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Fibcare® shows correlation with fibrinogen levels by the Clauss method during cardiopulmonary bypass

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ABSTRACT

Central laboratory measurements are time consuming, while rapid fibrinogen level measurements within the operating room improve transfusion strategies. We aimed to clarify the correlation between fibrinogen concentrations (measured using Fibcare® and the Clauss fibrinogen assay in a central laboratory) during cardiovascular surgery with cardiopulmonary bypass. Data of patients whose Fibcare, traditional laboratory-based testing, and thromboelastographic results were measured using the same blood sample during cardiopulmonary bypass from February 2021 to January 2022 were retrospectively examined. We analyzed correlation in categories of body temperature during cardiopulmonary bypass: total cases, mild hypothermia (28–34°C), and moderate or severe hypothermia (<28°C). The Clauss fibrinogen assay was performed in 123 cases, Fibcare in 107, and thromboelastography in 91. For mild hypothermia, moderate or severe hypothermia, and overall, the root mean squared error and R-square in Fibcare were 16.1 and 0.86, 13.1 and 0.87, and 14.9 and 0.87, respectively, and for thromboelastography, they were 3.26 and 0.74, 2.70 and 0.79, and 3.08 and 0.75, respectively. A significant relationship was noted between Fibcare and Claus fibrinogen analysis regardless of body temperature during cardiopulmonary bypass. The measurement of fibrinogen levels using Fibcare allows for faster transfusion preparation than that of the traditional Clauss fibrinogen assay.

Keywords: Fibcare, thromboelastography, platelet mapping, fibrinogen, cardiopulmonary bypass

Abbreviations:
CPB: cardiopulmonary bypass
TEG6s: thromboelastography
ActF-MA: maximum amplitude of activator f

INTRODUCTION

Cardiovascular surgery with cardiopulmonary bypass (CPB) changes coagulation function

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by several mechanisms, such as hypothermia, acidosis, and induction of the inflammatory cascade.[1-4] In addition, the decrease in coagulation factor activity during CPB is strongly related to hemostasis after CPB cessation. Coagulopathy associated with massive bleeding has been implicated particularly in the reduction of plasma fibrinogen levels.[5] Maintenance of high levels of coagulation factors, especially fibrinogen, is necessary for hemostasis during cardiovascular surgery.[6,7] Determination of fibrinogen concentration is important for hemostasis management,[8] and it is a general standard to keep the fibrinogen concentration above 150–200 mg/dL.

Devices such as thromboelastography (TEG6s®, Haemonetics Japan GK, Japan) have been recommended to guide transfusion during cardiovascular surgery.[9-11] Measuring coagulation function with these devices has been shown to improve transfusion outcomes in cardiovascular surgery.[12] These point-of-care tests have the advantage of bedside availability and immediate results compared to conventional laboratory blood tests. It often takes at least 30–40 min to obtain results of central laboratory measurements of plasma fibrinogen concentration,[13] and delayed measurement leads directly to delayed hemostasis management. Therefore, rapid monitoring of hemostatic coagulability is necessary. We previously reported a study of rapid estimation of fibrinogen concentrations using TEG6s during CPB.[14] However, the measurement cartridge of TEG6s, Platelet Mapping, is expensive and is not suitable for multiple measurements due to its cost.

Fibcare® (Atom Medical Co, Tokyo, Japan) is a monitor that can measure plasma fibrinogen levels in approximately 2 min, and Okahara et al and Imai et al reported a correlation between Fibcare and blood collection[15] and within the obstetric field,[16] respectively. However, there have been no reports evaluating Fibcare and central laboratory results in relation to body temperature in patients undergoing extracardiac cardiopulmonary bypass and receiving heparin. If Fibcare can accurately determine the fibrinogen concentration during CPB, including in heparinized and hypothermic patients, it would help in the effective management of post-CPB coagulopathy and bleeding. The purpose of this study was to clarify the correlation between fibrinogen concentration as measured by Fibcare and the Clauss fibrinogen assay in a central laboratory during cardiovascular surgery with CPB in our institution.

