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Are Viscoelastic Tests Clinically Useful to Identify Platelet-Dependent Bleeding in High-Risk Cardiac Surgery Patients?

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BACKGROUND: Postoperative use of platelet function testing to rule out microvascular bleeding due to platelet dysfunction after cardiac surgery still lacks strong reference data and reliable cutoff values, yielding a clinically adequate sensitivity and specificity. The present study aims to investigate the performance of two different point-of-care viscoelastic devices and platelet aggregometry in expressing surgery-dependent platelet dysfunction and anticipating postoperative major bleeding in a cohort of high-risk patients.

METHODS: Prospective cohort study of 50 adult patients who were on antiplatelet drugs discontinued for no more than 7 days (clopidogrel and prasugrel) or 5 days (ticagrelor) undergoing cardiac surgery with cardiopulmonary bypass (CPB). Coagulation and platelet function testing, including QUANTRA, ROTEM, and Multiplate, were assessed preoperatively and postoperatively. Chest drain blood loss was measured in the first 12 postoperative hours. Perioperative bleeding was assessed using a modified version of the Universal Definition of Perioperative Bleeding (UDPB) in cardiac surgery, modified to not consider anemia-correcting packed red cells transfusions in the absence of bleeding >600 mL/12 h. Major bleeding was identified as UDPB class II or higher.

RESULTS: Multiplate adenosine diphosphate (ADPtest) was significantly (P = .001) reduced after CPB, whereas TRAPtest was not. The platelet component (PC) as extrapolated by ROTEM data (EXTEM MCF–FIBTEM MCF) was unchanged after CPB, while the A10 PC (PC at 10 minutes) was significantly (P = .001) reduced. The QUANTRA platelet contribution to clot stiffness (PCS) was significantly (P = .001) reduced, as well. At the ROC analysis for the predictive ability of the post-CPB platelet function testing, the best discrimination was obtained by the QUANTRA PCS, with an area under the curve (AUC) (95% confidence interval [CI]) of 0.80 (0.66–0.91), P = .001, followed by the ROTEM A10 PC with AUC (95% CI) of 0.75 (0.51–0.99), P = .004, and PC with AUC (95% CI) of 0.74 (0.50–0.99), P = .009. The Multiplate ADPtest had an AUC (95% CI) of 0.67 (0.42–0.91), and the TRAPtest had an AUC (95% CI) of 0.62 (0.37–0.86). The cutoff values identified were 13 hPa for the QUANTRA PCS, 40 mm for the ROTEM A10, and 48.5 mm for the ROTEM PC, with negative predictive values of 84%, 81%, and 86%, respectively, and positive predictive values of 55%, 53%, and 69%, respectively.

CONCLUSIONS: QUANTRA PCS, ROTEM A10 PC, and Multiplate ADPtest showed a significant decrease after CPB, whereas ROTEM PC and Multiplate TRAPtest did not. Major bleeding was predicted with a moderate to good discrimination by the post-CPB viscoelastic tests (PCS, PC, and A10 PC). (Anesth Analg 2022;135:1198–206)

KEY POINTS

- **Question:** Are viscoelastic tests clinically useful to identify platelet-related bleeding in high-risk cardiac surgery patients?
- **Findings:** Viscoelastic tests, namely QUANTRA PCS and ROTEM A10 PC and PC, are adequate in predicting major bleeding after cardiac surgery with a moderate degree of discrimination, and relative cutoff values could be identified.
- **Meaning:** The identified cutoff values could be useful in ruling out postoperative bleeding due to the platelet-related factor within a wider protocol for the management of the postoperative bleeding.

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GLOSSARY

ADP = adenosine diphosphate; **aPTT** = activated partial thromboplastin time; **AUC** = area under the curve; **CFT** = clot formation time; **CI** = confidence interval; **CPB** = cardiopulmonary bypass; **CS** = clot stiffness; **CT** = coagulation time; **CTH** = coagulation time with heparinase; **CTR** = coagulation time ratio **FCS** = fibrinogen contribution to clot stiffness; **INR** = international normalized ratio; **IQR** = interquartile range; **MCF** = maximum clot firmness; **MEA** = multiple electrode aggregometry; **ML** = maximum lysis; **NPV** = negative predictive value; **PC** = platelet component; **PCS** = platelet contribution to clot stiffness; **PFTs** = platelet function tests; **POC** = point of care; **PPV** = positive predictive value; **PRC** = packed red cell; **ROC** = receiver operating curve; **TRAP** = thrombin receptor activating peptide; **UDPB** = Universal Definition of Perioperative Bleeding; **VET** = viscoelastic test

