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Point-of-care haemostasis and coagulation monitoring in cardiac surgery at IRCCS Policlinico San Donato

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A rational management of perioperative and postoperative bleeding in modern cardiac surgery requires a thorough application of point-of-care (POC) monitoring in order to prevent and readily treat alterations of the haemostatic process. Preoperative platelet dysfunction, residual heparin after extracorporeal circulation, coagulation factors, and/or fibrinogen deficiency could be ruled out and specifically addressed with an appropriate treatment. Our approach includes preoperative platelet function testing of patients administered with thienopyridines or ticagrelor within 7–10 days before planned surgery and platelet function testing-based surgery timing. In the case of postoperative bleeding, residual heparin is tested and additional protamine is eventually administered. Simultaneously, an overall activity of coagulation factors (except fibrinogen) is assessed and, if significantly reduced, correction with prothrombotic complex concentrate is considered. If fibrinogen deficiency is suspected, a specific test is run, and in the case of severe reduction, the deficiency is compensated by fibrinogen concentrate or appropriate volume of fresh-frozen plasma. If both coagulation factors and fibrinogen activity are reduced, fibrinogen is usually considered for correction as first line, followed by prothrombin complex concentrate in the case of further bleeding. It is our clinical practice not to test nor to treat patients until postoperative bleeding appears clinically relevant. At IRCCS Policlinico San Donato, we firmly believe in the importance of the POC-based strategy for haemostatic treatment and constantly update our knowledge through research projects targeted in answering clinically relevant questions.

Introduction

Within cardiac surgery setting, a point-of-care (POC) monitoring of the haemostatic function is of outstanding importance. Acute postoperative bleeding is a life-threatening and a major resource-consuming condition, thus all the possible efforts should be applied in order to timely and efficiently prevent and treat it.

There are a limited number of conditions associated with bleeding after a cardiac intervention and the main are platelet dysfunction due to the residual effect of preoperative antiplatelet therapies or platelet loss due to prolonged contact with foreign surfaces of the cardiopulmonary bypass (CPB), residual circulating heparin due to incomplete antagonization by protamine, reduced levels of coagulation factors and/or fibrinogen due to blood loss, haemodilution, consumption, or preoperative administration of oral anticoagulants. Specific POC devices are able to recognize them, guide therapeutic decision-making, and eventually check the efficacy of the administered haemostatic treatment.[1]

Within our cardiac surgery operating theatre, we organized a specifically designed place for a Coagulation and Hemostasis Monitoring Point-of-Care Laboratory equipped with a multiple electrode aggregometer Multiplate® (Roche Diagnostics GmbH, Mannheim, Germany), a thromboelastography TEG® (Haemoscope, Niles, IL, USA), and a thromboelastometer ROTEM® (TEM Innovations GmbH,

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Munich, Germany) (*Figure 1*). Both anaesthesiologists and perfusionists are trained to perform the analysis whenever required and a dedicated biologist is present during daytime for further support and quality control. Samples from other clinical units could be analysed on request. Support of POC monitoring is given to postoperative cardiac surgery and general intensive care unit, orthopaedics and traumatology, vascular surgery, urology, and pain therapy unit on regular basis.

Platelet aggregometer Multiplate®

Platelet receptor P2Y12 inhibitors (thienopyridines clopidogrel, ticlopidine and prasugrel, and ticagrelor) are nowadays a standard of care for coronary patients.[2,3] The achieved level of platelet dysfunction, however, and then the time needed for platelet function recovery are widely varied among individuals due to genetic and other factors.[4] Antiplatelet therapy administration is strongly associated with severe postoperative bleeding and transfusions after cardiac surgery.[5] International guidelines suggest discontinuation of antiplatelet drugs at least 5–7 days before intervention and a recent update from Society of Thoracic Surgeons introduces platelet function tests (PFT) as a reasonable guide for establishing the right timing for cardiac surgery with IIa level of evidence.[6]

