Coagulopathy During Cardiopulmonary Bypass: Inside Out

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Abstract

Objective: Nowadays, the coagulation status of the cardiac surgical patient is monitored using standard laboratory parameters. However, these tests involve long turnaround times, a critical limitation in settings where the patient's coagulation status can change very quickly. The aim of the present study is to describe, through serial blood controls, traditional tests and Point Of Care (POC), the coagulation status of patients undergoing cardiopulmonary bypass (CPB). *Design:* Observational study. *Setting:* Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, University of Turin, Italy. *Partecipants*: We enrolled 29 patients undergoing cardiopulmonary bypass for cardiac surgery at the 'Città della Salute e della Scienza' University Hospital in Turin between March and June 2021. *Interventions*: In all patients two series of blood samples were performed at T1 (before the start of CPB, after sternum opening, before UFH administration) and at T2 (after the end of CPB, after protamine administration and before any blood component transfusions). Laboratory tests included blood count, INR, aPTT, Fibrinogen and functional assay of coagulation factors (AT III, factors II, V, VII, VIII, IX, X, XI, XII, proteins C and S). An additional sample was obtained (both at T1 and T2) for ROTEM analysis. *Measurements and Main results*: Between the beginning and the end of the bypass we observed a significant decrease in coagulation factors II, X, XI, XII, protein C and S with an average percentage decrease of 32.58%, 34.11%, 36.69 %, 47.45%, 33.65% and 30.20%, respectively. Regarding viscoelastic parameters, we recorded a median increase of 22.64% of CT in Intem during CPB, with a reduction in MCF in Fibtem of 16.66%, as well as platelet contribution (MCF Extem-Fibtem), which was reduced by 7.69%. *Conclusions:* CPB-induced coagulopathy involve dilution, activation and consumption of all components of haemostasis, together with the need for profound anticoagulation. Our data seem to confirm the important reduction of all coagulation factors and platelets, together with a consensual change in traditional laboratory and viscoelastic parameters.

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INTRODUCTION

Bleeding, due to surgical or non-surgical causes, complicates 10% of[1-3] while up to 20-40% of elective procedures require blood products [4,5]. These percentages increase during urgent/emergency surgery and more complex and long-lasting procedures bypass (CPB)a technique used in several surgical settings to obtain an adequate operating fieldrequires a profound modification of patient's normal coagulation pattern, eventually leading to a multifactorial coagulopathy which is associated with an increased risk of non-surgical bleeding, both in the period immediately following weaning from CPB and in the first hours / days of hospitalization in the Intensive Care Unit (ICU) and, consequently, a longer hospital stay and a poorer long-term outcome. After the publication of the 2017 EACTS / EACTA guidelines on blood management in adult patients undergoing cardiac surgery procedures [6], several studies have addressed the topic of the pathophysiology of CPB-related coagulopathy and the management of blood products. Nevertheless, to date, there is no agreement in the literature on the optimal management to be applied in this specific context. Ternström and colleagues [7]described the coagulation factors activity following coronary artery bypass surgery and observed an inverse correlation between fibrinogen levels, platelets, FXIII and postoperative bleeding while no significant association was observed for other coagulation factors. Both Chandler and Ranucci [8,9] described the key role of haemodilution in reducing platelets, fibrinogen, and coagulation factors, but also in increasing blood products consumption in both operating room and ICU. Finally, Gielen and colleagues[10] emphasized the importance of haemodilution and hyperfibrinolysis in determining CPB coagulopathy. Nowadays, the coagulation status of the cardiac surgical patient is monitored using standard laboratory parameters, including prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), activated clotted time (ACT), fibrinogen concentration, and platelet count. Although these tests are widely and routinely used, they involve long turnaround times, a critical limitation in settings where the patient's coagulation status can change very quickly. Furthermore, PT and aPTT are generally described as useful to detect coagulation deficiencies [11,12] but, although they are normally used as guide for transfusion, they have been shown to be very poor predictors of bleeding. Viscoelastic methods are increasingly used in addition to standard laboratory tests. Conventional viscoelastic parameters recorded with TEG (Haemoscope Inc, Niles, Illinois) or ROTEM (Tem International GmbH, Munich, Germany) devices during CPB include ROTEM clotting time (CT), ROTEM maximum clot firmness (MCF), TEG reaction time (R), and TEG maximum amplitude (MA). Viscoelastic tests can be easily run at the point of care, decreasing the time required to obtain information about patients' coagulation status. Sharma and colleagues [13] compared TEG results and conventional tests in predicting postoperative bleeding, stratifying patients into two groups "bleeders" and "non-bleeders" and TEG parameters were the only ones found to be able to effectively predictive postoperative bleeding. Notwithstanding, haemostatic alteration of patients undergoing cardiac surgery is still unclear and is therefore still subject of debate. The aim of the present study is to describe, through serial blood controls, traditional tests and Point Of Care (POC), the coagulation status of patients undergoing CPB for cardiac surgery and to identify specific coagulation 'patterns'.

