

Literature review

Light transmission aggregometry in clinical practice: current roles, challenges and future perspectives

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Introduction

Platelets play a pivotal role in primary hemostasis, and abnormalities in platelet function can result in diverse clinical manifestations, ranging from bleeding disorders to arterial and venous thrombosis.^{1,2} In response to vascular injury, platelet function involves coordinated processes of adhesion, activation, secretion and aggregation, leading to the formation of a primary platelet plug and providing an essential initial response to prevent blood loss.^{1,2} Beyond their traditional role in hemostasis, platelets are recognized as important mediators of inflammation, immune responses and vascular homeostasis.^{3,4} Given the clinical consequences of platelet dysfunction, laboratory assessment of platelet function is an essential component of the diagnostic evaluation of patients with suspected inherited or acquired platelet disorders and is also commonly used to assess the pharmacodynamic effects of antiplatelet therapy in patients with cardiovascular disease.^{5,6}

Among the various methods available for evaluating platelet function, platelet aggregation testing remains one of the most widely used laboratory approaches. Since the introduction of light transmission aggregometry (LTA) by Gustav Born in 1962,⁷ LTA has become a well-established method for assessing platelet aggregation and investigating abnormalities in platelet function.⁸⁻¹⁰ It is recognized as the reference method for laboratory assessment of platelet aggregation and remains an important component of the diagnostic evaluation of suspected platelet function disorders. This may

provide valuable functional information that cannot be obtained through routine hematologic parameters, such as platelet count or morphology, alone.

Over the past several decades, the clinical applications of LTA have expanded considerably. In addition to its established role in the diagnosis of inherited platelet function disorders, such as Glanzmann Thrombasthenia (GT) and Bernard-Soulier Syndrome (BSS),¹¹ as well as selected subtypes of von Willebrand Disease (vWD),¹² LTA has also become an important tool for evaluating acquired platelet dysfunction associated with systemic diseases.⁹ Furthermore, LTA is increasingly used to assess the pharmacodynamic effects of antiplatelet agents, including aspirin and P2Y₁₂ inhibitors, and to characterize interindividual variability in platelet response to therapy. This application may support the evaluation of antiplatelet treatment efficacy and facilitate individualized patient management, particularly in patients with cardiovascular disease.¹³⁻¹⁸

Advances in platelet biology and laboratory technology have led to the development of several alternative platelet function assays, including whole blood impedance aggregometry, point-of-care platelet function testing, flow cytometry-based assays and microfluidic platforms.^{5,19} These emerging technologies complement conventional LTA by providing additional insights into platelet function under more physiological conditions, improving accessibility, reducing turnaround time and broadening the scope of platelet function assessment in both clinical and research settings.^{5,19} Despite these

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technological advances, LTA remains the reference method for assessing platelet aggregation and is commonly used to confirm suspected abnormalities in platelet aggregation.

Several challenges continue to limit the widespread implementation and standardization of LTA.^{10,20} These include pre-analytical variables, methodological heterogeneity, a lack of universally accepted reference intervals and significant inter-laboratory variability, which may affect the reproducibility and clinical interpretation of test results.²⁰⁻²² Furthermore, although LTA has shown promise in guiding individualized antiplatelet therapy and evaluating clinical outcomes,¹³⁻¹⁸ its routine use in many clinical scenarios remains controversial because of inconsistent evidence and varying guideline recommendations.¹³

This review aims to provide a comprehensive overview of LTA in contemporary clinical practice. We discuss the principles and methodology of LTA, summarize its current clinical applications, examine its limitations and challenges, and explore emerging technologies and future directions that may shape its role in clinical platelet function assessment.