Platelet function tests (PFTs) are supported by level IIB evidence in patients receiving antiplatelet therapies according to the guidelines on patient blood management and on bleeding prevention and treatment in cardiac surgery.[1–3]

In cardiac surgery, PFTs have been utilized to investigate platelet function in patients on dual antiplatelet therapy with the aim to determine the timing of surgery,[4,5] and after cardiopulmonary bypass (CPB) to investigate platelet function in patients with microvascular bleeding.[6,7] However, for the latter purpose, reference data are scarce and based on different technologies, and possible cutoff values for prompting interventions aimed to restore platelet count and function remain elusive. The Guidelines of the European Association of Cardiothoracic Anaesthesiologists and the European Association for Cardiothoracic Surgery on patient blood management in cardiac surgery,[1] and those of the European Society of Anaesthesiology on postoperative bleeding management[3] do not provide any reference value for postoperative PFT. The Society of Cardiovascular Anesthesiologists Guidelines[2] conversely suggest an approach based on a viscoelastic test (VET)-based indirect evaluation of platelet contribution to the hemostatic process. The basic concept underlying the use of VET for the diagnosis of a platelet-derived pathogenesis of postsurgical bleeding is based on the measure of clot firmness, that is the result of platelet and fibrin(ogen) interaction. The fibrinogen contribution to clot firmness is assessed by skipping the platelet contribution (through the use of platelet inhibitors), and the platelet contribution is calculated as the difference between the overall clot firmness (amplitude, mm) and the fibrinogen contribution to clot firmness. Some authors[8] and even Guidelines[2] suggest the use of platelet concentrates and/or desmopressin in bleeding patients with a poor clot firmness but a normal fibrinogen contribution. The Society of Cardiovascular Anesthesiologists Guidelines[2] suggest this strategy when the maximum clot firmness (MCF) at 10 minutes (A10) is <40 mm, and the fibrinogen component is >10 mm, that corresponds to a platelet component (PC) <28 mm.

However, this approach has been confuted by other authors[9,10] who suggested that the simple difference in amplitude between clot firmness and fibrinogen contribution should be replaced by the difference in elasticity, that is not linearly associated with the amplitude.

Recently, a new-generation VET has entered the market, the QUANTRA (HemoSonics LLC, Charlottesville, VA). This device provides a measure of clot firmness that is based on shear modulus and expressed as hectopascal (hPa).[11] The device provides a direct measurement of the platelet contribution to clot stiffness (PCS) expressed in hPa, and assessed as the difference between clot stiffness (CS) and fibrinogen contribution to clot stiffness (FCS).

Direct measures of platelet function may be obtained by different point-of-care (POC) technologies. Multiple electrode aggregometry (MEA) is most commonly used in European cardiac surgery institutions. MEA allows to measure platelet reactivity using different platelet activators. MEA has been used to investigate platelet reactivity before major surgery (namely, cardiac surgery) and establish the correct timing for the intervention[4,5]; and to identify a platelet-related bleeding and suggest platelet concentrate transfusion.[6,7]

The present study aimed to investigate the performance of 2 different VET and MEA in expressing the CPB-dependent platelet dysfunction and anticipating post-CPB major bleeding in a cohort of patients at high risk for bleeding related to antiplatelet agents.

Our hypothesis is that VET-based PFT is associated with post-CPB bleeding and may predict major bleeding. Secondary hypothesis is that PFT tests reflect the changes induced by surgery and CPB.

METHODS

This is a prospective cohort study of 50 adult patients prospectively enrolled at IRCCS Policlinico San Donato between May 2019 and June 2021. The study has been approved by the local Ethics Committee (IRCCS San Raffaele Hospital, protocol no. 71/2019,

approved April 11, 2019). A written informed consent has been obtained from all the patients enrolled.

Patient Population

Inclusion criteria were age >18 years, cardiac surgery with CPB, and treatment with platelet $P2Y_{12}$ receptor–inhibiting drugs discontinued for no more than 7 days (ticlopidine, clopidogrel, and prasugrel) or 5 days (ticagrelor). Exclusion criteria included congenital cardiac surgery, known coagulation disorders, and platelet count <100.000 cells/μL.