MATERIALS AND METHODS

It's an observational study including 29 patients undergoing cardiopulmonary bypass for cardiac surgery at the 'Città della Salute e della Scienza' University Hospital in Turin (Italy) between March and June 2021. The present study was approved by local Ethics Committee (local Ethics Committee approval number 585/2020, January 18th, 2021). All patients included signed the informed consent for the present study. Patients not providing written consent to data analysis, with an age lower than 18, with history of hematological or hepatic pathologies, undergoing urgent surgery or re-operations, or with an ejection fraction <25% were excluded.

Perioperative Management

All procedures were conducted under general anesthesia, according to standard practice, using Midazolam, Propofol or Etomidate, plus Fentanyl, Sufentanil or Remifentanil for induction. Neuromuscular block was achieved with induction bolus and continuous infusion of Cisatracurium. Anesthesia was maintained by total intravenous infusion of Propofol and Sufentanil tailored to achieve a BIS value index between 30-50. Intraoperative care, including Cardio-Pulmonary Bypass (CPB), was managed within standard practice, thus including One Lung Ventilation techniques as needed during surgery, ultrasound-guided vascular cannulation, mild hypothermic with indirect anterograde cardioplegia, and glycemic control and blood transfusions as needed by the patient.Upon completion of surgery, all patients were transferred to cardio-surgical intensive care unit (ICU) for monitoring, respiratory weaning, and standard post-operative management. Sedation was maintained by Propofol infusion as deemed necessary by on-duty intensivist.

Antithrombotic and anticoagulation management

Antithrombotic and anticoagulation therapy was managed according to European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on perioperative use of drugs in adult cardiac surgery[(14)]. Before CPB, 300UI/kg unfractionated heparin (UFH) was administered to achieve an activated clotting time (ACT) greater than 480 seconds. At the end of CPB, UFH neutralization was achieved using protamine sulfate 1 mg/100 UI of heparin. Postoperative anticoagulant strategy was managed with the application of a standardized protocol of administration of vitamin K antagonists (VKA) starting from the first postoperative day to reach an INR equal to 2.5 for mechanical prostheses and 2.0 for biological prostheses and valvuloplasty. Low molecular weight heparin (LMWH) bridging anticoagulation was used in the first 12-24 hours until the INR ratio goal was achieved.

Blood samples and laboratory tests

In all patients enrolled in the present study two series of blood samples were performed at T1 (before the start of CPB, after sternum opening, before UFH administration) and at T2 (after the end of CPB, after protamine administration and before any blood component transfusion). Laboratory tests included blood count, INR, aPTT, Fibrinogen and functional assay of coagulation factors (AT III, factors II, V, VII, VIII, IX, X, XI, XII, proteins C and S), with results expressed as percentage of activity. An additional sample was obtained (both at T1 and T2) for performing ROTEM analysis.

Data Collection and Analysis

Demographic characteristics, type and duration of surgery, preoperative antithrombotic or anticoagulant therapy, timing and dosage of postoperative antithrombotic and anticoagulant drugs, data related to the postoperative course as well as laboratory data (time activated partial thromboplastin, INR, platelet count, coagulation factors activity, ROTEM parameters) related to the day of surgery and postoperative day 1 were collected retrospectively from the medical record. Additionally, the following data were collected at T1 and T2: blood gas analysis, data related to any transfusions, core temperature and diuresis, data related to cardiopulmonary bypass. During ICU stay, blood losses from drains at 6-12-24 hours after surgery and any blood component transfusions administered were also collected .