We have been using multi-electrode aggregometer Multiplate® since 2009 as a preoperative PFT in patients undergoing cardiac surgery and administrated with thienopyridines or ticagrelor. Before 2009, it was our standard practice to discontinue antiplatelet therapy at least 5 days before surgery for elective patients; urgent or emergency operations were performed regardless of discontinuation time. The working rationale of the Multiplate® device is based on measuring increasing electrical impedance between two metallic wires covered by platelets aggregating upon specific activation. Whole blood, where free thrombin is inhibited with hirudin, is used and platelet aggregation is specifically driven by an activator. Adenosine diphosphate (ADP) test specifically measures the availability of P2Y12 receptor, target for thienopyridines and ticagrelor. A thrombin receptor-activating peptide (TRAP) test is usually performed together with ADP test; being thrombin the most potent platelet activator, in the absence of drugs targeting the thrombin or the final aggregation receptor GPIIbIIIa, this test is an indicator of the best platelet aggregating potential.

In a first retrospective study in 2011, we analysed preoperative platelet function and postoperative bleeding data from 87 patients under thienopyridine treatment and undergoing cardiac surgery. We found that the ADP test was independently associated with postoperative bleeding. We were able to settle a cut-off value for ADP test for avoiding major postoperative bleeding at 31 U [sensitivity 72%, specificity 66%, negative predictive value (NPV) 92%, and positive predictive value 29%] that was since then adopted at our institution. Surgery of patients with an ADP test lower than 31 U was postponed whenever feasible and the aggregation checked on a daily basis until acceptable level was achieved.[7]

The 31 U at ADP test cut-off was confirmed by a following study in 2013 performed on a larger cohort of 344 patients that once again remarked the significant incidence of thienopyridine resistance among cardiac surgery patients (28%) and that the time needed to reach either an acceptable or complete platelet function recovery was highly variable. In this study, a period of between 4 and 8 days following therapy discontinuation corresponded to a moderate platelet dysfunction, probably representing the optimal balance between major bleeding vs. thromboembolic risks, and thus the correct timing for cardiac surgery.[8]

We then explored the association between ADP and TRAP tests in predicting patients at excessive risk of postoperative bleeding. It is well known that during cardiac surgery with CPB, thrombin is massively generated.[9] The powerful platelet activation by thrombin through protease-activated receptors (PAR) is only partially dependent on P2Y12 inhibition,[10] and therefore, it is possible that it could rescue even a strong drug-induced P2Y12 inhibition. We found that both ADP test and TRAP test were significantly ($P = 0.001$) associated with postoperative

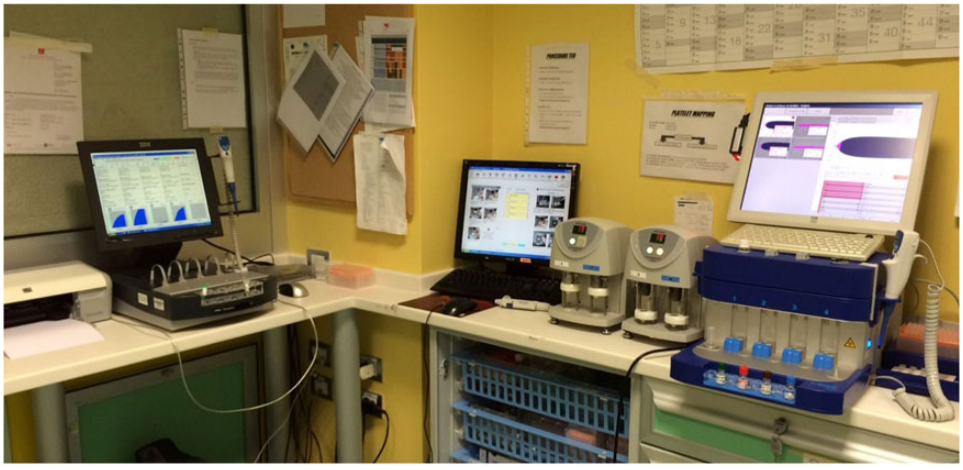

Figure 1 Coagulation and Haemostasis Monitoring Point-of-Care Laboratory placed within the cardiac surgery operating theatre of IRCCS Policlinico San Donato.

