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Point-of-Care Testing of Hemostasis in Cardiac Surgery

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Abstract

An excessive perioperative blood loss, that requires transfusion of blood products, sometimes occurs in patients undergoing cardiopulmonary bypass for cardiac surgery. Blood loss and transfusion requirements in these patients may be reduced with a better control of heparin treatment and its reversal. Blood component administration in patients with excessive post-cardiopulmonary bypass bleeding has been empiric for a long time due to turnaround times of laboratory coagulation tests. Devices are now available for rapid, point-of-care assessment of hemostasis alterations to allow an appropriate, targeted therapy. In particular, a quick evaluation of platelet and coagulation defects with new point-of-care devices can optimize the administration of pharmacological and transfusion-based therapy in patients with excessive bleeding after cardiopulmonary bypass.

Introduction

During cardiopulmonary bypass (CPB) high dose heparin is needed to prevent thrombosis of circuits used during extracorporeal circulation (ECC). Thus, an important issue is to rapidly monitor the degree of heparin-induced anticoagulation and its reversal. The activated clotting time (ACT), described by Hattersley [1] in 1966, has been the first bedside system employed to assess coagulation during CPB. ACT test, which is a modification of the Lee and White [2] whole blood clotting time, uses an activator, either kaolin or celite to accelerate coagulation by activation of the contact pathway. ACT has been used for many years to monitor heparin treatment specially in those conditions in which high blood concentrations (over 1 IU/mL) cannot be accurately evaluated by aPTT [3]. Today, ACT is performed with different automated devices which measure clotting time of native whole blood samples after contact activation. In particular, ACT has a widespread clinical use for CPB, interventional cardiology procedures and hemodialysis [4].

Critical care physicians and cardiac surgeons are engaged to improve the quality and outcomes of care. Now, technological advances in hemostasis bedside instrumentation or point-of-care (POC) laboratory equipment, which can rapidly assess coagulation and platelet function, facilitate these objectives. Assessment of hemostasis POC testing for use in cardiac surgery requires information about the devices available: the ease of employment, the clinical impact of different types of ACT and the knowledge of the advantages and disadvantages of new technologies. The purpose of this overview of hemostasis POC devices was 1) to review the old and emerging techniques used in cardiac surgery to monitor the anticoagulation by heparin, and 2) to consider whether the new POC instrumentation which assesses platelet function may be easily used in the field of cardiac surgery to predict bleeding after cardiac surgery.

Basic Perspectives of POC Testing in Hemostasis in Cardiac Surgery

Monitoring of anticoagulation and transfusion therapy guidance are the main targets in cardiac surgery. In the last years, different studies on clinical outcome through various hemostasis POC tests and devices have been consistently performed [4,5]. Indeed, POC testing in hemostasis – especially ACT test – has rapidly developed due to both clinical and technological advances. Several kinds of instrumentation with different detection methods (test principle) are now available with diverse equipments (bedside machines and/or bench-top apparatus) and with specific handling of samples and assay performances. Moreover, most of the POC devices, initially assigned to perform ACT test, are now able to do multiple clotting test, depending on which test tube or cartridge is selected. On the contrary, some apparatuses initially built to determine PT and aPTT, have been updated with ACT tests and diverse ACT methods to dose heparin and protamine administrations.

Despite the common use in cardiac surgery, few studies have evaluated the reliability – with the criteria of precision, accuracy and validity – of POC testing in clinical conditions. In particular, comparison studies between similar tests (celite-ACT vs kaolin-ACT; or bedside ACT vs bench-top ACT) and precision studies (evaluation of between-instrument and within instrument coefficient of variation - CV -) have been poorly performed. Actually, the clinical safety of POC tests in hemostasis is based on achievement of accurate and reliable results to ensure safe and appropriate patient care. The precision and the accuracy of ACT have been investigated by studies on duplicate samples which have demonstrated a good agreement on the average [6–9]. Most ACT devices do not assess duplicate patient samples due mainly to the use of a fresh blood microsample with cartridges, which avoid the handling of blood. However, the mean differences in ACT values can be significant during heparinization [6,8,9]. Therefore, when a single ACT measurement does not seem to match the patient's clinical conditions, this test should be repeated.