General background and concept of LTA

LTA was first described by Gustav Born in 1962 and is widely regarded as the gold standard method for the laboratory evaluation of platelet aggregation. The assay is based on the principle that platelet-rich plasma (PRP) becomes progressively clearer as platelets aggregate following stimulation with specific agonists, resulting in an increase in light transmission through the sample.⁷

In LTA, whole blood is collected into tubes containing 3.2% sodium citrate and centrifuged at a low speed of $200 \times g$ for 10 min to prepare PRP, which is used as the test specimen. The residual blood sample is then centrifuged at a higher speed of $1,500 \times g$ for 15 min to obtain platelet-poor plasma (PPP), which serves as the reference blank. Before testing, PPP is assigned a light transmission value of 100%, while PRP is assigned a baseline value of 0%. The PRP is incubated at 37°C under continuous stirring to simulate physiological

conditions, after which a platelet agonist is added to initiate platelet activation and aggregation. As platelets aggregate, the turbidity of the plasma decreases, allowing a greater proportion of light to pass through the sample.^{22,23} The resulting increase in light transmission is continuously measured by the aggregometer and displayed as an aggregation tracing over time.

A variety of agonists could be used in LTA to evaluate different platelet activation pathways, including adenosine diphosphate (ADP), collagen (COL), epinephrine (EPI), Ristocetin (RIS), arachidonic acid (AA), thromboxane A₂ (TXA₂) and thrombin or thrombin receptor-activating peptide (TRAP). Common platelet agonists used in LTA and their corresponding activation pathways are summarized in Table 1. Each agonist interrogates specific platelet receptors or signaling pathways, thereby providing valuable information regarding the functional integrity of platelet activation and aggregation mechanisms (Figure 1).²³ For example, arachidonic acid-induced aggregation is commonly used to assess the effects of aspirin therapy, whereas ristocetin-induced platelet agglutination (RIPA) is particularly useful for investigating defects involving von Willebrand factor (vWF) or the platelet glycoprotein Ib-IX-V complex.¹⁵

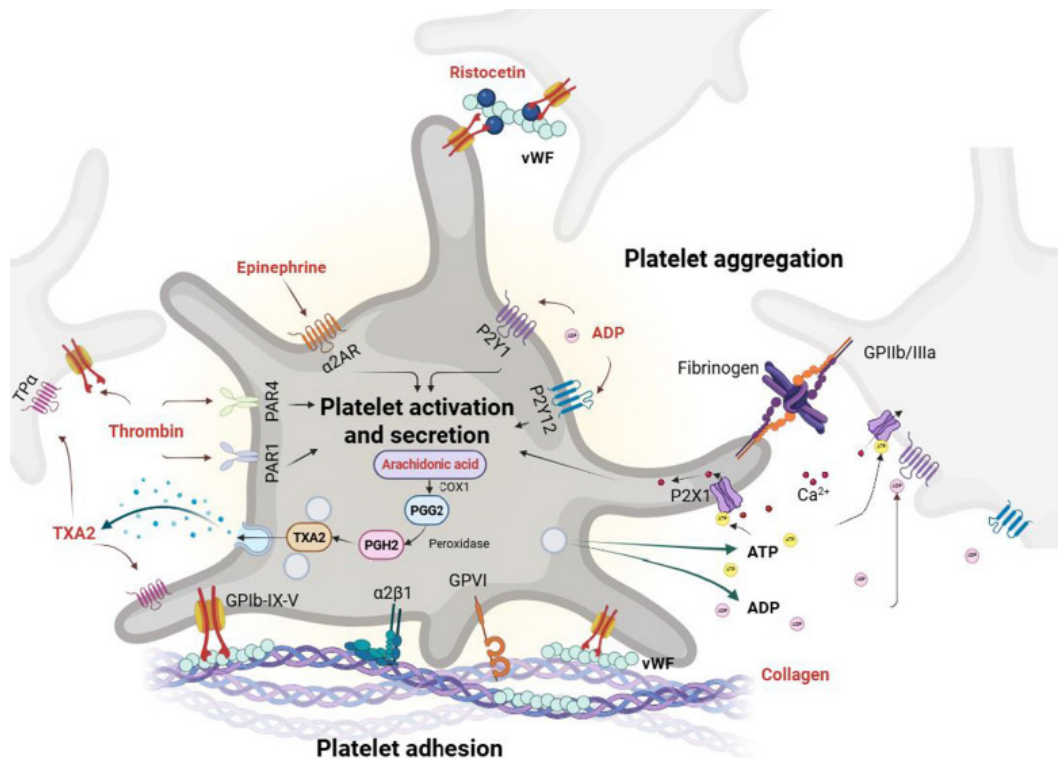
The primary parameters evaluated in LTA include maximal aggregation, the slope of aggregation, the lag phase and disaggregation (Figure 2A). The shape and characteristics of the aggregation curve may provide important diagnostic clues. For instance, low concentrations of ADP typically induce a biphasic aggregation response consisting of a primary wave, reflecting direct platelet activation, followed by a secondary wave resulting from the release of endogenous platelet agonists, such as ADP and thromboxane A₂ (Figure 2B). Disaggregation represents a reduction in light transmission following partial reversal of platelet aggregation. Abnormalities in these responses can help identify specific platelet function defects or the effects of antiplatelet medications. The characteristic aggregation patterns obtained from LTA and their clinical interpretations are summarized in Table 2.

