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Impact of Sonoclot hemostasis analysis after cardiopulmonary bypass on postoperative hemorrhage in cardiac surgery

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Abstract
Purpose. The Sonoclot Analyzer provides a functional test of whole blood coagulation by measuring the viscous property of the blood sample. In this study, we used a modified Sonoclot assay, using cuvettes with a glass bead activator containing heparinase, and compared the Sonoclot data before and after cardiopulmonary bypass (CPB) to assess the usefulness in predicting postoperative hemorrhage.
Methods. In 41 cardiac surgery patients, Sonoclot data were obtained immediately after heparin administration (pre-bypass) and just before protamine administration (post-bypass). Excessive bleeding was defined as chest tube drainage greater than $2\,ml \cdot kg^{-1} \cdot h^{-1}$ in 1 h during the first 4 h after surgery.
Results. There were no significant differences in Sonoclot values before and after CPB in patients with acceptable bleeding ($n = 29$). In patients with excessive bleeding ($n = 12$), Sonoclot variables reflecting fibrin formation (activated clotting time [ACT], rate of fibrin formation [clot rate], and peak clot signal) were preserved after CPB; however, the variables reflecting platelet-fibrin interaction (time to peak, peak angle, and clot retraction rate) were significantly different from their respective pre-bypass values. Sonoclot analysis showed impairment of clot maturation after CPB in patients with excessive postoperative bleeding.
Conclusion. Our results suggest that abnormal postoperative hemorrhage can be predicted by Sonoclot analysis with a new glass bead-activated heparinase test performed after CPB.

Key words Sonoclot · Cardiac surgery · Postoperative hemorrhage

Introduction

Postoperative bleeding is a major cause of morbidity and mortality after cardiac surgery [1,2]. Because the etiology of postoperative hemorrhage is multifactorial, it is often difficult to predict bleeding risks with conventional tests, including activated clotting time (ACT), prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, fibrinogen concentration, and platelet function tests. Each of these tests reflects an isolated portion of the hemostatic sequence, and therefore the overall complex interactions of coagulation defects may not be reliably evaluated.

The Sonoclot Coagulation and Platelet Function Analyzer (Sienco, Morrison, CO, USA) traces the transition of whole blood, from fluid to viscous clot, with a high-frequency (400-Hz) vibrating probe. Both clotting and late fibrinolytic state can be assessed with Sonoclot tracings, and defects of plasma factors, fibrinogen, and platelets may be detectable [3–5]. In this study, we report our initial experience of a modified Sonoclot assay using a cuvette containing a glass bead activator and heparinase. The use of glass beads improves the sensitivity of Sonoclot to platelet dysfunction, and heparinase allows testing to be performed during cardiopulmonary bypass (CPB). The aim of this study was to characterize the Sonoclot variables that are associated with increased postoperative bleeding after CPB. We hypothesized that hemostatic defects might be characterized by platelet-mediated mechanisms, and that the major proportion of cardiac surgical patients would develop characteristic Sonoclot variables during CPB.

Patients and methods

After Institutional Review Board (IRB) approval, informed written consent was obtained from 41 consecutive patients (24 men and 17 women) undergoing elective cardiac surgery using CPB. No patients had liver dysfunction, thrombocytopenia, or coagulopathy. Patients were excluded if they had received anticoagulant (warfarin or heparin) or antiplatelet (aspirin or ticlopidine) medications 7 days before surgery.

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Anesthesia care and perfusion management were according to our routine protocol. Briefly, general anesthesia was maintained with fentanyl, midazolam, vecuronium, and sevoflurane. CPB was managed with a membrane oxygenator at a flow rate of between 2.2 and 2.6 l·min^{-1}·m^{-2}, and hypothermia during CPB was in the range of 28ºC–32ºC. Anticoagulation was maintained with unfractionated heparin (300 U·kg^{-1}) for CPB. The celite ACT was measured every 30 min and if the ACT was less than 480 s, additional heparin (100 U·kg^{-1}) was administered during CPB. No antifibrinolytic drug was used during surgery. A Cell Saver (Haemonetics, Braintree, MA, USA) was used in all patients. After termination of CPB, protamine (1 mg per 100 U of heparin) was given to all patients.