bleeding. Cut-off values were further refined: a threshold of 22 U for ADP test and 75 U for TRAP test yielded an NPV of 94 and 95%, respectively. A combined threshold of ADP test <22 U and TRAP test ≥ 75 U was not associated with severe bleeding with an NPV of 100%.[11]

Currently, in our institution, all the patients scheduled for cardiac surgery who discontinued antiplatelet treatment within 1 week before the planned intervention are tested for platelet aggregation with ADP and TRAP tests. Patients showing an ADP test >25 U or an ADP test <25 U with TRAP test ≥ 75 U are admitted to surgery even 1 or 2 days after therapy discontinuation, whereas patients still showing severe platelet dysfunction are postponed whenever feasible and retested on a daily basis until the safe level of aggregation is reached (*Figure 2*).

Platelet count is always considered in the preoperative and perioperative evaluation of the patient. Platelet function testing on Multiplate® is not reliable for platelet counts lower than 75 000–100 000/μL because, even if perfectly aggregating, platelets are not able to cover completely the surface of the measuring electrodes and the amount of electricity passing through them does not correctly reflect platelet aggregability.[12]

Viscoelastic tests

Whenever a rapid assessment of the overall activity of the coagulation factors and of the interaction between platelets and fibrinogen as clot production and stability is required, viscoelastic measurements could be performed with a thromboelastograph like TEG® or a thromboelastometer like ROTEM®. Both devices use whole blood activated with kaolin (TEG®) or specific activators for intrinsic and extrinsic pathways (EXTEM and INTEM, respectively, ROTEM®). The growing viscoelasticity of the coagulating blood is continuously measured by electromechanical (TEG®) or optical (ROTEM®) sensors, translated into a graphical curve and visualized in real time on the monitor of a computer.

The overall activity of the coagulation factors (except made for fibrinogen concentration) is defined by the R-time in TEG® and CT (clotting time) in ROTEM®, i.e.