Table 1 Common platelet agonists used in LTA, recommended concentrations and their corresponding activation pathways.^{8-11,13-15,22}

Agonist	Typical concentration	Primary pathway/receptor assessed	Main clinical application
ADP*	Low: 0.5-2 $\mu\text{mol/L}$ High: 5-10 $\mu\text{mol/L}$ (up to 20 $\mu\text{mol/L}$)	P2Y ₁ /P2Y ₁₂ receptor-mediated activation; secretion-dependent amplification	Assessment of P2Y ₁₂ inhibitor effects; secretion defects; platelet signaling abnormalities
Collagen	1-5 $\mu\text{g/mL}$	GPVI-mediated activation and collagen-induced platelet signaling	Evaluation of platelet activation defects and secretion abnormalities
Epinephrine	5-10 $\mu\text{mol/L}$	$\alpha_2\text{A}$ -adrenergic receptor-mediated activation; amplification pathways	Detection of secretion defects and abnormal secondary aggregation responses
Arachidonic acid	0.5-1 mmol/L	COX-1/thromboxane A ₂ pathway	Assessment of aspirin effect and COX-1 pathway defects
Ristocetin	0.5-1.5 mg/mL (method dependent)	vWF-GPIb-IX-V interaction (platelet agglutination)	Diagnosis of von Willebrand disease and Bernard-Soulier syndrome
Thrombin (TRAPs)	5-15 $\mu\text{mol/L}$	PAR-1/PAR-4 thrombin receptor path- way	Assessment of thrombin-mediated platelet activation; research applications

*The interpretation of ADP-induced aggregation is concentration-dependent.

Abbreviations: ADP, adenosine diphosphate; COX-1, cyclooxygenase-1; GPVI, glycoprotein VI; GPIb, glycoprotein Ib; PAR, protease-activated receptor; TRAP, thrombin receptor activating peptide; vWF, von Willebrand factor.



Abbreviations: ADP, adenosine diphosphate; COX-1, cyclooxygenase-1; GPIb, glycoprotein Ib; GPVI, glycoprotein VI; P2Y₁ and P2Y₁₂, purinergic ADP receptors; TXA₂, thromboxane A₂; vWF, von Willebrand factor

Figure 1 The principal agonists used in platelet aggregation testing include ADP, collagen, epinephrine, arachidonic acid, thrombin (or thrombin receptor-activating peptide) and ristocetin, each interrogating distinct platelet activation pathways.