Whole blood samples were obtained from the brachial artery immediately after full heparin (300 U·kg^{-1} i.v.) administration (pre-bypass) and on termination of CPB just before protamine administration (post-bypass). Sonoclot coagulation analysis was performed by placing a small amount of whole blood (0.4 ml) into a cuvette consisting of a glass-bead activator with heparinase and a stir bar in which a vertically vibrating probe is suspended [3]. In contrast to the conventional celite or kaolin activators, the glass-bead activator initiates less contact activation, and therefore the onset of clot formation (ACT result) is more sensitive to heparin. With the use of heparinase, the glass-bead activation test may provide greater sensitivity to factor deficiencies in clot formation and clot retraction (platelet function). A comparative set of Sonoclot tracings from the preliminary experiments is shown in Fig. 1.

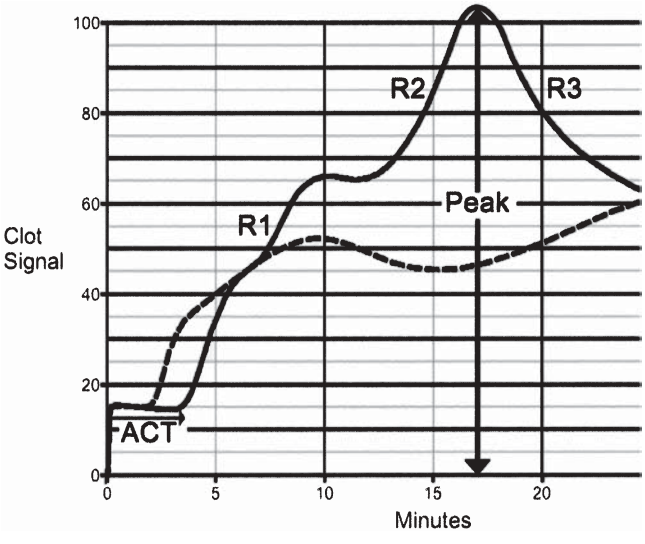

Fig. 1. Production of normal Sonoclot analysis (*solid line*) and abnormal Sonoclot analysis (*dotted line*). *ACT*, activated clotting time; *R1*, the primary slope; *R2*, the secondary slope; *R3*, the third downward slope; *peak*, peak impedance

The changes in mechanical impedance exerted on the probe by the changing viscoelastic properties of the forming clot are measured on a recorder. As fibrin strands form, impedance rises at various rates until the peak impedance is achieved. As shown in Fig. 1, the ACT is the onset time of the beginning of fibrin formation and the clot rate is the primary slope (R1) that reflects further fibrin formation from fibrinogen. This reaction is affected by both the quality of thrombin and the quantity of fibrinogen. After primary fibrin formation, an inflection point is often seen where the platelets start contracting the fibrin strands. The secondary slope (R2) reflects further fibrin formation and platelet-fibrin interaction that represents the completion of clot formation. The peak impedance (peak clot signal) reflects the completion of fibrin formation and represents the fibrinogen concentration. The time to peak is the value for the speed of clot formation, which depends not only on early fibrin formation but also on the dynamic combination of fibrin formation and early clot retraction. A downward slope after the peak signal (R3) represents clot retraction and is produced as platelets induce contraction of the completed clot. The peak angle is the angle between R2 and R3, and the clot retraction rate is the R3. The number of available platelets, as well as platelet function, determines the time to peak, peak angle, and clot retraction rate. Further decrease in impedance is caused by clot lysis [3,4]. Sonoclot data were analyzed by a single person who was blinded to the patients' demographics.

A separate blood sample was placed into an ethylene diamine tetraacetic acid (EDTA) tube, and platelet count and fibrinogen level were obtained.

The patient care team was not informed of the results of the Sonoclot measurements. Hemostatic product transfusion was guided by the conventional laboratory tests; fresh frozen plasma for PT more than 15 s and/or aPTT of more than 45 s, and platelet concentrates for platelet counts of less than $100 \times 10^3 \cdot mm^{-3}$.

We reviewed the Sonoclot and coagulation data of the patients based on the occurrence of excessive bleeding after surgery. Excessive bleeding was defined as chest tube drainage greater than 2 ml·kg^{-1}·h^{-1} in 1 h during the first 4 h after surgery [6]. Results are expressed as means ± SD. Statistical analysis was performed using two-way repeated analysis of variance, Student's *t*-test, or the X^2 test. A P value of less than 0.05 was considered significant.