METHODS

Study design and data collection

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Additionally, this single-center retrospective observational study conforms to the standards of the Declaration of Helsinki and was approved by the ethics committee of Nagoya University Hospital (approval number: 2021–0456; application for a change of period has been filed for a change of the target period). Individual informed consent was obtained from the patients using an opt-out method of enrollment via the hospital's website. Patients who were scheduled for cardiac or aortic surgery with CPB from February 2021 to January 2022, and with the Clauss fibrinogen assay in the central laboratory and Fibcare or maximum amplitude of activator f (ActF-MA) by TEG6s measurements on blood samples taken simultaneously during CPB, were enrolled. In short, the patients had only one Clauss measurement and only one Fibcare or ActF-MA measurement or both, and multiple blood samples were not collected from the same patient. The primary analysis item was the correlation between fibrinogen concentration as measured by Fibcare and the Clauss fibrinogen assay. We reexamined the correlation between ActF-MA, a previously reported rapid diagnostic method,[14] and the Clauss method for comparison with the primary endpoint. In addition, the height, weight, age, sex, and body temperature were

extracted during CPB.

Standard monitoring for cardiovascular surgery patients (non-invasive arterial blood pressure measurements, electrocardiography, pulse oximetry, bispectral index monitoring, radial artery cannulation, and pulmonary artery catheterization) was performed in all patients. Fentanyl and midazolam were administered intravenously to induce general anesthesia. Remifentanil and rocuronium were additionally used to facilitate tracheal intubation, and general anesthesia was maintained with air, oxygen, remifentanil, and volatile anesthetics. Porcine heparin (300 U/kg) was administered before starting cannulation for CPB, and additional heparin boluses (50 U/kg) were administered to maintain an activated clotting time of at least 400 s. Ventilation was re-started before separating from CPB, and CPB was terminated with inotropic drug support. Protamine (3 mg/kg) was administered to antagonize the heparin effect, and the patient was intubated and admitted to the intensive care unit. Red blood cell concentrates were transfused to maintain a hemoglobin level of >8 mg/dL during CPB. Coagulation function was monitored using a standard TEG6s assay, and fresh frozen plasma and platelet concentrate were administered appropriately.

Blood sampling and measurement protocols

Blood samples of 6.4 mL were collected via a radial artery cannula system with a closed circuit for blood sampling during CPB and were collected to obtain results at the same time

