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SHORT COMMUNICATION

Amplitude at 10 min in thromboelastography predicts maximum amplitude: a single-center observational study

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Abstract

Thromboelastography is a quantitative test widely used to measure the efficiency of blood clotting. However, awaiting the results of maximum amplitude (MA) is necessary for determining the need for platelet- and fibrinogen-containing products. A more rapid prediction of MA could facilitate faster preparation and administration of blood transfusion products, thereby resulting in coagulation improvement. In this retrospective study, we hypothesized that early amplitude at 10 min (A10) could be a predictor of MA. Therefore, we investigated whether MA can be rapidly inferred from thromboelastographic 6 s (TEG6s) measurements and evaluated its correlation with A10. We extracted TEG6s measurements obtained in operating rooms and intensive care units of our hospital between January 2018 and December 2022. The correlation of MA with display items of TEG6s results, including reaction time, kinetics, α angle, activated clotting time, and A10, was evaluated. The relationship between citrated rapid TEG (CRT)-A10 and CRT-MA, as well as between citrated functional fibrinogen (CFF)-A10 and CFF-MA, were evaluated if A10 and MA showed a good correlation. The results showed good correlations between CRT-A10 and CRT-MA, as well as between CFF-A10 and CFF-MA. Therefore, evaluating A10 using TEG6s could predict MA.

Keywords Thromboelastography · A10 · Prediction · Maximum amplitude · Observational study

In perioperative coagulation disorders during cardiac surgery, multiple factors, including decreased levels of coagulation factors, platelet abnormalities, and hyperfibrinolysis, are involved [1, 2]. Therefore, differentiating complex pathologies using activated partial thromboplastin and prothrombin times, which evaluate thrombin generation using plasma samples [3], is difficult. Additionally, the usefulness of general coagulation test results for diagnosing and treating perioperative coagulation disorders has not been demonstrated [4]. Evaluating hemostatic abnormalities in cardiac surgery using cardiopulmonary bypass requires a highly accurate and rapid differential diagnosis. Therefore, the guidelines of the European Society of Anesthesiology and the American Society of Anesthesiologists highly recommend the use of viscoelastic tests [5, 6]; moreover, hemostasis tests are incorporated in the guidelines for cardiac surgery.

Thromboelastography (TEG) is performed to quantitatively evaluate hemostasis. It provides waveforms and numerical values centered around the reaction time (R) and maximum amplitude (MA) that reflect the time until thrombin formation and the platelet- and fibrinogen-influenced clot strength, respectively. Since obtaining MA results requires approximately 30 min from the start of measurement and is necessary to determine a patient's need for platelet- or fibrinogen-containing preparations, rapidly determining MA would facilitate faster preparation and administration of transfusion products than previously feasible and provide patients with quicker coagulation improvement. The correlation between the amplitude at 10 min (A10) and maximum clot firmness has been shown using rotational thromboelastometry (Werfen Japan KK, Tokyo, Japan), which incorporates a viscoelastic testing instrument [7]. A10 has recently been measured using thromboelastographic 6 s (TEG6s) (Hemonetics Japan, Tokyo, Japan); however, studies clearly demonstrating the relationship between A10 and MA in TEG6s are scarce. We hypothesized that early determination of A10 would facilitate MA prediction. Therefore,