Data Collection and Definitions

Preoperative and postoperative data collected include demographics (age, sex, height, and weight), comorbidities, use of anticoagulants (warfarin, low molecular weight heparin, unfractionated heparin, direct oral anticoagulants) not discontinued before surgery, use of $P2Y_{12}$ inhibitors and time of discontinuation, preoperative serum creatinine levels, hematocrit, cardiac surgery type and details about CPB, postoperative blood loss, need for transfusion of blood products, surgical revision due to bleeding, use of fibrinogen concentrate, prothrombin complex concentrate, or other procoagulants. All the patients received a prophylactic dose of tranexamic acid (15 mg/kg after induction of anesthesia and 15 mg/kg after protamine administration).

Chest drain blood loss was measured in the first 12 postoperative hours. Perioperative bleeding was assessed using a modified version of the Universal Definition of Perioperative Bleeding (UDPB) in cardiac surgery.[11] Major bleeding was identified for UDPB class II or higher. This modified version of the UDPB does not consider packed red cells (PRC) transfusions done to correct anemia in the absence of bleeding >600 mL/12 h.

Devices and Measurements

For study purposes, blood samples were taken both preoperatively and postoperatively. Preoperative blood drawing was done after anesthesia induction and before surgical incision. Postoperative blood sample was taken within 10 minutes after protamine administration. Platelet count, activated partial thromboplastin time (aPTT), international normalized ratio (INR) of the prothrombin time, and fibrinogen concentration were measured at the central laboratory.

Point-of-Care Testing Included the Following Assessments: QUANTRA, ROTEM, and MEA

QUANTRA (HemoSonics LLC, Charlottesville, VA) is a fully automated cartridge-based POC device based on Sonic Estimation of Elasticity via Resonance Sonorheometry. The device and the underlying technology have been described in detail previously.[12] Briefly, the deformation generated when an ultrasound pulse hits a drop of whole blood is measured at regular intervals and defines the shear modulus of the sample (expressed in hectoPascals, hPa). The dynamic changes of the shear modulus are related to the viscoelastic properties of the coagulating blood sample. The QPlus cartridge consists of 4 channels prefilled with lyophilized reagents for simultaneous assessment. A 2.7-mL tube of citrated blood is required to run the test. In channel 1, coagulation is activated by kaolin, and the relative clotting time (CT, normal range 113–164 s) is measured. In channel 2, heparinase is added to kaolin neutralizing eventual heparin in the blood sample, and the relative clotting time (coagulation time with heparinase [CTH], normal range 109–150 s) is measured. The ratio between CT and CTH is calculated (coagulation time ratio [CTR], values <1.4 exclude residual heparin). In channel 3, the coagulation is activated by thromboplastin, and CS (normal range 13.0–33.2 hPa) is measured. In Channel 4, abciximab is added to thromboplastin to remove platelets from the clot polymerization, and FCS (normal range 1.0–3.7 hPa) is measured. The platelet contribution to clot stiffness (PCS, normal range 11.9–29.8 hPa) is calculated, subtracting FCS from the overall CS. The PCS parameter is calculated from measurements of clot elasticity.[9]

ROTEM delta device (Instrumentation Laboratory, Bedford, MA) is a semiautomated POC viscoelastic device, including 4 channels. Citrated blood is activated by the following: tissue factor (EXTEM test), ellagic acid (INTEM test), tissue factor + cytochalasin D (FIBTEM test), and ellagic acid + heparinase (HEPTEM test). The main parameters were collected for all the tests: coagulation time (CT, s), A10 (amplitude at 10 minutes after clot formation time [CFT], mm), MCF (mm), and maximum lysis (ML, %).

The Platelet Component Is Assessed as the Difference Between the EXTEM MCF and the FIBTEM MCF

MEA platelet aggregometry was performed on Multiplate device (Roche Diagnostics GmbH, Mannheim, Germany). Briefly, blood was collected in hirudin-coated tubes provided by the manufacturer, mixed with saline, and incubated for 3 minutes. Aggregation was triggered by the addition of adenosine diphosphate (ADPtest, final concentration 6.5 μM) and thrombin receptor-activating peptide (TRAPtest, final concentration 32 μM). ADP activates platelets via $P2Y_{12}$ receptors that are the target for the thienopyridine drugs and ticagrelor. The TRAPtest assesses the aggregation via the thrombin receptors that express the maximum aggregating potential of the platelets. The value of platelet reactivity is expressed based on the AUC (U). The reference range is 57–113 U for the ADPtest and 84–128 U for the TRAPtest.

The 4 PFT tests considered in this study were, therefore, the QUANTRA PCS, the ROTEM PC (with its derivate A10 PC), and the MEA ADPtest and TRAPtest.