In hemostasis POC testing it is important to examine the obtained values using difference plots or Bland-Altman analysis [10,11]. This analysis can reveal both the magnitude of the differences and the bias of the method, which can be systematic (to the same degree throughout the range of measurement) or proportional (to varying degrees throughout the range of measurement). Some studies have reported a large bias for hemostasis POC tests mainly during CPB [8,9,12–14]. Before introducing a POC test these relevant parameters should be considered when patients are under high doses of heparin.

Another main issue of POC devices is the lack of standardization which prevents comparison of results obtained in different laboratories or operating rooms employing different devices. This in turn prevents experience gained in a given center to be disseminated and employed in others. Method validation for ACT tests is difficult since a "gold standard" measurement for comparison does not exist. Different devices perform different ACT tests by using diverse activators (celite ACT, kaolin ACT, glass-bead ACT or different phospholipid mixture ACT - ACT+ -). This disparity of activators is the cause of different heparin sensitivity among the high-dose ACT tests, which cannot be compared without a chosen reference target time [9,12–14]. This is particularly true for celite and kaolin, both of which are used to monitor high-does of heparin: celite ACT values were found significantly longer than those from kaolin ACT [15]. Another ACT test (Max-ACT), which contains a cocktail of celite, kaolin and glass beads designed to maximize Factor XII activation tend to parallel the celite ACT, but to be shorter during CPB [16]. Therefore, identification of the assay/device is necessary to establish patient monitoring protocols and to understand studies on comparability between different ACTs and on their influence in clinical outcome. In vitro studies on sensitivity of different ACT tests to heparin [17,18] have demonstrated a linear responsiveness of ACT measurements to the heparin added in samples. Despite this linearity, in ACT from anticoagulated patient blood the degree of responsiveness from patient to patient during CPB can diverge due to different factors: resistance to heparin, low levels of antithrombin, haemodilution and body temperature variations (hypothermia) [19]. Due to this variability of patient response to heparin the ACT test is necessary during CPB. So, any new method should be performed in parallel with more assays (diverse ACT tests and/or heparin assays) to know its heparin sensitivity in patient samples [19].

A further main issue of hemostasis POC testing in cardiac surgery is the inadequate quality control (QC) of methods and equipment. Medical and laboratory instrumentation is enrolled in a quality assurance program adequate in maintaining accurate and reliable performance of equipments and tests. Complete records of such QC are kept in general laboratories. Despite routine QC testing and tracking are part of a comprehensive quality assurance program, for hemostasis POC devices the QC in operating room is unacknowledged. The manufacturers delineate QC for each ACT device which when switched on performs a functional check. Electronic monitors which simulate testing when inserted into the device are provided to meet regulatory requirements. Test cartridges or tubes should be periodically analyzed with liquid control material to evaluate both the integrity of the reagents and the precision of the test. In general, the CV obtained from

analyses of control material varies from 4% to 9% for the ACT tests (from manufacturer data sheet and R. Paniccia, unpublished data, 2000). As such, some laboratory professionals might think that they need not concern themselves with this type of devices. On the contrary, this is an area where well-trained laboratory professionals can have a far larger beneficial effect on patient care. The job of laboratory professionals responsible for hemostasis POC testing should be to establish a routine QC program in operating room, to help the anesthesiologists to set up the procedures and a logbook, to indicate the corrective actions which should be taken and eventually to internalize the concept of QC not only in operating rooms but also in intensive care units.

Hemostatic Alterations During CPB

Due to the complexity and the duration of cardiac surgery, marked hemostatic modifications occur in patients undergoing CPB. Moreover, other hemostatic abnormalities may be already detectable in patients before CPB, due to their type of disease and/or their pharmacological treatments (oral anticoagulants low-molecular-weight heparins, anti-aggregating drugs and anti-inflammatory agents). The most important factors which determine the hemostatic alterations during CPB are:

1. The use of ECC which triggers a contact system activation and a systemic inflammatory response [20,21].

2. The administration of high doses of both heparin during ECC and protamine at the end of surgery which are able to affect coagulation, fibrinolysis and platelet function [22–24].

3. The marked hemostatic activation due to surgery itself which causes a further consumption of clotting factors and platelets [25].

4. A variable degree of hypothermia during surgery which activates fibrinolysis and causes platelet dysfunction [26,27].

5. Substantial haemodilution due to administration of crystalloid solution – used both to prime the ECC circuits and as a component of cardioplegia – which may, in part, account for the decreases of coagulation factors and platelet count [20,28].