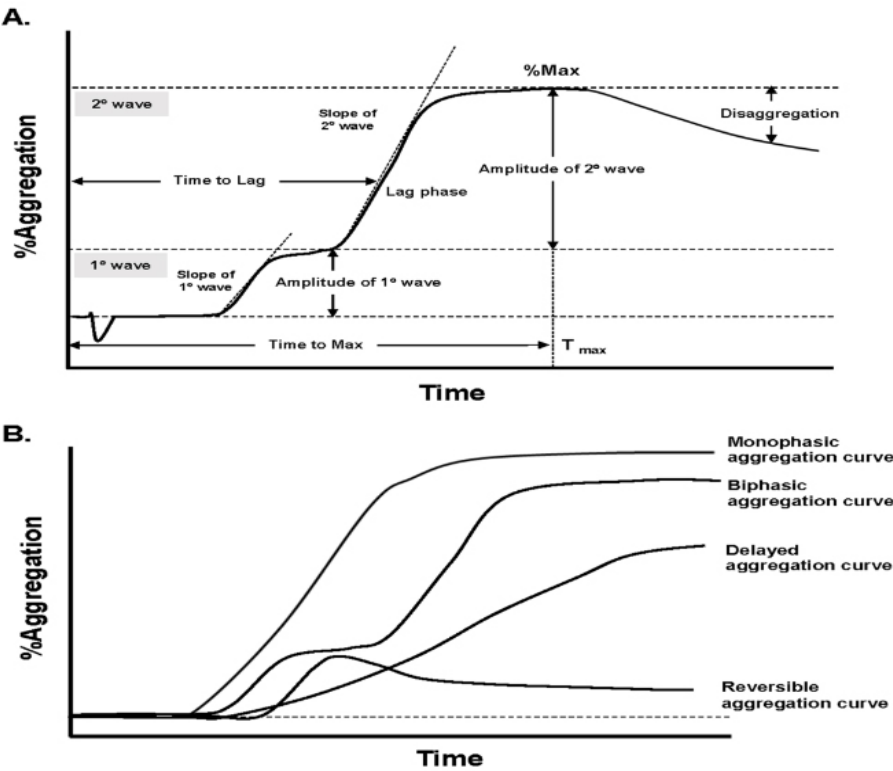


Figure 2 The major parameters used for interpretation and patterns of aggregation curves obtained from LTA. (A) Representative biphasic platelet aggregation curve demonstrating the major parameters used for interpretation, including lag phase, time to maximum aggregation (T_{max}), maximum aggregation (%Max), amplitude of the primary and secondary waves, slope of aggregation and disaggregation. (B) Representative patterns of platelet aggregation curves.

Table 2 The characteristic aggregation patterns obtained from LTA and their clinical interpretations^{7-9,20}

Curve pattern	Main feature	Common interpretation	Associated with
Monophasic	Single wave	Typical response to strong agonists; interpretation depends on agonist type and concentration	Normal platelet aggregation response when appropriate for the agonist and concentration
Biphasic	Primary + secondary wave	Normal secretion response	- Normal response when stimulated with weak agonist - Loss of the secondary wave may indicate: - Storage pool deficiency - Secretion defects - Aspirin effect (especially with arachidonic acid pathway inhibition)
Reversible	Aggregation followed by a decline	Transient or incomplete platelet activation; interpretation depends on agonist and concentration	- Low concentrations of ADP - Impaired platelet activation amplification.
Irreversible	Stable plateau	Strong platelet aggregation	- Normal response in many agonists at appropriate concentrations.
Absent	No aggregation	Platelet function defect	- Defects in platelet activation and/or aggregation
Delayed	Prolonged lag phase before aggregation.	Reduced responsiveness	- Reduced platelet responsiveness - Medication effects - Storage conditions
Hyperaggregable	Excessive aggregation response	Increased platelet reactivity; should be interpreted in relation to the agonist, concentration, platelet count, and clinical context.	May occur in selected hematologic or cardiovascular settings

Abbreviations: ADP, adenosine diphosphate.

Interpretation of LTA platelet aggregation patterns

Platelet responses are evaluated by assessing the degree and pattern of aggregation following stimulation with specific agonists.^{9,11,20} Normal platelet responses vary depending on the agonist used. ADP and epinephrine may demonstrate primary and secondary aggregation waves, reflecting platelet activation followed by secretion-dependent amplification. Collagen typically induces a delayed but sustained aggregation response, whereas arachidonic acid evaluates the cyclooxygenase-1 (COX-1)/thromboxane A₂ pathway. Ristocetin-induced agglutination assesses the interaction between vWF and the platelet glycoprotein IIb-IX-V complex.¹²

Absent aggregation with a preserved ristocetin response suggests a defect in platelet aggregation pathways, such as GT due to impaired GPIIb/IIIa function.^{11,24,25} In contrast, abnormal ristocetin-induced agglutination with normal responses to other agonists suggests abnormalities involving vWF or GPIb, as observed in vWD or BSS.^{11,12,24,26} Reduced responses to multiple agonists may indicate secretion defects, storage pool disorders

(SPD) or acquired platelet dysfunction. Among patients receiving antiplatelet therapy, selective inhibition of specific pathways can be identified, such as reduced arachidonic acid-induced aggregation with aspirin therapy or impaired ADP-induced aggregation with P2Y₁₂ inhibitors.^{8,14-16} Common LTA aggregation patterns and their interpretations are summarized in Table 3.

