves the peptide, generating p-phenylenediamine, which subsequently undergoes oxidation, losing two electrons. As the coagulation reaction proceeds, the generated current increases over time (Figure 2). This time correlates with the blood coagulation time PT [5, 6].

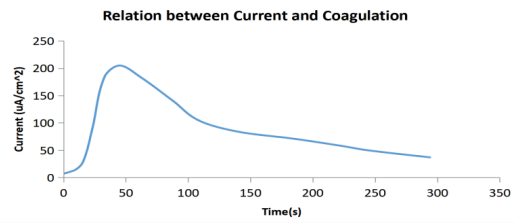

Figure 2. Relationship between current generated by thrombin cleavage of peptide and time

Impedance methods involve applying a voltage across the blood sample. The impedance changes before and after coagulation, and this change is used to reflect the clot formation time, which is then converted to the blood coagulation time. A typical current (corresponding to impedance) curve during blood coagulation is shown in Figure 3 [7].

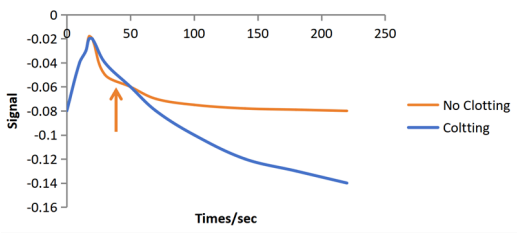

Figure 3. Relationship between impedance signal and time

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Amperometric detection targets thrombin generation, whereas impedance detection targets clot formation. Theoretically, impedance—but not amperometry—can track the post-thrombin phase where fibrinogen becomes fibrin.

2.2. Flow-based method

Coagulation involves a viscosity change. As viscosity increases, blood flow velocity changes. The basic principle can be described using Figure 4. The dashed line represents the flow curve of a sample without added reagent (non-coagulating), while the solid line represents the coagulation curve after adding an activator. The figure shows that over time (x-axis), the flow distance initially increases (y-axis). When a clot forms in the blood, the flow velocity (i.e., the slope of the curve) changes significantly. Detecting this change allows for the determination of coagulation time [8].

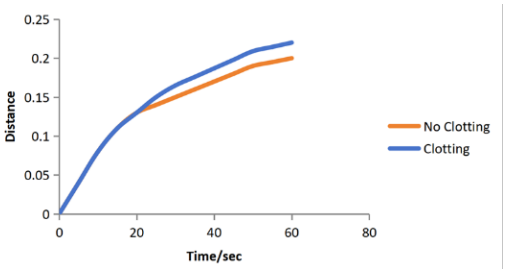

Figure 4. Principle of flow-based blood coagulation testing

2.3. Viscoelastic method

The viscoelastic method discussed here differs from conventional methods in how it detects viscosity (clot) changes. As shown in Figure 5, after sample addition, the blood oscillates back and forth within a channel under an external driving force. The coagulation time is determined by detecting the time required for the blood to pass the same sensor position before and after coagulation. In the signal representation below, the interval between successive signals is initially constant but begins to increase upon coagulation [9].

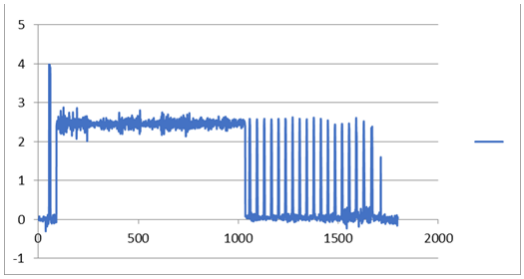

Figure 5. POCT viscoelastic method for detecting blood coagulation

3. Comparison of methodologies

3.1. PT detection

The Roche CoaguCheck system employs an electrochemical detection method. As described by Ye-Seul Kim et al. [10], using the ACL Top750 as a comparator and testing approximately 400 samples (including 126 from warfarin-treated patients), results indicated a strong correlation between

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electrochemically tested INR and the reference system. However, the ACL Top750 results were deemed more reliable in some high-value ranges. Bushra Moiz et al. [11] investigated the relationship between CoaguCheck and Sysmex CS2000i using clinical specimens. Results showed high agreement (94.5%) with laboratory results for most samples, but some results fell within medically decisive ranges, potentially affecting patient medication. Nurul Najmi Muhammad et al. [12] studied the agreement between CoaguCheck and a STAGO system. Results indicated high agreement when INR was below 4.0, but deviation increased for INR values above 4.0. The article recommends that patients with INR >4.0 undergo PT/INR testing in a professional laboratory. Another system using electrochemical testing is the ABBOTT i-STAT. According to research by J. A. Peña et al. [13], which evaluated 70 volunteers (50 warfarin-treated patients and 20 healthy individuals), results showed that although a few test results deviated from the reference, deviations were within controllable limits, and essentially all results met testing requirements.