Therefore, an appropriate heparin therapy is required to avoid the occlusion of ECC circuits and thromboembolic events. However, due to the high doses administered and to the numerous coexistent hemostatic alterations occurring during surgery, a quick monitoring of the effect of heparin is needed at close intervals. At the end of surgery and in the following hours, immediately after the reversal of heparin with protamine administration, heparin monitoring is carried out to verify whether a normal coagulability has been recovered [29].

The current practice of heparin administration during cardiac surgery is predominantly based on an initial heparin bolus followed by ACT monitoring to reach a target time (usually 480 secs). However, the ACT test may be influenced to varying degrees by aprotinin, an antifibrinolytic drug, often administered during cardiac surgery to prevent post surgical bleeding complications. This depends on the ACT activator employed: the celite ACT is prolonged, whereas the kaolin ACT is not affected by antifibrinolytic therapy [30].

As already mentioned, clotting alterations are not the only hemostatic alterations occurring during CPB. Platelet dysfunction is considered one of the major hemostatic disorders associated with CPB [31,32] and may account for a large percentage of all non surgical bleeding after cardiac surgery [31,33]. Actually, soon after cardiac surgery, the decrease in platelet count, platelet transient dysfunction caused by hypothermia [27] and the contact system activation by circuits of ECC [20] play a relevant role in the risk of perioperative blood loss. In the past the study of platelet function by the classical methods (i.e. bleeding time and Born aggregometry) was proved not to be useful to address the appropriate handling of these patients [34]. Recently new systems have been proposed and they are at present under consideration.

To optimize the heparin-induced anticoagulation, new methods and different devices measuring ACT have been set up. Moreover, other bedside instruments which evaluate blood viscoelastic properties and/or platelet function allow us to rapidly obtain further information about fibrinolysis and platelet function.

Main Automated Systems Measuring ACT

Most of the instruments available for monitoring heparin treatment are POC devices which perform multiple coagulation tests, depending on which cartridge or test tube is selected. In table 1 characteristics of different POC analyzers able to monitor high-dose heparin therapy are described.

1. Hemochron automated instruments (International Technidyne Corp, USA – ITC) have been the "reference" devices for monitoring heparin anticoagulation in cardiac surgery for 3 decades [17]. This system includes two types of devices employing respectively tubes containing celite or kaolin (Hemochron 401/801/8000/Response), or cartridges preloaded with a preparation of silica, kaolin and phospholipid, (Hemochron Junior II, Hemochron Signature). The first type of machine uses a magnet inserted

Table 1: Characteristics of main Activated Clotting Time (ACT) instruments for high-dose heparin therapy.

INSTRUMENT (Manufacturer)	ASSAY	ACTIVATORS	SAMPLE SIZE	SAMPLE TYPE
HEMOCHRON Series (ITC, USA)	ACT	Celite or Kaolin	2 mL	FWB
HEMOCHRON JR II and SIGNATURE (ITC, USA)	ACT+	Kaolin, silica and phospholipids	1 drop	FWB
ACT II, HEPCON HMS (Medtronic, USA)	ACT, HEMOSTATUS	Kaolin or celite	0.4 mL (×2)	FWB
RAPIDPOINT COAG (Bayer, USA)	HMT	Celite	1 drop	FWB CWB
I-STAT (ABBOTT, USA)	Celite-ACT	Celite	40 microL	FWB
COAGUCHEK PRO (Roche Diagnostics, USA)	ACT	Celite	1 drop	FWB
ACTALYKE (ARRAY	1) ACT	1) Celite or kaolin	1) 1 mL	FWB
MEDICAL, USA)	2) MAX-ACT	2) Celite, kaolin and glass cocktail	2) 0.5 mL	
SONOCLOT (Sienco, USA)	SONACT	Celite	0.4 mL	FWB CWB

ACT, activated clotting time; FWB, fresh whole blood; CWB, citrated whole blood.