Results

Table 1 shows the demographics, transfusion requirements, and blood loss of the study patients with excessive bleeding ($n = 12$) and those with acceptable bleeding

Table 1. Patient characteristics

	Acceptable bleeding ($n = 29$)	Excessive bleeding ($n = 12$)
Age (years)	50 ± 16	66 ± 8*
Sex (male/female)	16/13	8/4
Height	163 ± 9	161 ± 6
Weight	60 ± 11	56 ± 8
Operation performed		
Coronery artery bypass surgery	9	3
Aortic valve replacement	5	2
Mitral valve surgery	2	5
Atrial septal defect closure	13	0
Myxoma extraction	0	2
Aortic clamp time (min)	77 ± 38	129 ± 39*
Duration of CPB (min)	136 ± 37	188 ± 48*
MAP administration after CPB	4/29 (14%)	8/12 (67%)*
FFP administration after CPB	5/29 (17%)	8/12 (67%)*
Plt administration after CPB	1/29 (3%)	5/12 (42%)*
Postoperative blood loss during the first 4 h after surgery (ml)	97 ± 59	350 ± 134*

* Value significantly different from acceptable bleeding; $P < 0.05$
Values are means ± SD
CPB, cardiopulmonary bypass

Table 2. Coagulation data before and after CPB

	Acceptable bleeding ($n = 29$)		Excessive bleeding ($n = 12$)	
Variable	After heparin	Before protamine	After heparin	Before protamine
Platelet number ($10^3 \cdot mm^{-3}$)	221 ± 75	149 ± 57*	216 ± 69	90 ± 28*:**
Fibrinogen concentration ($mg \cdot dl^{-1}$)	268 ± 71	160 ± 37*	284 ± 49	154 ± 40*
ACT (s)	255 ± 48	241 ± 52	250 ± 58	246 ± 64
Clot rate ($signal \cdot min^{-1}$)	16.9 ± 7.3	15.7 ± 6.1	17.1 ± 5.2	16.3 ± 4.3
Peak clot signal	94 ± 12	94 ± 8	99 ± 13	93 ± 13
Time to peak (min)	12.1 ± 3.4	13.4 ± 3.7	12.9 ± 3.6	17.3 ± 7.2*:**
Peak angle (degrees)	83 ± 29	85 ± 24	86 ± 22	109 ± 29*:**
Clot retraction rate ($signal \cdot min^{-1}$)	3.0 ± 1.6	3.0 ± 1.4	2.7 ± 1.2	1.5 ± 1.1*:**

* Value before protamine significantly different from after heparin within group; $P < 0.05$;
** Value before protamine significantly different between acceptable and excessive bleeding; $P < 0.05$
Values are means ± SD
ACT, activated clotting time

($n = 29$). There were no significant differences between the two groups in terms of sex distribution, height, or weight. Patients with excessive hemorrhage were older than the nonbleeders. Aortic clamp and CPB times were significantly longer in patients who experienced excessive bleeding.

Coagulation data are shown in Table 2. Before CPB, platelet counts, fibrinogen levels, and Sonoclot values were similar in the groups with and without excessive bleeding. After CPB, platelet counts and fibrinogen concentrations significantly decreased from baseline in both groups, although post-bypass platelet counts were significantly less in bleeders than in nonbleeders (90 ± 28 and $149 \pm 57 \times 10^3 \cdot mm^{-3}$, respectively). There were no significant differences in Sonoclot values before and after CPB in nonbleeding patients. In the group with excessive bleeding, Sonoclot variables reflecting primary fibrin formation (ACT, clot rate, and peak clot signal) were preserved after CPB; however, the later variables, reflecting platelet-fibrin interaction (time to peak [12.9 ± 3.6 vs 17.3 ± 7.2 min], peak angle [86 ± 22° vs 109 ± 29°], and clot retraction rate [2.7 ± 1.2 vs 1.5 ± 1.1 $signals \cdot min^{-1}$]) were significantly different from their respective pre-bypass values.