Current roles of LTA in clinical practice

Despite the development of alternative platelet function assays, LTA provides a comprehensive evaluation of platelet responses to multiple agonists and enables investigation of specific pathways involved in platelet adhesion, activation, secretion and aggregation. Its major clinical applications include the diagnosis of inherited platelet function disorders, evaluation of acquired platelet dysfunction, assessment of antiplatelet drug effects and characterization of platelet reactivity in various clinical conditions.

The most established clinical application of LTA is the investigation of patients with suspected inherited

Table 3 Interpretation of common platelet aggregation patterns in LTA^{8,9,11,12,14-16,20,24,26}

Disorder	Aggregation response						
	ADP 1° wave	ADP 2° wave	Epinephrine	Collagen	High-dose Ristocetin	Low-dose Ristocetin	Arachidonic acid
Inherited disorders							
Storage pool disorders	Normal	Decreased or absent	Variable	Normal	Normal	Absent	Normal
Glanzmann thrombasthenia	Absent	Absent	Absent	Absent	Normal	Absent	Absent
Bernard-Soulier syndrome	Normal	Normal	Normal	Normal	Absent	Absent	Normal
von Willebrand disease (vWD)	Normal	Normal	Normal	Normal	Normal, decreased, or absent depend- ing on the type of vWD	Increased or normal in Type 2B vWD and platelet-type vWD	Normal
Acquired disorders							
Aspirin	Normal	Decreased or absent	Decreased or absent	Decreased or absent	Normal	Absent	Absent
P2Y ₁₂ inhibitor (e.g., clopidogrel)	Absent	Absent	Normal	Normal	Normal	Absent	Normal
Glycoprotein IIb/IIIa inhibitors (e.g., tirofiban)	Absent	Absent	Absent	Absent	Normal	Absent	Absent
Uremia	Normal	Decreased	Variable	Variable	Normal	Absent	Decreased

Abbreviations: ADP, adenosine diphosphate

platelet function disorders, particularly among patients presenting with unexplained mucocutaneous bleeding, excessive surgical bleeding or abnormal bleeding history despite normal platelet counts and coagulation screening tests.^{5-9,11,26} LTA allows identification of characteristic aggregation patterns associated with defects in platelet receptors, signaling pathways and secretion mechanisms. Beyond inherited disorders, LTA is frequently used to evaluate acquired abnormalities of platelet function associated with systemic diseases and hematologic disorders.²⁷⁻³² Regarding these conditions, LTA provides functional information that complements routine laboratory tests and may help characterize platelet dysfunction and distinguish primary platelet abnormalities from secondary causes of bleeding. However, interpretation requires careful consideration of the clinical context, as acquired platelet dysfunction often produces nonspecific abnormalities across multiple agonist pathways.²⁷⁻³² For example, among patients with uremia and liver disease, LTA may demonstrate variable abnormalities in platelet aggregation.^{29, 30} Myeloproliferative neoplasms may be associated with abnormal platelet aggregation responses, which may vary depending on the underlying driver mutation,³¹ while among patients with monoclonal gammopathies, paraproteins may contribute to impaired platelet function through interactions with platelet receptors and other components of primary hemostasis.³² Among such patients, LTA may be considered when clinically significant or unexplained bleeding cannot be adequately explained by routine laboratory findings.

The use of LTA in clinical practice should be guided by appropriate clinical indications and patient selection, with the assay performed and interpreted according to standardized preanalytical and analytical procedures.^{10,22,23,33} Consensus recommendations from the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) on the standardization of LTA support its use, particularly to

investigate suspected inherited or acquired platelet function disorders when clinical findings raise suspicion of a platelet defect despite unremarkable routine laboratory findings.²²