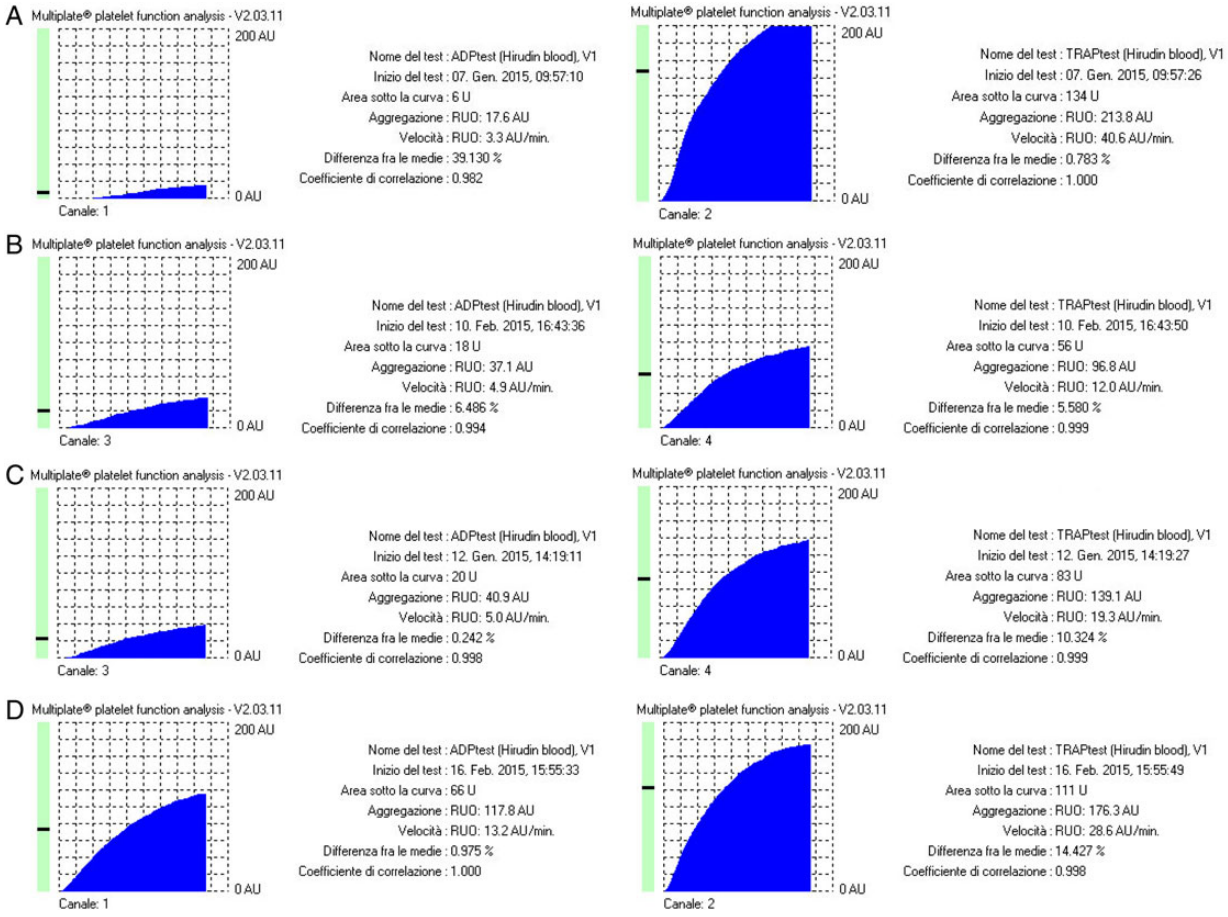

Figure 2 Images from Multiplate® device representing different pictures of platelet function and the application of preoperative cut-offs for cardiac surgery. (*A*) Very low adenosine diphosphate test (<10 U) with high thrombin receptor-activating peptide test—severe platelet dysfunction, surgery is to be postponed, if feasible, and aggregation retested on a daily basis; (*B*) low adenosine diphosphate test (<25 U) and thrombin receptor-activating peptide test (<75 U)—severe platelet dysfunction, surgery is to be postponed, if feasible, and aggregation retested on a daily basis; (*C*) low adenosine diphosphate test (<25 U) and high thrombin receptor-activating peptide test (>75 U)—moderate platelet dysfunction compensated by thrombin receptors activation, surgery could be performed; (*D*) normal adenosine diphosphate test (>25 U) and thrombin receptor-activating peptide test (>75 U)—no platelet dysfunction.

time until the gelification given by the first fibrin polymers assembling occurs. R and CT are prolonged in the case of inherited or acquired coagulation factors deficiencies and a prolongation of these parameters could be observed in postoperative bleeding. Fresh-frozen plasma (FFP), cryoprecipitates, or prothrombin complex concentrates (PCCs) are usually administered to compensate such deficiencies and a normalization of R-time/CT is indicative of the reestablishment of a due activity of the coagulation factors.[13,14]

An incomplete antagonization of heparin after a CPB may also result in excessive postoperative bleeding and is detectable with TEG®/ROTEM®. A difference between R-time of a test run with a standard cup and one coated with heparinase for TEG®, or normalization of an abnormal CT at INTEM with HEPTEM on ROTEM® indicates the presence of residual heparin and need for an eventual supplementary dose of protamine. Ruling out residual heparin with POC testing instead of blind supplementary protamine administration is important because protamine overdose has anticoagulation effect and may worse the ongoing bleeding.

The strength and stability of the forming clot is expressed by the maximum amplitude (MA) on TEG® and maximum clot firmness (MCF) on ROTEM®. This parameter incorporates the contribution of both platelets and fibrinogen, thus a reduced value of MA/MCF is not able to rule out the single deficiencies. The Functional Fibrinogen on TEG® and the FIBTEM test on ROTEM® inhibit platelet aggregation within the blood sample providing useful information about fibrinogen contribution to the clot. Fibrinogen deficiency is efficiently rescued by the administration of human fibrinogen concentrate[15] and the treatment effect is reflected by increasing clot strength both on the specific and standard testing. ROTEM® FIBTEM test is recommended by the manufacturer of fibrinogen concentrate (Haemocomplettan®P, CSL Behring GmbH, Marburg, Germany) for dose calculation targeted at achieving an MCF of 22 mm.[16]