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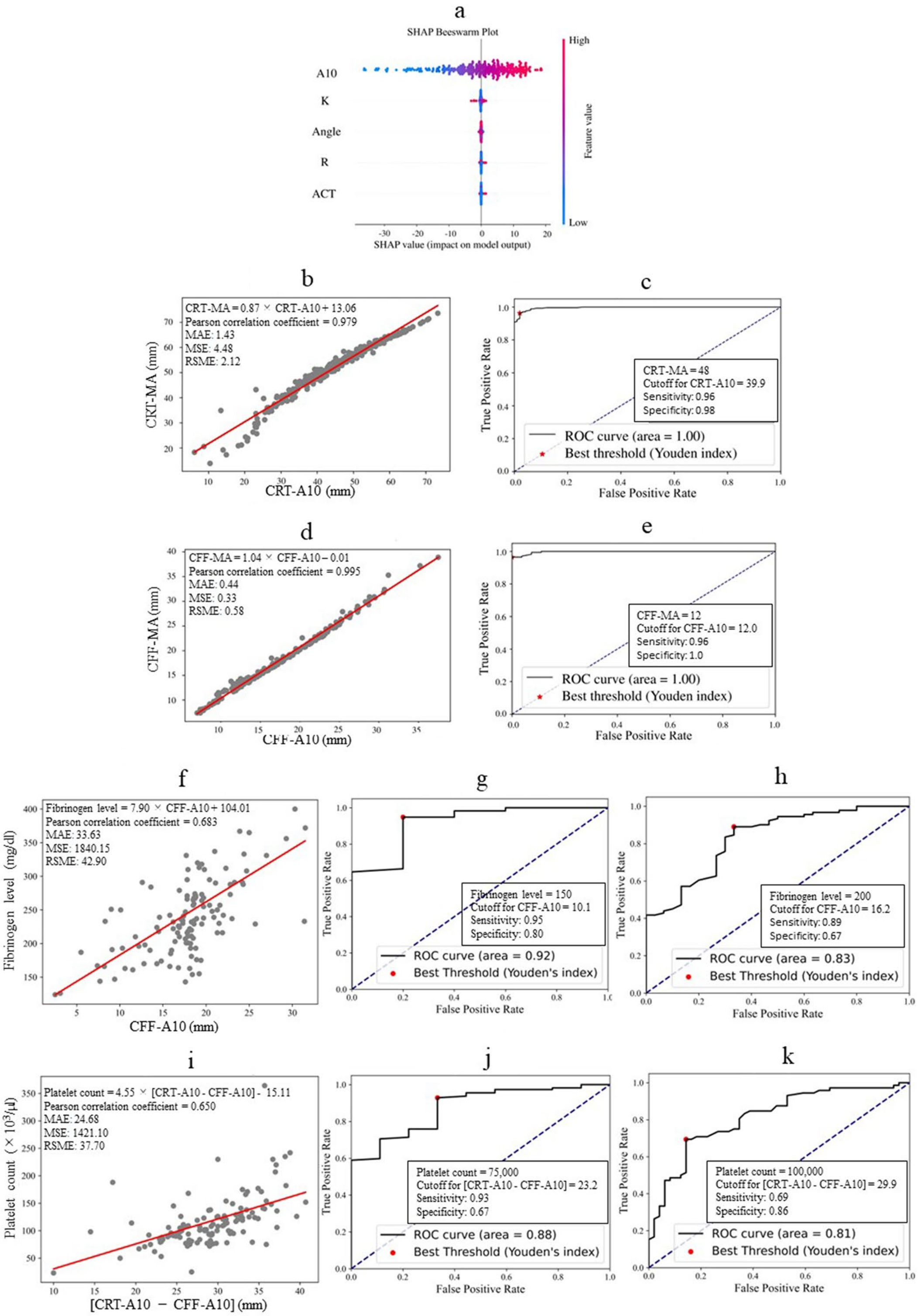

we determined whether MA could be rapidly inferred from TEG6s and evaluated the relationships between citrated rapid TEG (CRT)-A10 and CRT-MA in TEG6s and between citrated functional fibrinogen (CFF)-A10 and CFF-MA in TEG6s, designated as primary and secondary outcomes, respectively.

This retrospective study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and the standards of the Declaration of Helsinki. It was approved by Nagoya University Hospital's Ethics Committee (approval number and date: 2023–0070 and May 24, 2023). Informed consent was obtained from