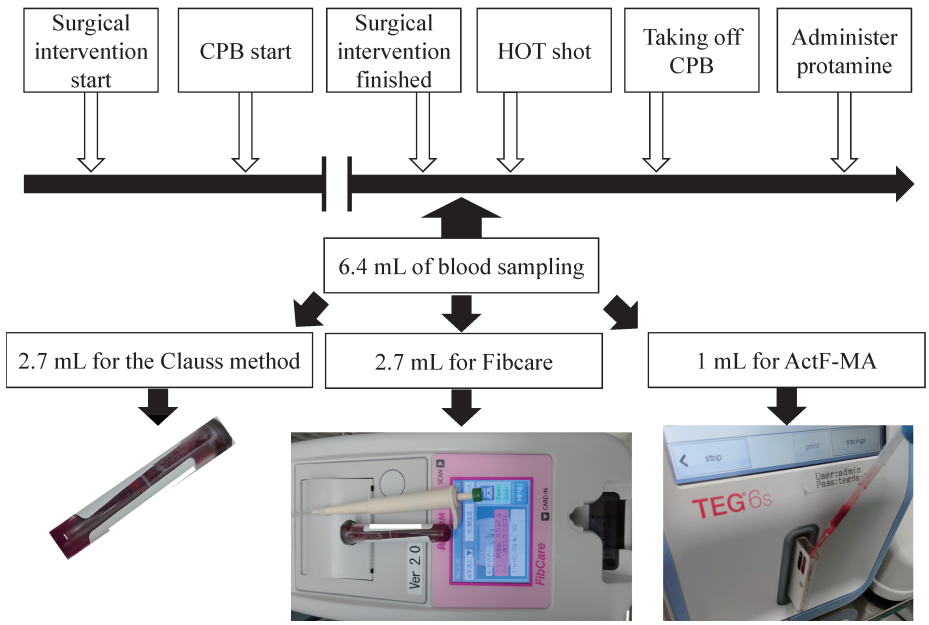

Fig. 1 Blood sampling

The sampling point was between the end of surgical procedure and HOT shot of cardio-plegia. In each patient, 6.4 mL blood sample was collected once, 2.7 mL was used for the Clauss method, 2.7 mL for Fibcare, and 1 mL for ActF-MA measurement. Traditional laboratory-based testing was used to measure fibrinogen concentration; specimens were submitted to our hospital's central laboratory and measured by the laboratory technician using Clauss fibrinogen assay. Fibcare was used to measure fibrinogen concentration, and ActF-MA was used to predict the fibrinogen concentration in the operating room.

CPB: cardiopulmonary bypass

HOT: warm blood cardioplegia

ActF-MA: maximum amplitude of activator f

points for fibrinogen concentration measurements for Fibcare, fibrinogen concentration measurements for our hospital's central laboratory, and ActF-MA. Fibcare was used to measure fibrinogen concentration, and ActF-MA was used to predict the fibrinogen concentration in the operating room. Traditional laboratory-based testing was used to measure fibrinogen concentration; specimens were submitted to our hospital's central laboratory and measured by the laboratory technician using Clauss fibrinogen assay (Analyzer: CN-6000; measuring reagent: Thrombocheck Fib [L], Sysmex Corporation, Kobe, Japan). Fibcare has a lower and upper limit of 80 and 300, respectively. If the result was <80, a value of 40 was imputed, while if the result exceeded the upper limit, the result was excluded from the analysis. ActF-MA by TEG6s has a lower limit of 2.0. If the result was <2.0, a value of 1.0 was imputed.

Statistical analyses

We evaluated the correlation between fibrinogen concentration via traditional laboratory-based testing by Clauss fibrinogen assay and Fibcare using Deming regression analysis. The correlation was analyzed in three categories of body temperature evaluated during CPB: mild hypothermia (28–34°C), moderate or severe hypothermia (below 28°C), and total patients.[17] We also examined the correlation between Clauss fibrinogen assay and TEG6s under the same temperature conditions. Robust regression detected outliers (Cook's distance >1), and Deming regression determined the slope and intercept of the linear prediction equation. Root mean squared error was obtained from Deming regression and R-square was obtained from ordinary least square. We performed 1000 bootstrap resampling to obtain the confidence intervals for root mean squared error and R-square. All analyses were performed using Stata 17 MP (Stata Corp, College Station, TX, USA).

RESULTS

Between February 2021 and January 2022, 123 patients were enrolled in the study. Patient information and surgical characteristics are shown in Table 1. Blood samples were collected once

Table 1 Demographic and surgical characteristics

	Total (n = 123)	**Mild[a] (n = 76)**	**Moderate or severe[a] (n = 47)**
Age (years)	65.33 ± 13.89	64.09 ± 14.36	67.32 ± 12.86
Height (cm)	161.66 ± 8.83	160.99 ± 8.45	162.74 ± 9.31
Body weight (kg)	62.16 ± 12.72	58.28 ± 11.24	60.11 ± 13.80
Body mass index (kg/m^2)	23.86 ± 3.83	22.09 ± 3.01	22.48 ± 3.57
Males:females	86:37	52:24	34:13
Surgical characteristics			
Anesthesia time	409.09 ± 134.54	393.70 ± 127.38	433.98 ± 141.87
Surgical time	326.05 ± 124.67	312.97 ± 118.10	347.19 ± 131.91
CPB time	167.62 ± 67.61	160.77 ± 61.44	178.60 ± 75.18
Minimum nasal temperature during CPB	28.62 ± 5.55	32.62 ± 1.86	22.57 ± 3.36
Minimum vesical temperature during CPB	31.83 ± 4.24	33.50 ± 1.50	29.13 ± 5.62
Minimum skin temperature during CPB	25.93 ± 3.23	25.61 ± 3.17	26.45 ± 3.26