Currently, LTA is widely used to assess the pharmacodynamic effects of antiplatelet agents by evaluating drug-induced changes in specific platelet activation pathways. Aspirin inhibits COX-1-mediated thromboxane A₂ production, resulting in reduced arachidonic acid-induced aggregation, whereas P2Y₁₂ receptor inhibitors (clopidogrel, prasugrel and ticagrelor) reduce ADP-induced platelet aggregation.¹³⁻¹⁶ Although LTA has improved our understanding of variability in antiplatelet response, its routine use for therapy guidance remains controversial, as platelet function-guided strategies have not consistently demonstrated improved clinical outcomes. Therefore, several consensus recommendations and current practice guidelines, including those from the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) and the Society for Cardiovascular Angiography and Interventions (SCAI), support the selective use of platelet function testing in specific clinical settings rather than routine monitoring.^{13,34-36}

LTA remains an important research tool for investigating platelet biology, drug responses and disease-associated changes in platelet function.^{8,26} Measurement of platelet reactivity using LTA has contributed to our understanding of the relationship between platelet reactivity and thrombotic or bleeding outcomes. However, despite its ability to characterize platelet reactivity, the routine use of LTA to predict clinical outcomes remains limited.^{13,35,36} LTA is also widely used in research settings to evaluate the effects of drugs, bioactive compounds, venoms and toxins on platelet reactivity and activation pathways.³⁷⁻⁴¹ In addition, LTA is frequently used as a reference method to validate newer platelet function assays and investigate novel antiplatelet therapies.¹³⁻¹⁶

Limitations and challenges of LTA

Despite its broad clinical utility, LTA has several limitations that restrict its widespread application in routine clinical practice. One of the major challenges is its susceptibility to pre-analytical and analytical variables, which can significantly influence test results. Factors such as blood collection technique, anticoagulant selection, the time interval between sample collection and testing, platelet count, sample handling and PRP preparation may affect platelet responsiveness and contribute to inter-laboratory variability.^{22,34,42} LTA results can be significantly influenced by a variety of commonly used medications and dietary components that modulate platelet function.^{37,38,43,44} In addition, analytical conditions, including agonist preparation, agonist concentration, instrument settings and interpretation criteria, require careful standardization to ensure reliable and reproducible results.^{19,20,22,34,42,45}

LTA is also technically demanding and requires specialized expertise for both test performance and interpretation. Unlike automated platelet function assays, LTA involves multiple manual procedures, including sample preparation, calibration and evaluation of aggregation curves, making the assay highly dependent on operator experience. The absence of universally accepted reference ranges and standardized protocols across laboratories further complicates the comparison of results between institutions and limits its application in multicenter studies and clinical decision-making.^{20,22,34}

Another limitation of LTA is the relatively high sample volume requirement and limited suitability for urgent testing. The assay generally requires fresh platelet samples and must be performed within a restricted time window after blood collection, which may pose logistical challenges, particularly among patients requiring rapid assessment of platelet function.^{22,34} Performing platelet aggregation in samples with low platelet counts remains problematic and is not well standardized across laboratories.^{33,46,47} Furthermore, LTA primarily evaluates platelet aggregation responses under *ex vivo* conditions

and may not fully reflect the complex interactions among platelets, vascular components, coagulation factors and inflammatory pathways occurring *in vivo*.²⁶

Nevertheless, despite these limitations, LTA remains an indispensable tool for comprehensive platelet function evaluation because of its ability to assess platelet responses to a wide range of agonists and investigate multiple activation pathways. It continues to serve as a benchmark method for validating and comparing newer platelet function technologies, particularly in research settings and in the investigation of inherited and acquired platelet disorders.

Trends and future directions

Over the past decade, several novel platelet function testing methods have been developed, with an increasing focus not only on improving standardization, reproducibility and clinical applicability but also on providing complementary insights into platelet biology beyond conventional aggregation measurements.^{8,19} One major trend is the development of more standardized and automated platelet function assays that reduce operator dependency and pre-analytical variability.⁴⁸ Whole-blood-based technologies, such as impedance aggregometry,⁴⁹ provide an alternative approach to assessing platelet aggregation in a more physiological environment, whereas flow cytometry-based platelet assays can evaluate platelet activation, granule secretion, receptor expression and procoagulant activity at the single-cell level.⁵⁰ These approaches may therefore help identify functional abnormalities that are not fully captured by conventional LTA. In parallel, microfluidic platforms that simulate vascular shear conditions are emerging as promising tools for evaluating platelet adhesion, activation and thrombus formation under more physiologically relevant flow conditions.⁵¹ The underlying principles, advantages, limitations and potential clinical applications of these platelet function testing methods are summarized in Table 4.