◀**Fig. 1** **a** Shapley additive explanations (SHAP). SHAP is a machine learning model that determines the contribution of each variable to the model's predicted results. The horizontal and vertical axes represent the target variable and the contribution level of the feature variable level, respectively. Red and blue indicate the positive and negative results, respectively. For example, the amplitude at 10 min (A10) shows red and blue distributions when the objective variable is larger (on the right) and smaller (on the left), respectively. This indicates that the objective variables' maximum amplitude and A10 were positively correlated. Specifically, the larger the SHAP value, the more likely it contributed to the prediction result; therefore, explanatory variables with a wider distribution on the horizontal axis can be interpreted as important. *ACT* activated clotting time; *K* kinetics; *R* reaction time. **b** Correlation between CRT-A10 and CRT-MA. The correlation between CRT-A10 and CRT-MA was very strong: CRT-MA (mm) = 0.87 × CRT-A10 + 13.06 (Pearson's correlation coefficient = 0.979). *A10* amplitude at 10 min; *CRT* citrated rapid thromboelastography; *MA* maximum amplitude; *MAE* mean absolute error; *MSE* mean squared error; *RMSE* root mean squared error. **c** ROC, cutoff value of CRT-A10 for indicating a CRT-MA of 48 mm. The cutoff value of CRT-A10 for indicating a CRT-MA of 48 mm was 39.9 mm. Sensitivity and specificity were 0.96 and 0.98, respectively. *A10* amplitude at 10 min; *CRT* citrated rapid thromboelastography; *MA* maximum amplitude; *ROC* receiver operating characteristic. **d** Correlation between CFF-A10 and CFF-MA. CFF-A10 and CFF-MA showed a very strong correlation: CFF-MA (mm) = 1.04 × CFF-A10−0.01 (Pearson's correlation coefficient = 0.995). See **b** and **c** for the abbreviations and their full definitions. **e** ROC, cutoff value of CFF-A10 for indicating a CFF-MA of 12 mm. The cutoff of CFF-A10 for indicating a CFF-MA of 12 mm was 12.0 mm. Sensitivity and specificity were 0.96 and 1.0, respectively. See **b** and **c** for the abbreviations and their full definitions. **f** Correlation between CFF-A10 and fibrinogen concentration. CFF-A10 and fibrinogen concentration showed a slightly strong correlation: Fibrinogen concentration (mg/dL) = 7.90 × CFF-A10 + 104.01 (Pearson's correlation coefficient = 0.683). See **b** and **c** for the abbreviations and their full definitions. **g** ROC, cutoff value of CFF-A10 for indicating a fibrinogen concentration of 150 mg/dL. The cutoff of CFF-A10 for indicating a fibrinogen concentration of 150 mg/dL was 10.1 mm. Sensitivity and specificity were 0.95 and 0.80, respectively. See **b** and **c** for the abbreviations and their full meanings. **h** ROC, cutoff value of CFF-A10 for indicating a fibrinogen concentration of 200 mg/dL. The cutoff value of CFF-A10 for indicating a fibrinogen concentration of 200 mg/dL was 16.2 mm. Sensitivity and specificity were 0.89 and 0.67, respectively. See **b** and **c** for the abbreviations and their full meanings. **i** Correlation between [CRT-A10−CFF-A10] and platelet count. [CRT-A10−CFF-A10] and platelet count showed a slightly strong correlation: platelet count ($\times 10^3/\mu$L) = 4.55 × [CRT-A10−CFF-A10]−15.11 (Pearson's correlation coefficient = 0.650). See **b** and **c** for abbreviations and their meanings. **j** ROC, cutoff value of [CRT-A10−CFF-A10] for indicating a platelet count of 75,000/μL. The cutoff value of [CRT-A10−CFF-A10] for indicating a platelet count of 75,000/μL was 23.2 mm. Sensitivity and specificity were 0.93 and 0.67, respectively. See **b** and **c** for the abbreviations and their full definitions. **k** ROC, cutoff value of [CRT-A10−CFF-A10] for indicating a platelet count of 100,000/μL. The cutoff value of [CRT-A10−CFF-A10] for indicating a platelet count of 100,000/μL was 29.9 mm. Sensitivity and specificity were 0.69 and 0.86, respectively. See **b** and **c** for the abbreviations and their full meanings.

patients using an opt-out method of enrollment via the hospital's website.