Data are presented as mean ± standard deviation or as number (of patients), as appropriate.
[a]The correlation was analyzed in three categories of body temperature evaluated during CPB with: mild hypothermia (28–34°C); moderate or severe hypothermia (<28°C); and total patients.
CPB: cardiopulmonary bypass

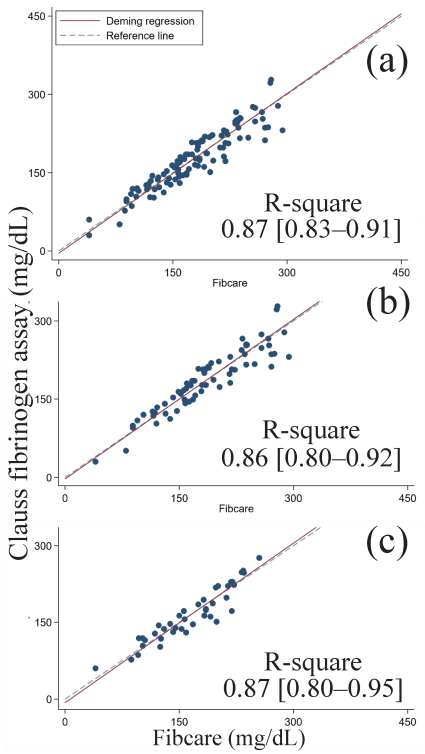

Fig. 2 Relationship between Fibcare and the Claus fibrinogen assay

Fibcare was measured in 107 cases with 66 of mild hypothermia and 41 of moderate or severe hypothermia. The correlation between fibrinogen concentration via Fibcare and the Clauss fibrinogen assay was evaluated using Deming regression analysis.

Fig. 2a: Relationship between Fibcare and the Claus fibrinogen assay in total cases (n=107). Fibrinogen Prediction Equation, RMSE, and R-square are 1.02×Fibcare -4.47, 14.9 [12.7–17.1], and 0.87 [0.83–0.91], respectively.

Fig. 2b: Relationship between Fibcare and the Claus fibrinogen assay in mild hypothermia cases (n=66). Fibrinogen Prediction Equation, RMSE, and R-square are 1.02×Fibcare -3.18, 16.1 [13.1–19.0], and 0.86 [0.80–0.92], respectively.

Fig. 2c: Relationship between Fibcare and the Claus fibrinogen assay in moderate or severe hypothermia cases (n=41). Fibrinogen Prediction Equation, RMSE, and R-square are 1.04×Fibcare -7.11, 13.1 [10.0–16.2], and 0.87 [0.80–0.95], respectively.

RMSE: root mean squared error

at the same time point from each patient for measuring the Clauss fibrinogen assay and Fibcare and/or TEG6s. The Clauss fibrinogen assay was measured in all cases. Fibcare was measured in 107 cases with 66 of mild hypothermia and 41 of moderate or severe hypothermia. ActF-MA was measured in 91 cases with 55 of mild hypothermia and 36 of moderate or severe hypothermia.

Values measured with the Clauss fibrinogen assay and those measured with Fibcare are demonstrated in Figure 2a (total), Figure 2b (mild hypothermia), and Figure 2c (moderate or severe hypothermia). Values measured with the Clauss fibrinogen assay and those measured with ActF-MA are demonstrated in Figure 3a (total), Figure 3b (mild hypothermia), and Figure 3c (moderate or severe hypothermia). No case was excluded in the Robust regression, ie, there was no outliers in both assays.