The number of hemostatic product transfusions was naturally higher in patients who bled excessively, but none of the study patients required surgical re-exploration of the chest for postoperative hemorrhage.

Discussion

In the present study, we observed that bleeding diathesis was associated with reduced platelet-fibrin

interaction that was evident on the Sonoclot tracings. Of note, initial Sonoclot variables reflecting primary fibrin formation were preserved even in patients who experienced excessive postoperative hemorrhage after CPB. Therefore, obtaining late Sonoclot variables that reliably reflect platelet-fibrin interaction is important for predicting bleeding tendency. The glass-bead activator preferentially activates platelets, and improves the sensitivity of Sonoclot to platelet dysfunction. The addition of heparinase to the glass beads cuvette circumvents the susceptibility of the clot signal to heparin anticoagulation. In our study, we used heparinase to assess coagulation function during rewarming (35.5°C) on CPB, and the total time required for obtaining pertinent Sonoclot variables was in the range of 14 to 27 min, which is reasonable considering the typical laboratory turnaround time of 45–60 min for coagulation assays. If Sonoclot variables are used to obtain pertinent variables reflecting platelet-fibrin interaction (prolonged time to peak, blunt peak angle, and reduced clot retraction rate) prior to protamine administration, they may allow us to determine the risk of bleeding and prepare for allogeneic transfusion if necessary.

A bleeding tendency after CPB reflects multiple coagulation defects, including platelet defects in quantity and/or quality, reduced coagulation factors, inadequate reversal of heparinization, and increased fibrinolysis [7–11]. Nevertheless, a number of investigators have attributed post-CPB bleeding to platelet defects [8–10]. Sonoclot variables have been shown to reflect platelet count as well as platelet function [3,4]. Our finding of decreased platelet-fibrin associated with bleeding is in agreement with such views. Shore-Lesserson et al. [12] reported that the intraoperative guidance of hemostatic transfusion with a Thrombelastograph (TEG; Haemoscope, Niles, IL, USA) could reduce bleeding after surgery. One useful TEG variable is the maximum amplitude, which reflects the interaction of fibrin with platelets [13]. Therefore, reduced platelet-fibrin interaction seems to be a critical indicator of platelet abnormality after CPB.

In our study, platelet concentrates were transfused to maintain the platelet counts at more than $100 \times 10^3 \cdot mm^{-3}$. However, 12 of the 41 study patients met the criteria of excessive bleeding after surgery. Possible factors that affect the efficacy of transfused platelets include the occupation of glycoprotein IIb/IIIa receptors by fibrin degradation products [14], and plasmin-mediated fibrinolysis and platelet activation [15]. The above receptors function as a major fibrinogen binding site, and therefore the platelet-fibrin interaction is reduced by their inhibition [16]. Because we did not implement routine antifibrinolytic therapy (e.g., aminocaproic acid or aprotinin), fibrinolysis might have contributed to the postoperative bleeding diathesis.

Conventional clotting tests such as PT and aPTT only reflect early clot formation, and therefore the kinetics and quality of clot formation are not reflected. Sonoclot coagulation analysis enables bedside determination of clot strength and function in a timely fashion. Several investigators have reported that the Sonoclot Analyzer is useful in predicting postoperative coagulation defects after CPB [17–19]. Tuman et al. [17] reported that Sonoclot analysis can be a reliable predictor of abnormal clinical hemostasis after CPB. Stern et al. [18] assessed platelet function by the Sonoclot parameter of the clot retraction rate in cardiac surgery patients taking nonsteroidal anti-inflammatory drugs. Miyashita and Kuro [19] reported that time to peak for the Sonoclot signature can predict approximate platelet function in cardiac surgery. The use of point-of-care coagulation assays has been consistently associated with reduced blood transfusion and postoperative bleeding after CPB [12,20].

In conclusion, Sonoclot analysis with the glass-bead activated heparinase test indicated the impairment of clot stability after CPB in patients who developed excessive postoperative bleeding. Prolonged CPB was associated with poor hemostasis performance and resultant postoperative hemorrhage. Our retrospective analyses provided us with preliminary data to support the usefulness of Sonoclot in guiding hemostatic therapy, and an additional study is ongoing to evaluate this monitor and antifibrinolytic therapy in a prospective manner.

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