Study outcomes

Primary objective was a quantitative and qualitative assessment of coagulation factors and changes in hemo-

static and coagulation parameters during cardiopulmonary bypass. Secondary objectives were the evaluation of the association between coagulation factors consumption and variation of viscoelastic parameters and differences on transfusion of blood products in the sternotomy group and in the minimally invasive access (Heart Port group- HP).

Statistical analysis

Data were tested for normal distribution by Shapiro-Wilk test and are expressed as mean and standard deviation (SD), mean with 95% confidence interval or median with interquartile range 25-75 (IQR) or percentages, as appropriate. Data analysis was performed for parametric variables with independent sample testing. Kruskar-Wallis non-parametric ANOVA was used for non-parametric continuous variables. Categorical variables were analyzed with Chi2 or Fisher's exact test, as appropriate. Statistical analyses were performed using SPSS statistics software, version 27 (IBM). A p value <0.05 was considered statistically significant.

RESULTS

During the study period, 36 patients were evaluated for eligibility. Seven patients were excluded: five because of inadequacy of the sample taken at T2 (hemolysis) and two because of need for re-entry into CPB for intraoperative issues. Twenty-nine patients were enrolled over a four-month period. Seventeen patients were assigned, based on the surgical approach performed, to the sternotomy group and 12 patients to the HP group. As shown in Table 1 the two groups were comparable both for demographic characteristics and type of antithrombotic or anticoagulant therapies used. Between the beginning (T1) and the end (T2) of cardiopulmonary bypass we observed an increase of 38.5% (from 1.14 to 1.58) of the INR and of 21.34% (from 0.89 to 1.08) of the aPTT, as shown in Table 2. At the same time, we observed a decrease in platelet count, fibrinogen, and AT III, with a median percentage decrease of 44.33%, 34.82%, and 30.10%, respectively. Between the beginning and the end of the bypass we also observed a significant decrease in coagulation factors II, X, XI, XII, protein C and S with an average percentage decrease of 32.58%, 34.11%, 36.69 %, 47.45%, 33.65% and 30.20%, respectively. We also observed a moderate reduction for factors V and VII (24.77% and 23.52%) and a modest reduction in factors VIII and IX (9.81% and 13.51%). Comparing the consumption of coagulation factors in the sternotomy group and in the HP group we observed how, at T1, patients belonging to the sternotomy group showed a statistically significant reduction in Protein C activity compared to the HP group (96.9 ± 18.9 vs 113.2 ± 21.8 respectively, $p = 0.04$) and a statistically insignificant reduction of factor XI activity (101.8 ± 29.6 vs. 122.7 ± 30.9, $p = 0.08$). (Table 3). Even at T2, the sternotomy group was characterized by a significant reduction in the activity of protein C (68.4 ± 12.4 vs. 83.4 ± 15.3, $p <0.01$) and factor XI ($65, 5 \pm 21.1$ vs 85.8 ± 24.5, $p = 0.024$), as well as a higher consumption of factors V and XII ($p = 0.049$ and $p = 0.07$ respectively) compared to the HP group (Table 4). Table 5 shows the negative correlation between the duration of CPB and aortic clamping and the factors consumption. As the duration of CPB and aortic clamping increases we see a progressive and statistically significant reduction of factors II, X, XI, XII, Protein C, and Protein S activity. Regarding viscoelastic parameters, we recorded a median increase of 22.64% of CT in Intem during CPB (159.0 [146.0-172.0] to 195.50 [189.0 - 248.0]), with a reduction in MCF in Fibtem of 16.66%, as well as platelet contribution (MCF Extem - Fibtem), which was reduced by 7.69% (Table 6). Comparing sternotomy group and HP group 2 (Table 7), CT elongation at T2 appeared to be more pronounced in patients undergoing sternotomy compared with those undergoing minithoracotomy (233.70 ± 59.9 vs. 200.3 ± 35.9, $p= 0.046$). The same was observed for platelet contribution (MCF Extem-Fibtem) at T2, although not statistically significant ($p=0.052$) Finally, we investigated differences in terms of post-CPB transfusion needs between sternotomy and HP group . We observed a greater need for transfusion of PRBCs and FFP in the sternotomy group compared with HP group ($p =0.02$ and 0.047, respectively) as shown in Table 8.