Transfusion Protocol

PRC was transfused for a hemoglobin value <7 g/dL while on CPB, and <8 g/dL after CPB. Postoperative bleeding was managed according to the institutional protocol that follows the Granducato algorithm.[13] For the purpose of the present study, clinicians taking care of the patients were not aware of the postoperative ADPtest that is included in the Granducato algorithm.

Statistical Analysis

Data are expressed as median and interquartile range, mean and standard deviation, or number and percentage. Differences between pre and post CPB values were investigated with a paired data *t* test, and differences between patients with or without major bleeding with unpaired *t* test. Logistic regression analyses were used to adjust for platelet count when assessing association with PFT.

The performance of the 4 PFTs in predicting major bleeding was tested on post-CPB values, using a receiver operating characteristics (ROC) analysis, with the measure of the area under the curve (AUC). For the definition of clinical relevance of the AUC, no prespecified dichotomous level of discrimination was settled; conversely, we referred to the definition of Schober et al,[14] where the discrimination is defined as chance (AUC 0.50), very poor (AUC 0.51–0.59), poor 0.60–0.69(0.60–0.69), moderate (0.70–0.79), good (0.80–0.89), and excellent (AUC ≥0.90). Cutoff values for each test were identified as the point where both sensitivity and specificity are maximized and equal.[15] For each cutoff value, the correspondent values of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed, with their 95% confidence interval (CI).

For all the *P* values, a Bonferroni correction for multiple comparison was considered. The correction considered the presence of 6 platelet-dependent variables (platelet count, MEA ADPtest, MEA TRAPtest, ROTEM PC, ROTEM A10 PC, and QUANTRA PCS), and the *P* values were tested for significance by multiplying their values by 6 and checking that they remained <.05.

Sample size was calculated as follows. Institutional data were explored for assessing the overall rate of major bleeding, that was 26%. Considering that we included patients with possible residual effects of antiplatelet agents, it was hypothesized a rate of events of 33%, with a ratio between events and no-events of 1:2. The target AUC was settled at 0.75. With an alpha value of 0.05 and a beta value of 0.20, the total number of patients required to reject the null hypothesis (AUC 0.50) was 45. We, therefore, settled the patient population at 50.

RESULTS

The general characteristics of the patient population are shown in Table 1, and the standard and POC coagulation parameters before and after CPB in Table 2, where is tested the secondary hypothesis that surgery and CPB induce changes in coagulation parameters.

The majority of patients received clopidogrel, followed by ticagrelor. Three patients had a clopidogrel discontinuation time of 10 days, due to postponed surgery for causes external to the study protocol; 2 patients in the ticagrelor subgroup had a drug discontinuation of 7 and 10 days, for the same reason. The remaining 45 patients had a drug discontinuation time fulfilling the study protocol and were admitted to the following statistical analyses.

Overall, as shown in Table 2, after CPB, there was a well-known prohemorrhagic pattern characterized by a reduced activity of soluble coagulation factors with a significantly (*P* = .001) prolonged CT at

Table 1. General Characteristics of the Patient Population (N = 45)

Variable	Media (IQR) or n (%)
Age (y)	68.7 (62.6–74.4)
Male sex	35 (77.8)
Weight (kg)	77 (67–85)
Ejection fraction (%)	52 (44–60)
Congestive heart failure	2 (4.4)
Active endocarditis	1 (2.2)
Creatinine (mg/dL)	0.96 (0.81–1.14)
Chronic obstructive pulmonary disease	4 (8.9)
Cerebrovascular accident	1 (2.2)
Diabetes (on medication)	9 (20)
Hematocrit (%)	41 (36.2–43.6)
Previous cardiac surgery	3 (6.7)
Type of antiplatelet agent	
Clopidogrel	30 (66.7)
Discontinuation days	5 (4–6)
Prasugrel	3 (6.7)
Discontinuation days	5 (2–5)
Ticagrelor	12 (26.7)
Discontinuation days	4.5 (3–5)
Low molecular weight heparin	4 (8.9)
Warfarin	1 (2.2)
Preoperative conditions	
Elective	31 (68.9)
Urgent	14 (31.2)
Emergent	0 (0)
Type of surgery	
Isolated coronary surgery	26 (57.8)
Isolated valve surgery	9 (20)
Combined surgery	10 (22.2)
Cardiopulmonary bypass time (min)	81 (61–109)
Total heparin dose (IU)	25,000 (21,000–28,000)
Total protamine dose (mg)	240 (205–255)

Abbreviation: IQR, interquartile range.