Our protocol for POC management of postoperative bleeding is initiated only in case a microvascular bleeding is observed in the operating theatre or of an ongoing bleeding of more than 1.5 mL/kg/h for 2 consecutive hours (or 4 mL/kg for at least 30 min) in intensive care unit. The residual heparin is always checked and additional protamine administered if needed. In the case of a reduced MA/MCF or whenever a fibrinogen deficiency is suspected, specific test is run, 1–2 g of fibrinogen concentrate or an appropriate amount of FFP (if volume supplementation is required as well) are administered as first-line treatment. PPCs are administered as first line in the case of a significantly prolonged R-time/CT without evidence of residual heparin or fibrinogen deficiency, or as a second line in the case of a prolonged R-time/CT after fibrinogen/FFP supplementation. The effect of the administered therapies is usually checked.

We are not testing every patient after the intervention because an overall alteration of the haemostatic system is very common after cardiac surgery but is associated with excessive bleeding only in a limited part.

Thromboelastography TEG® and heparin-like effect in ECMO

We routinely perform TEG® monitoring of anticoagulation efficacy in our ECMO patients. At our institution, bivalirudin is preferred over unfractioned heparin for post-cardiotomy veno-arterial or veno-venous ECMO anticoagulation unless there is blood stagnation inside cardiac chambers.[17] In these heparin-free ECMOs, we expected to find no difference between standard kaolin and kaolin plus heparinase test, but we actually noticed that some patients developed a heparin-like effect (HLE) a few days after ECMO initiation (*Figure 3*). Heparin-like effect has been previously described in acute liver failure, sepsis/SIRS, and cancer due to different mechanisms but never reported in ECMO setting.[18–20]

Thus, we retrospectively analysed clinical data and available TEG® profiles of patients treated with ECMO on bivalirudin in order to further investigate the phenomenon.[21]

An R-time of the heparinase tracing at least 30% shorter than the correspondent standard kaolin tracing was indicative of an HLE. Heparin-like effect was detected in 56, 1% (23 out of 41) of patients during the first week on ECMO,

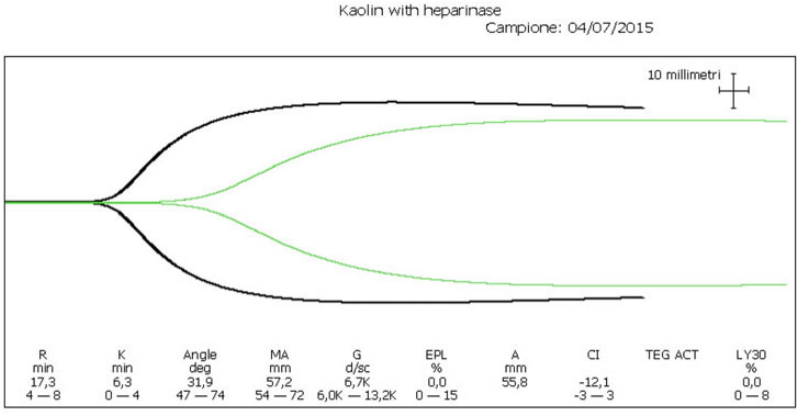

Figure 3 Example of heparin-like effect on TEG®. Green tracing, kaolin activation without heparinase; black tracing, kaolin activation with heparinase.

and decreased over time after the seventh day on procedure. This phenomenon was not due to liver failure nor heparin coating of the ECMO system, but there was a higher incidence of sepsis in patients with HLE vs. those without (30 vs. 6%). We believe that sepsis was probably the leading cause of HLE in approximately one-third of patients; in the remaining, the phenomenon was likely driven by a natural inflammatory reaction to the blood exposure to the foreign surfaces and endothelial disturbance.

Despite being burdened by a number of limitations and potential therapeutic implications still to be defined, this study gives an interesting insight into pathophysiology of the ECMO procedure and warns clinicians about multifactorial, subtle but potentially serious endothelial and inflammation disturbances likely occurring in that setting and readily detectable with a POC monitoring approach.