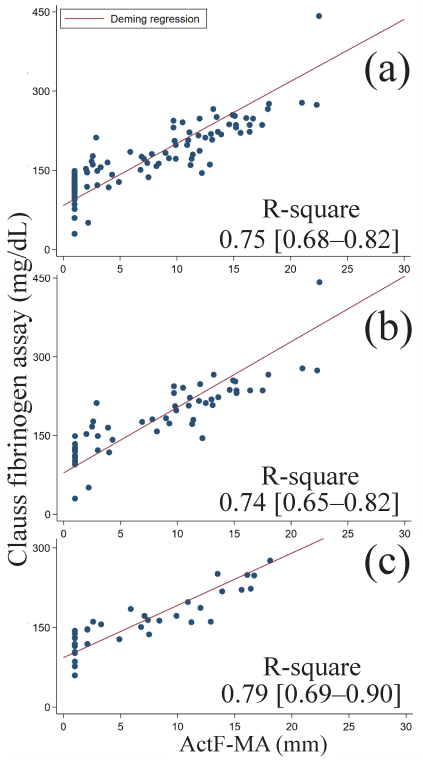

Fig. 3 Relationship between ActF-MA and the Claus fibrinogen assay

ActF-MA was measured in 91 cases with 55 of mild hypothermia and 36 of moderate or severe hypothermia. The correlation between fibrinogen concentration via Fibcare and the Clauss fibrinogen assay was evaluated using Deming regression analysis.

Fig. 3a: Relationship between ActF-MA and the Claus fibrinogen assay in total cases (n=91). Fibrinogen Prediction Equation, RMSE, and R-square are 11.7×ActF-MA +83.5, 3.08 [2.64–3.52], and 0.75 [0.68–0.82], respectively.

Fig. 3b: Relationship between ActF-MA and the Claus fibrinogen assay in mild hypothermia cases (n=55). Fibrinogen Prediction Equation, RMSE, and R-square are 12.5×ActF-MA +78.9, 3.26 [2.67–3.85], and 0.74 [0.65–0.82], respectively.

Fig. 3c: Relationship between ActF-MA and the Claus fibrinogen assay in moderate or severe hypothermia cases(n=36). Fibrinogen Prediction Equation, RMSE, and R-square are 9.84×ActF-MA +93.4, 2.70 [2.19–3.21], and 0.79 [0.69–0.90], respectively.

ActF-MA: maximum amplitude of activator f

RMSE: root mean squared error

The values of root mean squared error and R-square are shown in Table 2. The results of Fibcare were 14.9 [12.7–17.1] and 0.87 [0.83–0.91] in total, 16.1 [13.1–19.0] and 0.86 [0.80–0.92] in mild hypothermia cases, and 13.1 [10.0–16.2] and 0.87 [0.80–0.95] in moderate or severe hypothermia cases. The results of ActF-MA were 3.08 [2.64–3.52] and 0.75 [0.68–0.82] in total, 3.26 [2.67–3.85] and 0.74 [0.65–0.82] in mild hypothermia cases, and 2.70 [2.19–3.21] and 0.79 [0.69–0.90] in moderate or severe hypothermia cases.

Table 2 Root mean squared error and R-square

Measurement	Fibrinogen Prediction Equation	RMSE	R-square
Fibcare			
Total	1.02×Fibcare – 4.47	14.9 [12.7–17.1]	0.87 [0.83–0.91]
Mild	1.02×Fibcare – 3.18	16.1 [13.1–19.0]	0.86 [0.80–0.92]
Moderate or severe	1.04×Fibcare – 7.11	13.1 [10.0–16.2]	0.87 [0.80–0.95]
ActF-MA			
Total	11.7×ActF-MA + 83.5	3.08 [2.64–3.52]	0.75 [0.68–0.82]
Mild	12.5×ActF-MA + 78.9	3.26 [2.67–3.85]	0.74 [0.65–0.82]
Moderate or severe	9.84×ActF-MA + 93.4	2.70 [2.19–3.21]	0.79 [0.69–0.90]

Data are presented as mean ± standard deviation or as number (of patients), as appropriate.
The correlation was analyzed in three categories of body temperature evaluated during CPB with: mild hypothermia (28–34°C); moderate or severe hypothermia (<28°C); and total patients.
CPB: cardiopulmonary bypass
ActF-MA: maximum amplitude of activator f
RMSE: root mean squared error

DISCUSSION

This study analyzed the correlation between fibrinogen concentration via traditional laboratory-based testing by Clauss fibrinogen assay and Fibcare. The results of this study revealed that Fibcare results strongly predict fibrinogen concentration during CPB, whether during hypothermia or not. In addition, the results of this study showed that more accurate blood concentration prediction was possible than with the rapid diagnosis method (ActF-MA) that we proposed until now.