inside the glass specimen tubes. Blood (2 mL), transferred into an ACT tube, is mixed by a manual, steady shaking of the tube. After the tube is inserted into a 37°C heat block chamber, it rotates inside the instrument in a magnetic field. As the blood clots, it displaces the magnet which activates a proximity switch. The clotting time is the time the clot takes to displace the magnet in a given distance. This value shows a linear relationship with the concentrations of heparin in the blood specimen [6]. Recently another study of reproducibility in vitro and in vivo [17] has evaluated the CVs of Hemochron celite and kaolin ACT values. A variability of less than 10% was reported for both tests when control plasma (40 lots with normal and 40 lots with abnormal ACT level) and when fresh whole blood specimens – where heparin up to 5 U/ml blood was added – were assayed. Clinical evaluation included 56 samples from CPB cardiac surgery patients (celite ACT values up to 744 secs) and reported a mean differences between duplicates of 7.5 secs. Today, one precision study [35] has validated the Hemochron Response device – the third generation POC coagulation analyzer – showing CV data similar to those reported by Zucker et al [17]. Despite the Hemochron machines – except Response device – are still widely used for CPB, most of clinical studies have mainly investigated more the comparison to with other devices, the correlation with heparin levels and the predictive value for post-surgical bleeding than the reproducibility of the test. The well-known basic study of Despotis et al. [19] has confirmed the variability of the heparin dose response in a previous study [2] and also the lack of correlation between ACT and plasma heparin levels. They demonstrated that during CPB ACT values (based on both celite – Hemochron – and kaolin-Medtronic – activation) drop gradually after the heparin bolus administration, whereas heparin levels (both from plasma and whole blood) at the beginning are subjected to a rapid decrease followed by a more gradual one. When heparin dosing was guided by ACT values (i.e. <480 s with subsequent heparin administration), heparin levels widely varied (2.7 U/mL = mean absolute deviation for 32 patients) from those with similar ACT values before CPB. The high values of ACTs may reflect the effect of the hemodilution and hypothermia rather than anticoagulant effect of heparin. Recently, a comparison study [8] between Hemochron and i-STAT ACT values (Abbott, USA) obtained in patients undergoing CPB has reported a bias analysis between the two methods with a mean difference of 95 ± 94 sec with a wide interval between upper and lower 95% limits of agreement. Probably, this lack of correlation may be due to the coefficient of variation of Hemochron ACT measurements found higher (13 ± 13%) than that of i-STAT ACT values (5 ± 4%).

The second type of device is a microcoagulation system and utilizes cartridges (ACT+) to monitor heparin anticoagulation, in which blood sample flows into capillaries [6]. After a drop of whole blood sample is placed into an ACT+ cartridge, the machine measures precisely 15 microL of blood and automatically moves it into the test channel within the cartridge. Sample/reagent mixing and test beginning are performed automatically, requiring no operator interaction. The sample is then moved back and forth within the capillary. The clot detection mechanism consists of two led optical detectors aligned with the test channel. The speed at which the blood sample moves between the two detectors is measured. As clot formation occurs, blood flow is impeded and the movement slows down. The stopping of this flow, expression of blood clotting, is optically detected and the test automatically terminates. The machine displays the Celite equivalent ACT value in order to provide a recognizable clinical format and thus facilitate clinical test result interpretation. The ACT+ is unaffected by aprotinin and demonstrates in vitro a linear correlation to the heparin levels between 1.0 and 6.0 IU/mL of blood [18]. According to a clinical evaluation of Carter et al [6] the ACT+ values were 10% to 20% longer when compared with celite ACT test and the range of differences between the two tests was -100 + 150 secs.

Recently, the study of Giavarina et al [36] has been performed during ECC to investigate the diagnostic accuracy of ACT+ in comparison with other devices (Heparin Management Test, Bayer, USA). A weak correlation with heparin levels was reported for both devices, confirming data of Despotis et al [19], whereas the bias (29.0 secs) and the 95% limits of agreement (-60.7 to 22.3) between the two methods were found acceptable.