Thromboelastometry ROTEM® and human fibrinogen concentrate administration

A decrease in the plasma activity of all the coagulation factors generally occurs after cardiac surgery. Among these, only fibrinogen and FXIII levels were associated with postoperative blood loss.[22] Preoperative fibrinogen concentration seems to be a poor predictor of severe bleeding risk,[23] probably because of a number of surgery-related factors involved, thus, correction of a verified fibrinogen deficiency is the most logical approach. Fibrinogen concentrate is more efficient than FFP in replenishing consumed fibrinogen[24] and a POC-guided dose calculation is recommended to achieve a correct level of correction[25] and check the efficiency of the treatment. We designed a prospective, randomized, double-blinded, placebo-controlled study to be performed in our institution as a single centre to verify the hypothesis that a totally FFP-free strategy of bleeding control in complex cardiac surgery patients is feasible, effective, and safe.[26] The trial was based on fibrinogen concentrate supplementation after completion of CPB in cardiac surgery patients at high risk of severe postoperative bleeding, eventually followed by PCC, targeted at the avoidance of any allogeneic blood component transfusion. A total of 116 patients were randomized and dosed with either human fibrinogen concentrate or placebo and ROTEM EXTEM and FIBTEM tests were performed both before and after drug administration. The treated patients have not received any FFP supporting the experimental hypothesis that a FFP-free strategy is