Table 2. Hemostatic Profile Before and After Cardiopulmonary Bypass (N = 45)

Variable	Before	After	Mean difference (95% CI)	P[a]
Standard central laboratory tests				
Platelet count (×1000/μL)	192 (62)	160 (53)	32 (23–41)	.001
aPTT (s)	33.5 (11)	35.4 (7)	−1.9 (−4.2 to 0.29)	.087
PT (INR)	1.17 (0.12)	1.46 (0.25)	−0.29 (−0.39 to −0.24)	.001
Fibrinogen (mg/dL)	349 (87)	266 (53)	83 (66–99)	.001
ROTEM tests				
Clotting time EXTEM (s)	82 (25)	107 (42)	−24 (−36 to −14)	.001
Maximum clot firmness EXTEM (mm)	67 (5.8)	60 (6.8)	6.3 (5.3–7.3)	.001
Maximum lysis EXTEM (%)	8.2 (4.9)	7.4 (4.1)	0.88 (−0.71 to 2.46)	.270
Maximum clot firmness FIBTEM (mm)	18.4 (5.5)	12.4 (4.2)	6.0 (5.0–7.0)	.001
Platelet component (mm)	48.3 (3.5)	48.0 (4.6)	0.29 (−0.76 to 1.36)	.576
Platelet component A10 (mm)	42.4 (4.1)	39.7 (5.4)	2.63 (1.55–3.72)	.001
Clotting time INTEM (s)	286 (182)	309 (155)	−23 (−91 to 45)	.496
Maximum clot firmness INTEM (mm)	62 (11.4)	55 (8.3)	6.7 (3.1–10.3)	.001
Clotting time HEPTEM (s)	240 (92)	335 (210)	−95 (−169 to −22)	.012
QUANTRA tests				
Clotting time (s)	145 (55)	164 (40)	−19 (−40 to 2.5)	.082
Heparinase clotting time (s)	134 (17.0)	152 (26.7)	−17.6 (−26.8 to −8)	.001
Clot stiffness (hPa)	24.1 (9.2)	16.2 (4.9)	7.9 (5.9–9.9)	.001
Fibrinogen contribution to clot stiffness (hPa)	3.2 (2.1)	2.1 (0.80)	1.06 (0.58–1.55)	.001
Platelet contribution to clot stiffness (hPa)	21.1 (8.4)	14.2 (4.3)	7 (5.0–8.9)	.001
Multiplate tests				
ADP AUC (U)	43.6 (27.7)	30.4 (24.7)	13.2 (6.7–19.7)	.001
TRAP AUC (U)	99.2 (29.6)	96.3 (41.2)	2.9 (−5.8 to 11.6)	.506

Data are mean (standard deviation).

Abbreviations: ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time; AUC, area under the curve; CI, confidence interval; INR, international normalized ratio; PT, prothrombin time; TRAP, thrombin activating peptide.

[a]Significance criterion $P < .05$.

ROTEM and increased INR. The overall clot firmness was significantly ($P = .001$) reduced both at ROTEM and QUANTRA, with significantly ($P = .001$) reduced fibrinogen levels at Clauss analysis, FIBTEM, and FCS. With respect to platelet count, there was a significant ($P = .001$) decrease after CPB; platelet function at MEA ADPtest was significantly ($P = .001$) reduced, whereas it was not at TRAPtest. With respect to platelet function assessed with VET, the PC as extrapolated by ROTEM data was unchanged after CPB, while the A10 PC was significantly ($P = .001$) reduced. The PCS as measured with QUANTRA was significantly ($P = .001$) reduced. Once corrected for multiple comparisons, all the aforementioned P values remained significant.

Table 3 reports the bleeding and transfusion data. Eighteen (36%) patients with major bleeding were identified. Overall, 26 (57.8%) patients required allogeneic blood products. Table 4 reports the pre- and post-CPB values in patients with or without major bleeding. There were significant differences for pre-CPB platelet count and ROTEM A10 PC, and for post-CPB platelet count, ROTEM A10 PC, ROTEM PC, and QUANTRA PCS. After correction for multiple comparisons, only the post-CPB platelet count, and the VET tests remained significantly different between groups. Platelet count before and after CPB was >100,000 cells/μL in 14 (93%) and 11 (73%) patients, respectively.

A multivariable logistic regression analysis with correction for platelet count resulted in a loss of significance for all the PFTs, except post-CPB QUANTRA PCS, that were independently associated with major bleeding (odds ratio, 0.747; 95% CI, 0.567–0.933; $P = .037$).