DISCUSSION

Data from this study seem to suggest that cardiopulmonary bypass induces a reduction in platelets and coagulation factors, mainly fibrinogen and factors II and X, associated with a consensual modification of la-

boratory parameters (both traditional and viscoelastic). Several reviews attempted to describe CPB related coagulopathy to provide suggestions and recommendations for the transfusion management during cardiac surgery. However, only Hofer [15] and colleagues reported on the reduction of different haemostasis components, traditional laboratory and viscoelastic parameters following CPB. We found an increase in INR of 38.5% and aPTT of 21.34%, close to 33.3% and 17.9% found by Hofer. We then found a reduction in platelet count of 44.33%, substantially in line with what has already been reported (44.5%), whereas for fibrinogen the reduction was 34.82% compared with 36.4% reported in the literature.

reduction in Fibtem of 16.6% at the end of CPB, while the MCF – MCF difference, indicative of platelet contribution to clot strength, was reduced by 7.69%. Hofer for these parameters found a decrease of 33% and 34%, respectively. data confirm the association between CPcoagulation factors consumptionCT showed an increase of 22.64%, confirming that the entire coagulation cascade and the mechanism of thrombin generation seem severely subverted during CPB. In the study population, 17 patients underwent cardiac surgery with sternotomy access (sternotomy group) and 12 with minimally invasive access (HP Group). The two groups did not show significant differences regarding anthropometric parameters, major comorbidities, CPB length and aortic clamping, baseline values of Hct, PLTS, INR, aPTT, Fibrinogen, AT III (Table 1). We analysed the two groups to identify those variables better explaining the modification induced by the surgical approach. At T1, Protein C content was reduced in the sternotomy group ($p < 0.04$) (Table 3) and the difference was amplified at T2 ($p<0.01$) (Table 4). In the absence of a baseline value, it cannot be excluded that the detected difference at T1 was already present at baseline. However, a trend towards a higher protein C consumption in the sternotomy group seems confirmed. To our knowledge, there are no previous study on the trend of protein C during CPB. Even with the limitations illustrated above and in the specific context of the present study, we do believe this observation interesting since it could support a rational approach to the diversified use of clotting factor concentrates: in patients who have undergone a sternotomy, the administration of products containing protein C, when available, may be more suitable than products that do not. This is also confirmed by the fact that the sternotomic access group received a higher number of PRBCs and FFP. As also confirmed by the literature [8,9], it seems that the sternotomy approach is associated with a greater alteration of haemostasis compared to the minimally invasive approach, as evidenced by the greater variations in viscoelastic parameters and the greater number of transfusions of blood products. However, it should be emphasized that the two surgical approaches differ from each other in many respects, including the practical management of CPB (use of negative pressure for venous drainage, relative volume and metabolic impact of the different types of cardioplegia, differences in the feasibility of retropriming). All these variables, which are difficult to standardize, can contribute to the development of coagulopathy, making it difficult to identify which factors are most related to transfusion needs. Overall, the data we collectedseem to support the trend towards an increased use, in cardiac surgery, of minimally invasive techniques that already proved their effectiveness in improving postoperative outcomes[16]. This study has limitations: first, the lack of randomization, which obviously exposes the risk of bias. It is also underpowered but, due to the lack of previous studies, it was not possible to calculate, a priori, an adequate power. Finally, variables such as techniques and practical aspects of CPB circuit are difficult to standardize, with a possible impact on study

CONCLUSION

CPB-induced coagulopathy is a known but still unclear phenomenon heavily impacting an already surgically complex procedure which dilution, activation and consumption of all components of haemostasis, together with the need for profound anticoagulation. Data from the present study seem to confirm the important reduction of all coagulation factors and platelets, together with a consensual change in traditional laboratory and viscoelastic parameters, especially during sternotomy surgery.

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