2. Both Automated Coagulation Timer II (ACT II) and Hepcon Hemostasis Management System (HMS) (Medtronic Hemotec, USA) are devices which measure an ACT using kaolin or, less commonly, celite as activator. HMS is based on the measurement and maintenance of individually calculated target heparin levels. Blood specimens (400 microL) are inserted in each of the two wells of a cartridge. This machine uses a mechanical plunger-flag assembly that is dipped in and out of activated blood samples in the cartridge. The machine optically senses the time that it takes to move the plunger through the blood specimen in the cartridge and the presence of clot is based on the detection of a decreased rate of drop of the plunger-flag assembly: clotting time is defined as the time at which a certain "drop time" threshold for the plunger is reached. The kaolin ACT test is not affected by the aprotinin therapy [30], but it, like Hemochron celite ACT test, is susceptible to the factors associated to CPB, such as hypothermia and hemodilution [19]. Hepcon instruments can perform besides kaolin ACT and HMS, also whole blood heparin concentration measurements using an automated heparin protamine titration method [37]. A thromboplastin reagent is used to accelerate coagulation via the tissue factor pathway, and the device measures clotting times in several channels which contain varying amount of protamine. The first clotting occurs in the chamber in which the ratio protamine/heparin is nearest the neutralization. Because the first channel to clot – not the absolute ACT – is the endpoint, this method is unaffected by reduction in clotting factors and platelets during CPB [38]. Heparin levels assayed with this method during CPB have been reported 1) to correlate significantly with antiXa plasma heparin measurements and 2) to diverge with the behavior of kaolin ACT values [19,38]. Other studies showed that patient-specific heparin concentration can be maintained using this method [39] and found that in CPB automated assay on Hepcon tended to overestimate the heparin dose that was required compared to ACT based manual method [38]. Moreover, in a prospective trial, Despotis et al [40] have evaluated the impact of Hepcon system on bleeding and blood transfusion when compared with an ACT-based protocol: patients of the intervention group received greater doses of heparin and had a lower protamine to heparin ratios when compared with control group. The intervention group did not show excessive postoperative bleeding, whereas the control group required twice as many transfusion of blood components during the perioperative period. This observations have been confirmed by a recent study [41].

3. Heparin management Test (HMT), performed with Rapidpoint Coag machine (Bayer, USA), uses disposable test cards containing a reaction chamber with test-specific reagents (celite and stabilizers) and paramagnetic iron oxide particles (PIOPs) which move in response to an oscillating magnetic field. When 30-microL blood is added to the reaction chamber it dissolves the dry reagent. The occurrence of coagulation results in a slowing and cessation of PIOPs movement. This technology is based on infrared sensing of PIOPs motion, which causes a change in light transmission. A light source shines on the PIOPs which reflects the light onto a photodetector that records signals as a function time. HMT has been reported to be able to monitor heparin concentrations between 1 and 10 IU/mL [42,43]. Gibbs et al [42] have demonstrated that the CV was less for HMT values (7.3–14.2%) when compared to celite ACT and a good linearity between HMT values and heparin levels added to specimens. Also Wallok et al [43] in their in vitro analysis reported a significant ($r^2 = 0.988$) dose – response of HMT from 0.078 – 10 U/mL heparin and in vivo investigation reported results of HMT similar to those from ACT. Moreover, HMT values have been reported to show a better correlation with heparin levels than Hemochron ACT and ACT II [12,44]. Fitch et al [12] have reported that during cardiac surgery in all 53 patients the correlation of HMT with anti-Xa heparin plasma levels was greater ($r = 0.82$, $p < 0.001$) than the correlation between ACT and anti-Xa heparin plasma levels ($r = 0.72$, $p < 0.001$); the bias analysis of the HMT and ACT showed a mean difference of -32.5 secs with 95% limits of agreement of -258.5 to 193.5. Also Slaughter et al [44] have demonstrated a better correlation ($r = 0.84$ $p < 0.05$) between HMT values and anti-Xa values when compared to kaolin ACT values ($r = 0.75$).

4. i-STAT analyzer (ABBOTT, USA) is a bedside instrument, initially developed as a blood gas and electrolyte analyzer [45], designed for whole-blood-based testing. ACT test is performed with celite preloaded cartridges. The endpoint of this method is indicated by the conversion of a thrombin substrate and an electrochemical sensor is used to indicate the event of this conversion. The substrate used in the electrogenic assay has an amide linkage that mimics the thrombin-cleaved amide linkage in fibrinogen. Thrombin cleaves the amide bond at the carboxy-terminus of the arginine residue, because the bond structurally resembles the thrombin-cleaved amide linkage in fibrinogen. This reaction produces an electroactive compound which is detected amperometrically. The use of this new type of technology to perform ACT test during cardiac surgery is still under consideration. A recent inves-

tigation has reported significant relationships of the values obtained from the i-STAT Celite ACT test with those from Hemochron 401 and with the plasma levels of heparin during CPB and during hemodialysis [9]. Significant correlations were observed between the duplicates from both devices ($r = 0.99$, $p < 0.001$) and between ACTs obtained by the two different systems ($r = 0.96$, $p < 0.001$). During CPB strong relationships between anti-Xa activity and Hemochron ACTs ($r = 0.78$, $p < 0.001$) and i-STAT ACTs ($r = 0.89$, $p < 0.001$) were observed. As reported above in Hemochron paragraph a new report by Schneuwly et al [8] has revealed low CV of i-STAT ACT values ($5 \pm 4\%$).