The predictive ability of post-CPB PFT and platelet count was investigated with an ROC analysis (Figure; Table 5). Overall, a good discrimination was obtained by the QUANTRA PCS, with an AUC of 0.80 (95% CI, 0.66–0.91), whereas platelet

Table 3. Bleeding, Transfusions, and Hemostatic Products

Variable	Median (IQR) or N (%)
Chest drain blood loss (12 h, mL)	525 (287–750)
UDPB class	
Insignificant	21 (46.6)
Mild	9 (20)
Moderate	12 (26.7)
Severe	3 (6.7)
Massive	0 (0)
Major bleeding	15 (33.4)
Surgical revision due to bleeding	1 (2)
Packed red cells transfusion	26 (57.8)
Number of units	3 (2–6)
Fresh frozen plasma	0 (0)
Number of units	0 (0)
Platelet concentrates	11 (24.4)
Number of units	1 (1–1.5)
Desmopressin	12 (26.7)
Fibrinogen concentrate	5 (11.1)
Prothrombin complex concentrate	2 (4.4)

Abbreviations: IQR, interquartile range; UDPB, universal definition of perioperative bleeding.

Table 4. Platelet-Derived Variables in Major Versus Nonmajor Bleeding Patients

Variable	Major bleeding n = 15	Nonmajor bleeding n = 30	Mean difference (95% CI)[a]	P[b]	P[a]
Pre-CPB					
Platelet count (×1000/μL)	165 (71)	206 (53)	42 (−8 to 92)	.030	.180
QUANTRA PCS (hPa)	18.9 (7.2)	22.3 (8.8)	3.4 (−3.7 to 10.5)	.201	1.000
ROTEM A10 PC (mm)	40.7 (5.2)	43.3 (3.1)	2.61 (−0.76 to 6.0)	.044	.264
ROTEM PC (mm)	47.0 (4.1)	49.0 (3.0)	2.0 (−0.91 to 4.9)	.071	.426
MEA ADPtest (U)	35.6 (25.4)	47.4 (28.4)	11.5 (−11.9 to 35)	.191	1.000
MEA TRAPtest (U)	91.5 (26.7)	103 (30.6)	11.5 (−13.6 to 37)	.203	1.000
Post-CPB					
Platelet count (×1000/μL)	131 (51)	175 (49)	44 (1.01–87)	.008	.048
QUANTRA PCS (hPa)	11.1 (3.9)	15.7 (3.6)	4.6 (1.5–7.6)	.001	.006
ROTEM A10 PC (mm)	36.3 (6.6)	41.6 (3.7)	5.2 (1.2–9.2)	.001	.006
ROTEM PC (mm)	45.3 (5.2)	49.4 (3.1)	4.1 (1.1–7.3)	.002	.012
MEA ADPtest (U)	22.3 (19.0)	34.3 (26.5)	12.0 (−8.8 to 32.8)	.125	.750
MEA TRAPtest (U)	85.2 (40.2)	101.9 (41.1)	16.7 (−18.1 to 51.5)	.203	1.000

Data are mean (standard deviation).

Abbreviations: ADP, adenosine diphosphate; CI, confidence interval; CPB, cardiopulmonary bypass; MEA, multiple electrode aggregometry; PCS, platelet contribution to clot stiffness; TRAP, thrombin activating peptide.

[a]*P* values after Bonferroni correction significant if $P < .05$.

[b]Unadjusted *P* values significant if $P < .05$.

count (AUC, 0.77; 95% CI, 0.55–0.98), ROTEM A10 PC (AUC, 0.75; CI 95%, 0.51–0.98), and PC (AUC, 0.74; 95% CI, 0.50–0.99) all yielded a moderate discrimination. All the *P* values remained significant after correction for multiple comparisons. The MEA PFT had a poor discrimination with AUCs of 0.67 (ADPtest) and 0.62 (TRAPtest). The cutoff values identified for the QUANTRA PCS, the platelet count, the ROTEM A10, and the ROTEM PC yielded NPV and PPV in the range of 85% and 60%, respectively (Table 5).