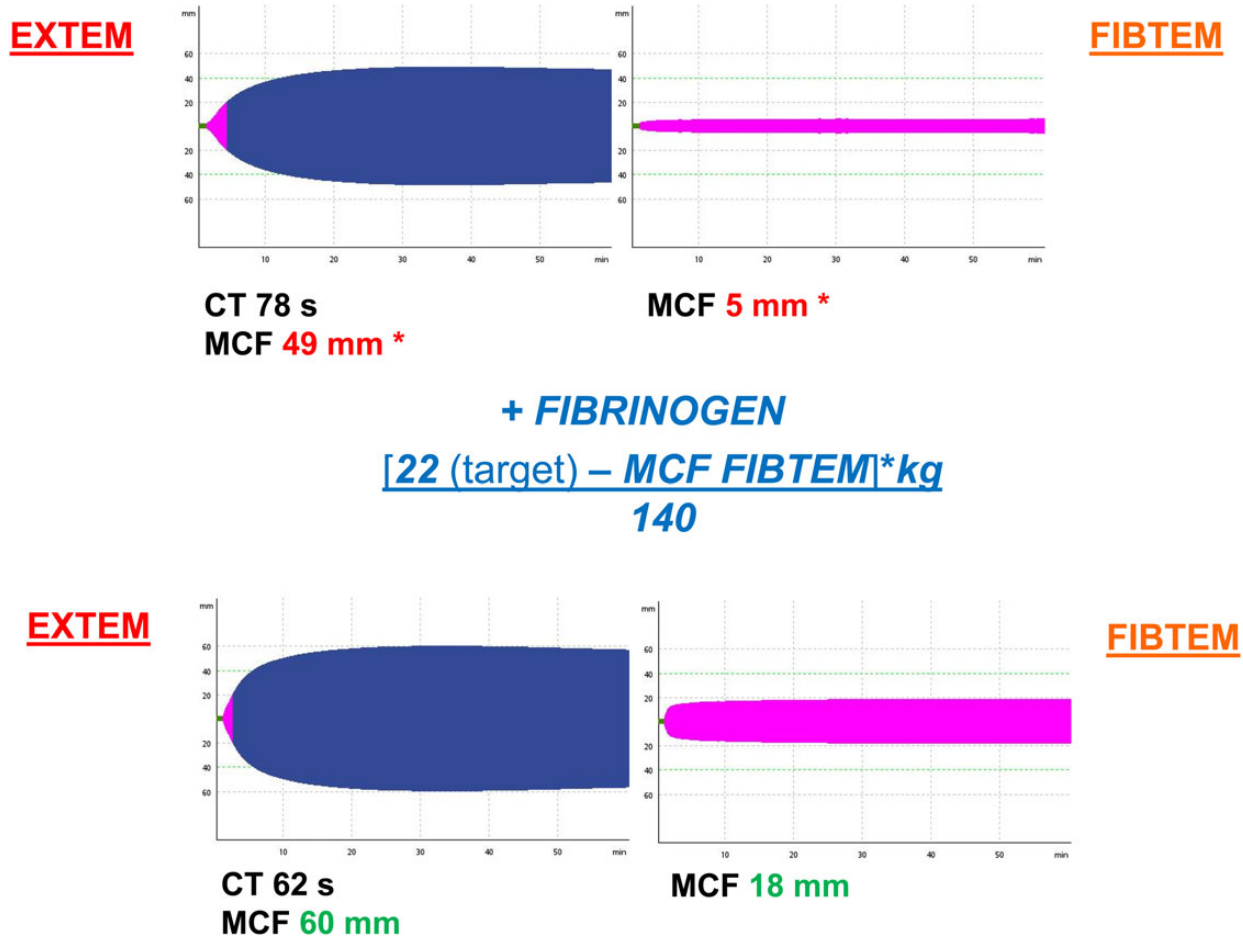

Figure 4 Effect of fibrinogen concentrate administration on ROTEM® EXTEM and FIBTEM tests. Additional fibrinogen not only increases MCF of both tests but also reduces the CT of EXTEM. MCF, maximum clot firmness; CT, clotting time.

feasible even in complex cardiac surgery, moreover these patients have not received any platelet transfusion and packed red cell transfusion were significantly lower than in the control group. Nevertheless, we are not suggesting routine prophylactic administration of fibrinogen concentrate, even in high-risk subgroup of patients; we designed this pragmatic and proof-of-concept trial in order to investigate the efficacy of a zero-plasma approach in a controlled environment, laying foundation for a more comprehensive multi-centre research.

Fibrinogen administration not only increased MCF of both FIBTEM and EXTEM but also decreased the clotting time on EXTEM, supporting the hypothesis that a better clot strength improves thrombin generation (*Figure 4*). A *post hoc* analysis on postoperative bleeding and FIBTEM MCF post-dosing made clear that a lower target (17 mm instead of 22 mm recommended by the manufacturer) was sufficient to achieve a 100% NPV for severe bleeding (>1000 mL in the first 12 postoperative hours) and that a threshold of 13.5 mm at FIBTEM predicted severe bleeding with 80% sensitivity and 72% specificity. In conclusion, our study demonstrated the efficacy of a zero-plasma strategy in complex cardiac strategy with an almost absolute requirement for a POC to guide dosing and check the treatment effect.

As previously reported, low levels of FXIII were found to be associated with bleeding after cardiac surgery in adult[22] and paediatric patients.[27] A large randomized, placebo-controlled clinical trial based on administration of recombinant FXIII after CPB completion in moderate risk cardiac surgery showed that the replenishment of FXIII levels after cardiac surgery had no effect on transfusion avoidance, transfusion requirements, or reoperation.[28] Currently, recombinant FXIII is not commercialized for clinical use.

Final remarks

In our Cardiac Surgery Department and intensive care unit, the application of a comprehensive POC preoperative and postoperative monitoring strategy allowed a significant reduction in every kind of blood products transfusions and led to an increase in specific substitution drugs administration. In particular, following the introduction of platelet function monitoring in 2009 and the adoption of the platelet aggregability cut-off values in 2011, we were able to constantly reduce the incidence of platelet concentrate transfusion from ~12% in 2010 to 8% in 2014. Thromboelastographic monitoring of residual heparin and coagulation was introduced in 2005 and administration of FFP drastically felt from 24% in 2005 to an almost constant 6% since 2012. We believe that the incidence of FFP will be further slightly reduced in the following years thanks to fibrinogen concentrate but it likely has already reached its specific niche of application (administration of coagulation factors together with volume load). The optimization of the postoperative haemostasis achieved by the application of a POC-based approach was reflected by a decrease in postoperative bleeding from ~600 to 400 mL in the first 12 h, followed by a reduction in PRC transfusions from 65 to 40% in the 2005–14 period.

Conflict of interest: M.R. received honoraria from Verum Diagnostica (Roche), CSL Behring, Medtronic and Grifols. E.B. none declared.

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