5. CoaguCheck Pro (ROCHE Diagnostics, USA), initially set up only to evaluate PT and aPTT, is a microcoagulation system recently modified to obtain ACT using cartridges preloaded with celite. An optical detector records a laser beam crossing through blood. When blood clots, laser beam is blocked and a photodetector registers the clotting formation. This instrument has been used only in Intensive Care Units [46,47], whereas its performances in cardiac surgery are still to be evaluated. Only a new study [36] has reported an evaluation during ECC of this system with other machines, but the CoaguChek Pro ACT results were over the upper detection limit (500 secs) in 37 of 40 determinations and were not taken into consideration.

6. The Actalyke Activated Clotting Time (Array Medical, Somerville, NJ) test system employs instruments and test tubes interchangeable with other ACT systems using electromagnetic clot detection such as Hemochron series. In addition to celite ACT, this system performs the MAX-ACT, a new type of ACT which uses tubes containing a "cocktail" of activators (celite, kaolin and glass beads) to maximally convert all Factor XII to XIIa. However, the principle of endpoint detection is slightly different from Hemochron. This system uses a two-point clot detection mechanism – one at 0° and another at 90°. This two-point system enables the analyzer to detect a clot at early fibrin formation. As the clot forms, the magnet travels away from detector 1 toward detector 2. Once it reaches the 46° threshold, the detectors in tandem indicate an endpoint. A recent report [16] has demonstrated that this test in cardiac surgery has performances similar to those of Hemochron ACT; it tends to have significant shorter values than ACT after bolus of heparin and during ECC with condition of hypothermia. This difference probably is due to the complete activation of the intrinsic coagulation cascade caused by the combination of activators present in MAX-ACT. Because the statistical divergence between two methods occurs during hypothermia, this suggests the this test is less susceptible to the factors that increase ACT during ECC.

Automated Systems Evaluating Blood Clotting Formation and/or Platelet Function

New and old systems exist. Thromboelastography (TEG), abandoned for many years by hemostasis laboratories, is still used as a bedside hemostasis monitor for special types of surgery such as cardiac or hepatic surgery. Although new instruments are based on the same principles as old ones, they are computer-aided, lightweight and more compact than old ones [48,49].

Recently, new methods and equipment able to study also platelet function are developed [50]. In table 2 the different technologies of point-of-care analyzers which investigate hemostasis are described.

1. Today, the TEG device consists of a bench-top instrument comprising a dual-channel Coagulation Analyser (Teg^R – Hemoscope, USA) and a Teg^R analytical software. TEG gives a graphic representation of aspects of clot formation and lysis. It is performed on a small quantity of whole blood that is placed in a warmed (37°C) oscillating cup. The cup oscillates 4°.45' in either directions every 4.5 secs. A pin is suspended in the cup by a torsion wire that is mechanically or electrically transduced to a chart recorder or computer monitor, respectively. Blood is added and a torque is first transmitted as the clot forms linking the cup and pin together, increasing as the clot strengthens and decreasing as the clot lyses. Initially, when no clot exists, the motion of the cup does not affect the pin and a straight-line trace is recorded. As the blood in the cup clots, the motion of the rotating cup is transmitted to the pin. Five parameters are measured: 1) the *R* time; 2) the *k* time; 3) the maximum amplitude (MA); 4) the amplitude at 60 min (MA60); 5) the *alpha* angle. These parameters give information about clotting factors, their inhibitors, platelet function and fibrinolysis. The TEG analyzer provides a global POC test of hemostasis that can identify if the bleeding after CPB is due to surgery, coagulopathy or residual heparin. In a prospective study, Shore-Lesserson et al [51] showed a reduction in postoperative transfusion incidence of blood products from 25% in the standard test-guided group to 5.6% in the TEG-guided group. So, the use of TEG analysis in a transfusion algorithm during cardiac surgery has allowed identification and appropriate treatment of specific intraoperative alterations of hemostasis.

2. The ROTEG analysis (Pentapharm, GMBH) is based on rotation thromboelastography, which is related to, but in some aspects different from classical analysis with TEG [52]. In ROTEG analyzer the pin (sensor) is fixed on the tip of a rotating shaft which is guided by a high precision ball bearing system. The shaft rotates back and forth with an angle of 4°.75'. It is connected with a spring for the measurement of blood elasticity. The exact position of the

Table 2: Different types of technologies for hemostasis point-of-care testing.