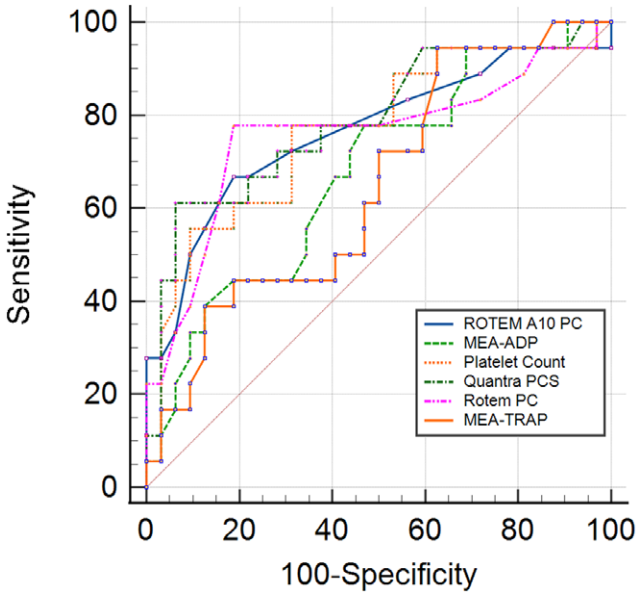

Figure. Receiver operating characteristics analysis for the 6 post-cardiopulmonary bypass platelet function and count variables. Data on the area under the curve in the text. ADP indicates adenosine diphosphate; MEA, multiple electrode aggregometry; PC, platelet component; PCS, platelet contribution to clot stiffness; TRAP, thrombin-activating peptide.

DISCUSSION

The use of POC coagulation tests to guide platelet transfusions in bleeding patients after CPB is still a matter of debate. VET is certainly useful in guiding the use of procoagulant drugs and blood derivates, and their use results in a decrease in transfusion needs.[16] Some of the variables triggering specific interventions are relatively well defined: this applies to protamine supplementation in case of differences in clotting time with or without heparinase; prothrombin complex concentrate or fresh frozen plasma in case of prolonged clotting time in tests with heparinase; and fibrinogen concentrate or cryoprecipitate in case of low fibrinogen component of clot firmness. Conversely, the trigger value for restoring platelet function with platelet concentrate and/or desmopressin remains elusive, with only 1 Guideline suggesting an A10 PC at ROTEM <28 mm[2].

Various attempts have been made to find a possible trigger value using MEA. Petricevic et al[7] proposed an ADPtest <27 U, a TRAPtest <77 U, an ADPTEM <36 Ohm·min, and a TRAPTEM <46 Ohm·min, however with a PPV never exceeding 50%.

Agarwal et al[17] did not find any property of postoperative MEA and Thromboelastography Platelet Mapping in predicting bleeding. Similar results were produced by Sivapalan et al.[18]

The largest attempt to find an acceptable trigger value using MEA was done by our institution, with a prospective study enrolling almost 500 patients.[6] Despite the large patient population, the results were disappointing, with only the ADPtest showing an AUC of 0.712 for major bleeding prediction, and a cutoff settled at 12 U, with a poor PPV of 35%.

An even greater gap in knowledge exists with respect to cutoff values based on the VET PC of clot

Table 5. Performance of Post-CPB Platelet Count and PFT in Predicting Major Bleeding

Variable	AUC (95% CI)[a]	P[b]	P[a]	Cutoff	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
QUANTRA PCS (hPa)	0.80 (0.61–0.99)	.001	.006	13.8	73 (45–92)	70 (51–86)	55 (39–70)	84 (65–92)
Platelet count (×1000/μL)	0.77 (0.55–0.98)	.001	.006	155	80 (52–96)	70 (51–83)	57 (42–71)	87 (71–95)
ROTEM A10 PC (mm)	0.75 (0.51–0.99)	.004	.024	40	67 (38–88)	70 (51–85)	53 (37–68)	81 (66–90)
ROTEM PC (mm)	0.74 (0.50–0.99)	.008	.048	48	73 (45–92)	73 (58–94)	69 (48–84)	86 (73–94)
MEA ADPtest (U)	0.67 (0.42–0.91)	.064	.384	22	67 (38–88)	57 (37–74)	43 (31–57)	77 (61–88)
MEA TRAPtest (U)	0.62 (0.37–0.86)	.189	1.000	88	47 (21–73)	50 (31–69)	32 (20–67)	65 (51–77)

Abbreviations: ADP, adenosine diphosphate; AUC, area under the curve; CI, confidence interval; CPB, cardiopulmonary bypass; MEA, multiple electrode aggregometry; PC, platelet component; PCS, platelet contribution to clot stiffness; PFT, platelet function tests; PPV, positive predictive value; TRAP, thrombin activating peptide.

[a]*P* values after Bonferroni correction significant if $P < .05$.

[b]Unadjusted *P* values significant if $P < .05$.

firmness. Apart from the already quoted value of A10 PC <28 mm contained in one guideline,[2] and replicating what suggested in a previous algorithm,[8] no sound studies could propose a cutoff value for PC with an acceptable PPV. Recently, Matzelle et al[19] investigated a series of 200 patients, ending up with a cutoff value for ROTEM PC of 35 mm, however with a PPV of 24% only.