Only TEG6s measurements obtained in our operating rooms and intensive care units (ICUs) between January 2018 and December 2022 were extracted. We evaluated the correlation of MA with R, kinetics (K), α angle, CRT-activated clotting time (TEG-ACT, displayed on the screen), and A10, which are display items of TEG6s results. If a good correlation was observed between A10 and MA, we evaluated the relationships between CRT-A10 and CRT-MA, and between CFF-A10 and CFF-MA. We calculated the cutoff values of CRT-A10, where CRT-MA is < 48 mm [8], and CFF-A10, where CFF-MA is < 12 mm. Here, these cutoff values were used because they correspond to a blood fibrinogen concentration of 150 mg/dL frequently used clinically in Japan [9, 10]. In this present study, fibrinogen concentrations and platelet counts measured using TEG6s and concurrent blood sampling were employed to assess the following associations: CFF-A10 and fibrinogen concentration (mg/dL) and [CRT-A10−CFF-A10] and platelet count (/μL). [CRT-MA−CFF-MA] indicates the clot strength of platelets alone [10]. [CRT-A10−CFF-A10] was used as a predictor of [CRT-MA−CFF-MA] in this study. We calculated the cutoff values of CFF-A10 and [CRT-A10−CFF-A10], where the fibrinogen concentrations were 150 and 200 mg/dL and platelet counts were 75,000/μL and 100,000/μL, respectively.

Data and the relationship between A10 and MA were analyzed with mechanical learning using Python 3.10.10 (https://www.python.org/) and Pearson's correlation coefficient, respectively. A set of features (R, A10, K, α angle, and ACT) was identified to predict MA using the SHapley Additive exPlanations (SHAP) method, a machine learning model that determines each variable's contribution to the model's predicted results, with feature importance visualization. We developed a linear regression model using randomly selected 80% of the dataset and evaluated its performance on the remaining 20%. The regression line and results are presented in the accompanying figures. The Youden index was used to calculate the threshold for A10 in relation to MA, fibrinogen concentration, and platelet count. Missing values were not analyzed.

During the study period, we collected and analyzed 1846 paired measurements each of CRT-A10 and CRT-MA, CRT-K and CRT-MA, CRT-angle and CRT-MA, and CRT-ACT and CRT-MA data, along with 991 paired measurements of CFF-A10 and CFF-MA data. Data measured by the simultaneous sampling of TEG6s and central laboratory assays in our hospital included 667 and 603 samples for fibrinogen concentration and platelet count, respectively.

From SHAP results, A10 was the strongest predictor of MA (Fig. 1a). The correlation between CRT-A10 and CRT-MA was very strong (Fig. 1b), with a Pearson's correlation coefficient of 0.979, CRT-MA = 0.87 × CRT-A10 + 13.06, and a cutoff value of CRT-A10 indicating a CRT-MA of 48 mm of 39.9 mm (sensitivity: 0.96, specificity: 0.98; Fig. 1c).

CFF-A10 and CFF-MA had a very strong correlation (Fig. 1d), with a Pearson's correlation coefficient of 0.995, CFF-MA = 1.04 × CFF-A10 − 0.01, and a cutoff value of CFF-A10 indicating a CFF-MA of 12 mm of 12.0 mm (sensitivity: 0.96, specificity: 1.0; Fig. 1e).

Figure 1f shows the relationship between CFF-A10 and fibrinogen concentrations in the analyzed samples collected simultaneously, with a Pearson's correlation coefficient was 0.683 and fibrinogen concentration (mg/dL) = 7.90 × CFF-A10 + 104.01 (mean absolute error: 33.63, mean squared error: 1840.15, root mean squared error: 42.90); the cutoff values of CFF-A10 for indicating fibrinogen concentrations of 150 and 200 mg/dL were 10.1 and 16.2 mm, respectively (sensitivity: 0.95 and 0.89 and specificity: 0.8 and 0.67, respectively; Fig. 1g and h).

Figure 1i shows the relationship between [CRT-A10−CFF-A10] (mm) and platelet count ($\times 10^3/\mu$L) in analyzed samples collected simultaneously, with a Pearson's correlation coefficient of 0.650 and platelet count ($\times 10^3/\mu$L) = 4.55 × [CRT-A10−CFF-A10]−15.11 (mean absolute error: 24.68, mean squared error: 1421.10, root mean squared error: 37.70); the cutoff values of [CRT-A10−CFF-A10] for indicating platelet counts of 75,000/μL and 100,000/μL were 23.2 and 29.9 mm, respectively (sensitivity: 0.93 and 0.69 and specificities: 0.67 and 0.86, respectively; Fig. 1j and k).