DEVICE (MANUFACTURER)	MAIN TESTS	PRINCIPLE	TYPE OF DETECTION
Hemochron series (ITC, USA)	ACT, PT, aPTT RxDX system	Magnet position	Optical detection of change in magnet position in a slowly rotating reagent-filled tube
Hemochron Junior II and Signature (ITC, USA)	ACT+ and LR, PT, aPTT	Fluid oscillation	Optical detection of slowing of oscillatory motion in a test channel
ACT II, Hepcon HMS (Medtronic Hemotec, USA)	HRACT, LRACT, HR-HCT, HMS, HEMOSTATUS PT, aPTT	Plunger motion	Optical detection of change in the fall rate of a plunger assembly that is raised and lowered
RapidpointCoag (Bayer, USA)	PT, PT-ONE, aPTT, HMT	Particle motion	Optical detection of slowing of motion of paramagnetic iron oxide particles in pulsating magnetic field
I-STAT (ABBOTT, USA)	Celite-ACT	Electrochemical conversion	Amperometrical detection of an electroactive product from the conversion of thrombin substrate
CoaguChek Plus and Pro (Roche Diagnostics, USA)	PT, aPTT, ACT	Pattern recognition	Optical detection of change in laser interference pattern from slowing cell motion
ACTALYKE (Array Medical, USA)	ACT, MAX-ACT, PT, aPTT	Electromechanical recognition	Two point electromechanical soft-clot detection
Teg^{R} Analyzer (Hemoscope, USA)	Thromboelastogram	Cup oscillation	Mechanical or electrical detection in changes of oscillation of cup and pin together
ROTEG^{R} Analyzer (Pentapharm, BMBH)	Thromboelastogram	Shaft rotation	Optomechanical detection of loss of motion of shaft
SONOCLOT (Sienco, USA)	Sonoclot Signature	Impedance on vibrating probe	Impedance detection of changes in viscoelastic properties of celite-activated blood sample
PFA-100 (Dade Behring, USA)	ADP/CT, EPI/CT	Pressure	Detection of change in pressure across porous aperture when platelet aggregates occlude openings

ACT, Activated Clotting Time; ACT+, Activated Clotting Time plus (for high levels of heparin); ACT LR, ACT low range (heparin); aPTT, activated Partial Thromboplastin Time; ADP/CT, Closure Time by activation with adenosindiphosphate; EPI/CT, Closure Time by activation with epinephrine; HMS, Hemostasis Management System; HMT, Heparin Management Test; HRACT, High Range ACT; HR-HCT High Range Heparinase Clotting Test, ITC, International Technidyne Corp; LRACT, Low Range ACT; MAX-ACT, Maximum Factor XII activation ACT; PFA, platelet function analyzer; PT, Prothrombin Time; RxDX, Heparin and Protamine Response tests

axis is detected by the reflection of light on a small mirror which is attached to the shaft. The loss of elasticity upon clotting of the sample leads to changes in the rotation of the shaft. These changes are opto-mechanically detected with an appropriate technology by a computer. The changes in blood elasticity give as result a graph which is similar to that of TEG. The use of this device during cardiac surgery is still under consideration and only one recent report [53] is available which indicates that ROTEG provides significant data to predict bleeding disorders following CPB. ROTEG alpha angle is a better predictor than the adenosine diphosphate – Platelet Function Analyzer-100 test (PFA-100) (DADE, USA). Its high (82%) predictive value supports early identification and targeted treatment of surgical bleeding by distinguishing it from a significant coagulopathy.