Cutoff values are important and well received by the clinicians. Their NPV is usually high (>80%) meaning that for values above the threshold, clinicians may be confident that no specific intervention is required. Things are more difficult when looking at the PPV. Values below the threshold should prompt platelet concentrate transfusion and/or desmopressin. In our series, we could identify cutoff values with a PPV not exceeding 69%. Lower levels of PFT are required to increase the PPV and avoid deprivation of adequate interventions; however, this invariably leads to a decrease in NPV, with the possibility of inappropriate interventions. Larger patient populations are required to validate these cutoff values.

In our study, we could find that VET may actually offer insights into the platelet-derived post-CPB bleeding, and even an acceptable prediction of major bleeding in patients at high risk. The identified cutoff values for QUANTRA PCS, ROTEM PC, and ROTEM A10 PC yielded a PPV for major bleeding by far higher than the previously published, despite the relatively low patient population.

There are some possible explanations for this finding. The first is that we selected a patient population at high risk for platelet-derived bleeding. As many as 33 (73%) of the patients had preoperative ADPtest values below the lower limit of normal range. This selected patient population allowed on one side to achieve a sufficient number of major bleeding events, on the other to increase the probability of a platelet-derived bleeding. It is likely that the disappointing results of previous studies aiming to identify a PFT cutoff value to address the need for platelet function/count restore are mainly due to the multifactorial pattern of postcardiac surgery bleeding, where platelet dysfunction is only one of the possible factors.

A second explanation is that our major bleeding definition is based on the well-established and validated UDPB in cardiac surgery. The only modification that we applied to the UDPB was related to PRC transfusions done in absence of a clinically relevant bleeding, with the aim of correcting an anemic state.

The best performance in terms of major bleeding prediction was obtained by the QUANTRA PCS, with a good discrimination at ROC AUC. QUANTRA is a novel device that has been validated for correlation with other VET in various studies.[20–24] The PCS parameter correlates with platelet count[22] and function.[23] In our series, the post-CPB QUANTRA PCS was the only independent factor associated with major bleeding once corrected for platelet count.

The relative novelty of the QUANTRA PCS with respect to ROTEM PC is that it is based on differences in elasticity rather than in amplitude, and this may be of importance, given the fact that the two entities are not linearly correlated. From a theoretical point of view, PCS should be superior to PC in assessing platelet count and function.[9,10]. In our study, both PCS and A10 PC showed a post-CPB decrease, even if in a different fashion. In terms of major bleeding prediction, there was a nonsignificant higher discrimination of PCS versus A10 PC and platelet count.

Platelet count maintains its role as a predictor of major bleeding. However, the level of discrimination was superior for QUANTRA PCS; additionally, QUANTRA PCS is a value that can be obtained in a few minutes, while the turnaround time is certainly longer for platelet count. This adds a value in terms of prompt interventions to prevent/stop bleeding.

The role of platelet count in the setting of PFT remains a matter of possible bias. Actually, both the MEA and the VET tests are influenced by

platelet count.[25,26] Within this pattern, it is important that QUANTRA PCS, differently from the other MEA and VET tests, maintains an independent association with major bleeding once corrected for platelet count. From a clinical point of view, a test that incorporates both platelet count and function has a potentially important role, because under the conditions of thrombocytopenia and/or platelet dysfunction, in a bleeding patient, the therapeutic approach remains the same.

An important finding of our study is that the proposed cutoff values for prompting platelet transfusion[2,8] and/or desmopressin should actually be revised. Actually, no patient in our population met the criterion of an A10 EXTEM <40 mm with an A10 FIBTEM >10 mm (PC <28 mm). From our data, the correct cutoff value is considerably higher (40 mm).

The main limitation of our study is the relatively low sample size that warrants further studies; another inevitable limitation is that postoperative bleeding is certainly multifactorial. Even if we measured other coagulation parameters, the relatively limited sample size does not allow us to create a multifactorial model, that is in any case outside the purposes of the present study. This is certainly an exciting issue for future large population studies. The strengths of our study are the use of a bleeding definition based on the UDPB and the selection of patients likely to suffer from a platelet-derived postoperative bleeding.

In conclusion, our study highlights that VET, when correctly used, may be useful in predicting major bleeding in a selected population of cardiac surgery patients at high risk for platelet-derived bleeding.

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Contribution: This author helped acquire, analyze, and interpret the data of the work, also helped write the manuscript and revise it critically, and gave their final approval to the version to be published.
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