There are some reports on A10 using rotational thromboelastometry [11, 12]; however, to the best of our knowledge, there is only one report indicating that A10 can be effectively used in TEG6s evaluations in trauma [13], but it is not on cardiac surgery. Most importantly, this study shows that CRT-A10 and CFF-A10 can predict CRT-MA and CFF-MA, respectively. Because A10 results can be obtained more quickly than MA results, these findings suggest that rapid MA diagnosis is possible based on A10 measurements, even when using TEG6s. Consequently, decisions regarding the administration of platelet- and fibrinogen-containing products can be made more quickly for patients requiring them. More specifically, from our results, the cutoff value of CRT-A10 for indicating a CRT-MA of 48 mm was 39.9 mm. When CRT-A10 decreases below this level, an elevated CRT-MA of < 48 mm is predicted when CRT-A10 decreases below this level, facilitating rapid decision-making regarding platelet transfusion based on reports, clinical findings, and other tests. Contrastingly, the cutoff value of CFF-A10 for indicating a CFF-MA of 12 mm was 12.0 mm. Therefore, fibrinogen-containing preparations may be considered based on reports if CFF-A10 decreases below this value since CFF-MA is < 12.0 mm at a high rate.

TEG6s is not an instrument for measuring fibrinogen concentrations or platelet counts. Therefore, applying the study results depends on consensus, including each institution's TEG algorithm. TEG6s algorithm in our operating room and ICU are presented in Online Resource 1, and additional discussions have been included. The initial target is a fibrinogen concentration of ≥ 150 mg/dL and CFF-A10 of > 12 mm. Certainly, these values are not absolute and can vary depending on the clotting and hemostasis situation of surgical field, and consensus among surgeons and anesthesiologists is necessary for establishing these values. For example, if CRT-A10 shows a slightly lower value of 11 mm or fibrinogen concentration shows a slightly lower value of 130 mg/dL, and hemostasis is complete in the operative field, transfusion may not be performed. Even if the CRT-A10 shows a value of 15 mm, arterial bleeding from the prosthetic-aorta anastomotic site will continue after cardio-pulmonary bypass withdrawal, and fibrinogen-containing product will be transfused to patients whose fibrinogen levels are expected to be low in a short period of time. Using viscoelastic testing as a "common language" to comprehensively discuss the need for blood transfusion among multiple professions is preferred rather than focusing solely on "The viscoelastic test value is improved," considering the patient's background, surgical field, and the amount of drain drainage in the ICU. Viscoelastic testing in cardiac surgery is becoming the standard of care, and its use for transfusion management is considered a valuable contribution to patient blood management. Because blood products are a limited resource obtained from blood donors, high ethical standards are required for their use. Various aspects, including safety considerations for potential disadvantages, balancing supply and demand, balancing the effects of insufficient or excessive transfusions, healthcare costs, tax, and the financial burden on recipients, require consideration, all of which are directly linked to patient blood management.

This study has some limitations. First, the independence of repeated measurements was assumed. We implemented TEG6s algorithm-based transfusion decision-making in our operating room and ICU [14] and obtained multiple measurements for the same patient. However, the coagulation status might have changed because these measurements were taken several hours apart both during and immediately after cardiac surgery rather than as a result of continuous procedures. This ensured the independence of repeated measurements. Second, this was a retrospective study. However, whether it is a prospective or retrospective study, the study results would be the same. Lastly, this study was not designed to determine the amount of blood transfused from the A10 results. Reports of the relationship between TEG6s results and fibrinogen concentrations are available [10]. Additionally, several reports have indicated the amount of fibrinogen, cryoprecipitate, or fresh frozen plasma that should be administered to reach the target fibrinogen concentration [15, 16].

In conclusion, we obtained good correlations between CRT-A10 and CRT-MA, and between CFF-A10 and

CFF-MA. Therefore, A10 can be adopted for the prediction of MA using TEG6s.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-023-03301-5.

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Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interest Takahiro Tamura, Tatsuro Yokoyama, and Kimitoshi Nishiwaki have no conflict of interest.

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