The Alere INRatio system uses an impedance method for PT testing. A study by Uwe Taborski et al. [14] involving 82 patients compared the agreement between this system and laboratory results. Test results indicated good agreement (r=0.954) between impedance-based INR and laboratory results, with a mean relative deviation of 6.87%. 81% of results agreed with conventional methods, demonstrating very good accuracy and precision. However, conclusions from another study [15] contradict the above, indicating that for warfarin-treated patients (high INR values), results obtained with this system were significantly higher than those from traditional methodologies.

The MicroINR system is a typical representative using the flow-based method. J. Joubert et al. [16] arranged an evaluation involving 210 warfarin-treated patients, using the Sysmex CS2100i as the comparator. Results showed a correlation coefficient of 0.96 between the two systems, a dosage agreement rate of 93.8%, and clinical agreement of 95.7%. Alan K. Jacobson et al. [17] conducted a comparative test using the same method, with results largely consistent with the above. These test results indicate that flow-based PT testing is also reliable.

Robert D. McBane II et al. [18] used a variant of the viscoelastic method to test PT and also compared it with an electrochemical system. The study selected 299 warfarin-treated patients for evaluation. Test results indicated that the viscoelastic method had larger systematic deviations and slightly poorer agreement with laboratory PT results.

Table 1. Comparison of common products' methodologies and forms

Brand	Methodology	Product Form
CoaguCheck	Electrochemical	
i-STAT	Electrochemical	

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Table 1. (continued)

MicroINR	Flow-based	
InRatio	Impedance	
HemoChron	Viscoelastic	

As shown in Table 1, which displays the physical implementations of products based on the different methodologies described, except for the last product (HemoChron), other products require a blood volume of approximately 5–20 µl. The performance evaluation of these products at the user end is shown below. From Table 2, it can be seen that there are significant differences in results between different methodologies. The best-performing methodology is electrochemical, followed by flow-based. Some methodologies were not included in this table, as they lacked this specific test data.

Table 2. Performance comparison of products using different methodologies

Brand	Precision (CV%)		Accuracy (Bias)		Trueness (Agreement)
	INR<2.5	INR>2.5	INR<2.5	INR>2.5	
Roche CoaguCheck	3%	3%	No	No	100%
iLine MicroINR	<5%	6%~6.3%	0.06 INR	No	97%
InRatio	5.6~5.9%	7.40%	2.30%		>94%
HemoChron	7.4%~9.1%		1.50%	-14.50%	>94%

From a testing principle perspective, the electrochemical method is least affected by interfering substances because, for the peptide substrate, thrombin is the primary enzyme in blood that cleaves it. Therefore, factors affecting the current generation rate mainly originate from blood coagulation itself. For the flow-based method, factors directly affecting flow velocity include not only blood coagulation but also blood lipids, proteins, etc., as well as the consistency of the flow channel. While the former can be partially compensated for by comparison, the effect of these substances on velocity during coagulation is variable and cannot be entirely eliminated. Even with high-precision fabrication, dust or stains can still disrupt flow. Impedance can also be considered an electrochemical method. Compared to the amperometric method generating current, the voltage applied across the blood may be influenced by conductive substances in the blood, which vary slightly between individuals, leading to higher CV. For the viscoelastic variant, the sensor's fixed, long sampling window—unshortenable relative to total assay time—drives the high CV and bias seen in Table 2.

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3.2. APTT detection

Currently, reported POCT detection methods for APTT include electrochemical and viscoelastic methods, such as those used in CoaguCheck and HemoChron systems. Although J. Niederdockl et al. [19] indicated that the APTT results from the electrochemical method met testing requirements compared to the reference APTT, the data showed a CV of 8.4%, exceeding general laboratory requirements. It may be suitable for emergency use but questionable for routine testing. The article also evaluated the electrochemical method, finding that its testing precision, positive/negative sample concordance, and interference resistance met requirements, but linearity was not assessed.

Another method for APTT detection is the viscoelastic method. A. J. Carter et al. [20] evaluated APTT testing in heparinized samples using this method. They positively acknowledged its advantages, such as time to result (average 3.5 minutes vs. 56 minutes typically required in the lab). However, the article also noted that the correlation between APTT results and the comparator instrument was not optimal (r=0.79), a figure insufficient to meet clinical needs.