3. The Sonoclot analyzer (Sienco Inc, USA) measures changes in the viscoelastic properties of blood clot. This device consists of an open-ended disposable plastic probe, mounted on an ultrasonic transducer, which is immersed in warmed (37°C) cuvette containing celite. The viscous force of the forming blood clot creates impedance to the ultrasonic vibrating probe that is converted in an output signal. The changes in the viscolelastic properties of blood clot are recorded in the form of a graph (Sonoclot signature) which shows: a) a lag period, corresponding to ACT (called SonACT), measured in seconds; b) a primary wave which reflects the fibrin polymerization (Clot RATE) ; c) an inflection which is produced as platelets are incorporated into the fibrin mesh; d) a secondary upslope leading to peak which occurs at completion of fibrin formation; e) a subsequent downslope produced as platelets induce further clot retraction. The time to peak (TP), measured in minutes, reflects clot retraction, and is an indicator of platelet count and function. This equipment alone could give useful information about antithrombotic therapy management [54] and the evaluation of excessive blood loss. Recent studies have reported that Sonoclot analysis may provide helpful indications on platelet function in patient after ECC allowing to predict bleeding disorders following CPB [55–57]. In particular, Miyashita and Kuro [56] have found during cardiac surgery – before heparin administration and after its neutralization – significant correlations of Sonoclot TP values with collagen-induced whole blood aggregations, platelet counts and fibrinogen levels. So, Sonoclot TP is able to investigate platelet function in patients undergoing cardiac surgery. This predictive ability of Sonoclot TP to identify possible bleeding due to platelet dysfunction has been confirmed by Paniccia et al [57]. A new in depth validation study by Forestier et al [14] has evaluated the reproducibility of TEG, Sonoclot, celite and kaolin ACT values: TEG and Sonoclot tests showed CV values between 3.1% and 9.5% and between 5.8% and 33.6% respectively, according to different conditions and parameters, whereas

celite and kaolin ACT values showed similar CVs both in health subject and in patients during cardiac surgery. Forestier et al [14] concluded that celite and kaolin could be considered interchangeable only in non heparinized conditions, whereas in heparinized patients and during CPB, results from different tests are not interchangeable, stressing the importance of establishing appropriate instrument-specific values for monitoring anticoagulation during cardiac surgery.

4. The Platelet function Analyzer-100 (PFA-100, DADE Behring, USA) assesses whole blood platelet function by measuring the closure time (CT) [58] required for platelets in citrated whole blood to occlude a precisely defined aperture cut into a synthetic membrane coated with either collagen and epinephrine or collagen and adenosine diphosphate. Whole blood, placed in disposable cartridges with different type of membranes is drawn by means of a vacuum through a capillary producing high shear forces and then through the aperture into the membrane. The platelets adhere, activate themselves and aggregate at the aperture, forming a platelet plug which blocks the blood flow. This equipment determines the duration of the test until membrane occlusion. This interval will be elongated depending on the platelet activity. The use of two different cartridges with distinct agonists allows to distinguish the platelet function alterations due to intrinsic defects or to therapy with antiplatelet drugs. Recent reports have showed that the study of platelet function using PFA-100 provide useful information for eventual blood loss in patient after ECC [57,59], but these findings are not supported by other Authors [60]. Therefore, the use of this device in operating room needs further clinical investigations.

5. The Platelet-Activated Clotting Test (PACT), or Hemostatus test, performed on the Hepcon HMS device (Medtronic Hemotec, USA), has been recently proposed as a tool to investigate platelet dysfunction during cardiac surgery [61]. The principle of this test is to measure the ACT in the presence or absence of increasing concentrations of platelet-activating factor (PAF) added to the reagent mixture of ACT test tube. PAF is a potent endogenous platelet activator and stimulates in vitro thrombosis. This test evaluates the effect of PAF in shortening kaolin-ACT. A six-channel test cartridge contains kaolin, heparin and increasing levels of PAF (0 to 150 nM) and the result is a clot ratio. Despotis et al [61] have found a correlation between PACT values and postoperative blood loss. Moreover, an in vitro investigation [62] has demonstrated that increasing amounts of Abciximab, a potent platelet inhibitor, cause dose-dependent decreases in clot ratios of PACT. Despite this evidence, the usefulness of this test to predict bleeding following cardiac surgery is controversial, because other studies have found weak or no correlation between PACT values and blood loss after CPB [63–65].

Conclusions

POC testing in the hemostasis field has had a long history and is rapidly spreading out due to technological improvements. In cardiac surgery the most important applications of POC coagulation testing are the monitoring of anticoagulation and the handling of transfusion therapy. ACT devices have been the only tool used for many years in the management of heparin treatment during CPB. The availability of new instruments able to evaluate also platelet number and function and fibrinolytic activation, will allow a more appropriate use of drugs and blood products in cardiac surgical patients with excessive blood loss after CPB.

Competing interests

None Declared.

Authors' contributions

DP conceived the paper and participated in its design and coordination.

RP conceived the paper, coordinated its design and drafted the manuscript.

Both Authors read and approved the final manuscript.

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