Fibrinogen replacement therapy for hemostasis can be managed by transfusion of fresh frozen plasma, cryoprecipitate, and fibrinogen concentrate. Some guidelines have suggested the use of transfusion to maintain a target fibrinogen concentration above 150 mg/dL.[18-21] Therefore, for hemostatic coagulation management, it is important to know the fibrinogen concentration after discontinuing CPB. However, it can take 40–60 min for traditional fibrinogen concentration measurement assays to report test results. Therefore, if fibrinogen concentration during CPB can be quickly determined using Fibcare, which provides results in approximately 2 min, rapid coagulation management is possible. Our results clearly indicate that measurement of fibrinogen levels using Fibcare allows for faster transfusion preparation than the traditional Clauss fibrinogen assay.

We previously reported a significant relationship between ActF-MA and the Clauss fibrinogen assay.[14] In ActF-MA, fibrinogen reaction occurs through reptilase, an enzyme found in the venom of snakes such as the Fer de lance; fibrinogen is converted to fibrin, and stabilization of the fibrin is facilitated by activated factor XIII and composes what has been called activator f. Thus, ActF-MA does not directly measure fibrinogen levels because it activates fibrin formation using a thrombin-free pathway. Fibcare and the CG02N coagulation analyzer (A&T, Kanagawa, Japan) are based on the same principle: an improved device based on CG02N using the dry hematology system by measuring whole blood. CG02N requires diluting blood samples with a solution manually, and there is a risk of error during the measurement process. For this reason, rapid measurement is difficult during cardiovascular surgery with CPB. In contrast, Fibcare does not require diluting blood samples, and thus concentrations can be measured rapidly. Reports examining the accuracy of CG02N in cardiovascular surgery have shown that plasma fibrinogen levels can be accurately measured even in CPB cases, and that the dry hematology method is not affected by dilution or heparin administration.[22]

Fibcare is also attractive because of the lower cartridge cost per measurement of ActF-MA: approximately USD 10 per Fibcare cartridge in comparison to USD 100 per TEG6s cartridge. TEG6s was not originally designed to directly measure fibrinogen concentration. These devices are used to measure comprehensive coagulation functions, including coagulation factors, platelets, and fibrinogen; to determine the need for transfusions such as fresh frozen plasma and platelet concentrate; and/or to conduct post-transfusion assessment of coagulation functions.[9-11] For this reason, it would be advantageous to utilize the inexpensive Fibcare in order to quickly determine the fibrinogen value only.

This study has substantial limitations that should be addressed. First, as can be determined from measured values, the prediction equation is not absolute, and variations exist. Even the Clauss fibrinogen assay can have different results at different institutions. However, variations in Fibcare results and correlations may be considered acceptable in clinical practice and do not create a problem for the rapid determination of fibrinogen concentrations in the range >200 mg/dL, 150–200 mg/dL, or <150 mg/dL. Second, fibrinogen concentration is most commonly measured using the Clauss fibrinogen assay. However, instruments such as coagulation analyzers and thrombin reagents are not well standardized between hospitals. A previous study showed that fibrinogen concentration measured by the Clauss fibrinogen assay varies considerably between hospitals.[23] For this reason, our findings may differ in another hospital. Further multicenter studies are needed to evaluate our findings in order to eliminate bias at each center and to evaluate the association with the Clauss fibrinogen assay.

In summary, our results show a significant relationship between Fibcare and the Clauss fibrinogen assay. Low fibrinogen concentration can be estimated more quickly by Fibcare than by traditional methods, and Fibcare allows fast prediction of fibrinogen concentration and rapid transfusion preparation in cardiac surgery.

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DISCLOSURE STATEMENT

None of the authors has any conflicts of interest to declare in relation to this work.

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