The physical appearance of mature APTT products is essentially the same as their PT counterparts (CoaguCheck, HemoChron) and will not be detailed here. As mentioned earlier, APTT activators are negatively charged substances. A significant difference from the extrinsic pathway (PT) is the wide variety of negatively charged substances used, leading to different activators being employed by different methodologies. This results in significant differences in activation efficiency. Common activators include ellagic acid, kaolin, silica, glass beads, etc. These substances vary greatly, and even the same substance with different particle sizes can impart vastly different negative charges. When these substances contact blood, due to the long APTT coagulation time, minor differences in activation efficiency are amplified in the final coagulation time. Referencing Yuan Teng's research [21], the experimental results are largely consistent with A. J. Carter's data [20]. The correlation coefficient between the tested POC-APTT and reference APTT was only 0.385, with a mean difference of approximately 7.78 seconds, and a 95% confidence interval for the mean difference of about -32.49 to 48.05. These data indicate poor performance for POCT APTT results. One reason is that the POC-APTT reagent used was kaolin, whereas the laboratory reagent was a mixture of silica and ellagic acid.

4. Testing challenges and requirements

POCT PT/APTT coagulation tests typically use fingertip blood or venous non-anticoagulated/ anticoagulated whole blood, differing from the sample type used by reference laboratories (centrifuged plasma). The key difference is the presence or absence of blood cells. Blood cells dilute the plasma, reducing the concentration of various coagulation factors. A decrease in coagulation factor concentration prolongs PT/APTT times, leading to results different from the laboratory. Since hematocrit varies between individuals, the extent of factor dilution also varies, making it impossible to calibrate results effectively.

Current literature largely indicates that POCT products need to be confined to specific ranges to maintain sufficient agreement with laboratory results and provide meaningful reference value for patients or physicians. POCT PT is primarily used for self-testing in warfarin patients, using fingertip blood, with applicable Hematocrit (HCT) ranges generally between 15% and 55%. Warfarin monitoring is a relatively isolated need. APTT is mainly used for monitoring high molecular weight heparin and detecting deficiencies related to the intrinsic pathway, using fingertip blood or venous non-anticoagulated blood, with applicable HCT ranges also generally between 15%

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and 55%. This description suggests their primary use is within the hospital environment, where patient conditions are complex and variable. The HCT range alone may not cover all patients.

Due to significant differences in POCT methodologies, results from different methodological products can be comparable but sometimes exhibit discrepancies. Ashley Connelly et al. [22] found that among 163 samples tested, 75.8% of samples with low fibrinogen had prolonged PT, and 50.3% had prolonged APTT. For the electrochemical method, its principle suggests that FIB abnormalities should not affect PT/APTT results (this method only detects up to thrombin generation). However, based on Ashley Connelly's research, Fib does affect these two parameters, indicating that electrochemical detection may not be equivalent to laboratory results. For the flow-based method, in principle, anything affecting flow velocity (e.g., blood lipids) can potentially influence test results. Central laboratories have various additional methods to mitigate or eliminate the impact of these interferences.

For the APTT parameter, since the activators used are generally insoluble solid particles (or soluble like ellagic acid but requiring mixing with blood for uniform activation), achieving consistent activation is challenging. In practice, the electrochemical method lacks a mixing step due to the absence of a designed power source within the system. For the variant viscoelastic method, its inherently high CV and poor accuracy mean that even with a mixing step, good results are not guaranteed.

5. Conclusion

This paper summarizes POCT methodologies for PT and APTT coagulation testing and compares different detection methods. Common detection methods include electrochemical, impedance, flow-based, and viscoelastic methods. Investigation of extensive literature indicates that for PT detection, electrochemical and flow-based methods are relatively more accurate and reliable, with higher clinical concordance, followed by impedance methods, and finally viscoelastic methods. This is related to the principle design of each methodology and its susceptibility to interference. APTT detection methodologies currently include only electrochemical and viscoelastic methods, but the performance of both is suboptimal, with poor clinical correlation closely tied to their principle design. Therefore, actual POCT APTT products are far from meeting practical clinical application requirements.

Future evolution of products based on various methodologies demands a wider applicable range (e.g., beyond patient self-testing for PT) and better anti-interference capability (e.g., against redox substances affecting electrochemical methods and lipids affecting flow-based methods). Simultaneously, simulating laboratory procedures within the methodology, such as incorporating centrifugation and mixing steps (for both PT and APTT), would significantly enhance test result accuracy (by eliminating HCT effects, improving reagent response efficiency, and ensuring its consistency).

In light of the above, the focus for POCT PT/APTT coagulation products should remain on performance. For PT, resolving the remaining discrepancies with clinical results will be a key research area and a critical factor in final comparisons between different methodological products. Compared to PT, the basic performance of APTT products is insufficient for large-scale application. Therefore, improving existing theories or researching new testing methods is more crucial for APTT, aiming for better linearity, precision and accuracy.

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