Table 4 Comparison of LTA and novel platelet function assays^{11,20,42-46}

Test	Principle	Advantages	Disadvantages	Main Clinical Applications
Light Transmission Aggregometry (LTA)	Measures change in light transmission through PRP as platelets aggregate in response to agonists	Gold standard reference method; evaluates multiple platelet activation pathways; flexible agonist selection; useful for inherited platelet disorders	Time-consuming; labor-intensive; requires PRP preparation; high operator dependency; poor standardization; pre-analytical variability	Diagnosis of inherited/acquired platelet function disorders; research reference method; validation of new assays
Automated LTA (e.g., Sysmex CS-2100i/CS-2500, Thromboscope platforms)	Uses the same principle as conventional LTA but with automated sample handling, reagent dispensing, data acquisition, and analysis	Improved standardization and reproducibility; reduced hands-on time; enhanced workflow efficiency; integrated quality control; reduced operator variability	Still requires PRP preparation and specialized expertise; high instrument cost; limited availability	Clinical platelet function testing; high-throughput platelet function analysis
Multiple Electrode Aggregometry (Multiplate)	Measures change in electrical impedance as platelets aggregate on electrodes in whole blood	Rapid; uses whole blood; more standardized; suitable for near-patient testing; better physiological conditions than PRP	Affected by platelet count and hematocrit; limited sensitivity for mild defects; fewer diagnostic pathways than LTA	Monitoring antiplatelet therapy; perioperative hemostasis assessment
VerifyNow System	Optical detection of platelet aggregation on fibrinogen-coated beads in cartridge system	Fully automated; rapid; minimal sample handling; standardized cartridges	Limited to specific drug pathways; expensive; less informative for inherited disorders	Monitoring aspirin, P2Y12 inhibitors, and GPIIb/IIIa antagonists
PFA-100 / PFA-200	Measures time to occlusion of an aperture under high shear flow using whole blood	Simple; rapid; screening tool; sensitive to severe platelet dysfunction and vWD	Low specificity; influenced by platelet count and hematocrit; cannot identify specific defects	Screening for vWD; initial assessment of platelet dysfunction
Flow cytometry platelet function testing	Detects platelet activation markers (e.g., P-selectin, GPIIb/IIIa activation) using fluorescent antibodies	High sensitivity; small blood volume; receptor-specific information; powerful for mechanistic studies	Requires expertise and expensive equipment; poor standardization; limited clinical reference ranges	Diagnosis of receptor defects (e.g., Glanzmann, Bernard-Soulier); research; platelet activation studies
Microfluidic platelet function assays	Simulates vascular shear conditions to assess platelet adhesion and thrombus formation	Physiological flow conditions; models <i>in vivo</i> thrombosis; research-oriented precision	Not standardized; limited availability; high cost; complex interpretation	Research; drug development; personalized hemostasis studies

Abbreviations: GPIIb/IIIa, glycoprotein IIb/IIIa; LTA, light transmission aggregometry; PFA, platelet function analyzer; PRP, platelet poor plasma; vWD, von Willebrand disease.

Another important direction is the integration of platelet function testing with omics-based approaches, including transcriptomics, proteomics and metabolomics, to identify novel biomarkers and improve patient stratification in bleeding and thrombotic disorders.^{52,53} Furthermore, applications of artificial intelligence (AI) and machine learning are gaining increasing interest and may improve the interpretation of complex platelet aggregation patterns, thereby enhancing diagnostic accuracy.⁵⁴

Conclusions

LTA remains the historical gold standard and reference method for evaluating platelet function due to its ability to assess multiple platelet activation pathways using a wide range of agonists. Although novel platelet function assays have emerged to address the limitations of LTA, most assess specific aspects of platelet activation and cannot yet replace the comprehensive information provided by LTA. Future advances, including flow cytometry-based technologies, multiomics approaches and AI-assisted analysis, are expected to enhance platelet function assessment by improving diagnostic precision and clinical decision-making. A complementary approach combining LTA with emerging technologies will likely provide a more comprehensive understanding of platelet function in clinical and research settings.

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