The Molecular Effect of Tubing Length in Cardiopulmonary Bypass on Coagulation Factors

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Abstract

Aim: Coagulation factors may be affected depending on the tubing line lengths of cardiyopulmoner bypass (CPB). The aim of this retrospective study was to evaluate the effect of CPB tubing line lengths on coagulation factors and to assess the relationship of these effects with bleeding and transfusion rates and early clinical outcomes

Methods: In this planned retrospective study, after applying the exclusion criteria, the included patients were divided into two groups based on tubing line lengths. Those with shorter tubing line lengths were defined as Group 1 and those with longer tubing line lengths than the first group were defined as Group 2. Coagulation factors, bleeding and transfusion rates of the groups were compared and statistical analyses were performed.

Results: Demographic, descriptive and preoperative data of the groups included in the study were similar ($p>0.005$). There was a statistically significant difference between the postoperative day 1 and early postoperative clinical outcomes including prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), activated partial thromboplastin time (APTT), factor 4, platelets, haemoglobin, haematocrit, erythrocytes, postoperative bleeding rate, postoperative transfusion rate, postoperative intubation time and ICU length of stay ($p<0.005$). However, there was no significant difference between the groups in terms of reoperation due to bleeding and length of hospital stay ($p>0.005$).

Conclusions: In this study, we found that tubing line lengths in CPB-guided cardiac surgery have effects on coagulation factors and also increase the postoperative bleeding rate and consequently increase the transfusion rate. The findings of this clinical study suggest that longer CPB tubing sets not only affect laboratory coagulation parameters but also trigger coagulation and inflammation pathways at the molecular level through blood-biomaterials interactions. This can be linked to molecular events such as thrombin production, platelet activation, and the release of endothelium-derived pro-inflammatory markers, providing an explanatory mechanism for the clinical outcomes of the study.

Keywords: *Cardiopulmonary bypass; coagulation factors; tubing lines; bleeding; molecular mechanisms; blood–biomaterials interaction*

1. Introduction

A bloodless and immobilised environment is needed in cardiac surgical applications performed with cardiopulmonary bypass (CPB), so a perfusion device (heart-lung machine) is used, which temporarily performs the pump of the heart and the respiratory properties of the lungs. In this process, the patient's heart and lung functions are disabled and perfusion is performed for a certain period of time with the heart-lung machine. Depending on this perfusion process, various changes may occur in metabolism and organs during or after CPB.[1,2] During CPB, mechanical pumps move blood in a non-laminar fashion from tubing lines, including the oxygenator, over non-biological surfaces. This repetitive action triggers the intrinsic coagulation cascade, whose prolonged disruption is believed to play an important role in consumptive coagulopathy during CPB. A recent shift in paradigm suggests that extrinsic pathway disruption is also an important part of CPB-mediated coagulopathy. The extrinsic pathway, activated by tissue factors released from surgical wounds, causes thrombotic stimulation through activation of coagulation factors. Such consumptive coagulopathy may be further potentiated by haemodilution due to prime solution within the CPB circuit. In addition, the contact of blood with foreign surfaces, i.e. tubing lines, during CPB also affects the bleeding coagulation system and organ function. Due to these effects, coagulation factors associated with cardiac surgery may contribute to haemorrhage and also to

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increased morbidity and mortality. Modifiable and non-modifiable factors may contribute to the development and progression of adverse conditions during cardiac surgery. Knowledge of the effects of preoperative coagulation factors strongly suggests that they may be predictive of adverse outcomes. It also reveals the importance of optimal line lengths. In this study, we aimed to evaluate the effect of CPB on coagulation factors depending on tubing line lengths, its effect on bleeding and transfusion rates and the relationship of these effects with early clinical outcomes.[3-7]

During CPB, the prolonged contact time of blood with polymeric tubing surfaces does not only create mechanical and haemodynamic effects; it also initiates molecular events such as platelet activation, complement system activation, and cytokine cascades through blood-biomaterials interaction. These molecular responses can lead to the consumption of coagulation factors, disruption of the fibrinolysis balance, and increased systemic inflammation, which may explain the clinically increased postoperative bleeding and transfusion requirements. This study highlights the importance of molecular perfusion techniques by linking the indirect contribution of tubing length to this molecular response chain with clinical laboratory indicators.

The aim of this retrospective study is to evaluate the effect of tubing line lengths on coagulation factors in patients undergoing CPB-guided cardiac surgery [coronary artery bypass graft (CABG)] and the relationship between these effects and bleeding and transfusion rates and early clinical outcomes. Additionally, it involves interpreting the clinical data obtained in the context of blood-biomaterials interaction and cellular and coagulation signalling pathways.

2. Materials and Methods

This study is retrospective clinical research.

2.1. Ethics Committee Approval

In this study, approval was obtained from the institution and the local ethics committee before the study (Date: 29.04.2024 - Approval no: HRÜ/24.05.23). The study was conducted following the principles of the Declaration of Helsinki. Since only anonymized patient data was used and there was no risk or impact on patient care, informed consent was not required. This consent waiver was approved by the Institutional Review Board and Ethics Committee and complies with regulatory and ethical guidelines for retrospective studies.

2.2. Study Population and Inclusion Criteria

Work data and patient data from the last two years were retrospectively reviewed. A total of 386 patient records were screened. A total of 231 adult male and female patients aged between 20 and 85 years who underwent consecutive CPB-guided cardiac surgery, i.e. CABG, were included in the study after applying the exclusion criteria.

2.3. Exclusion Criteria

Patients treated with anticoagulant drugs preoperatively, patients with bleeding and coagulation disorders, patients undergoing emergency cardiac surgery, patients undergoing mechanical mitral valve and mechanical aortic valve replacement, patients undergoing additional cardiac surgery such as aortic aneurysm or dissection, patients with known systemic inflammatory diseases, patients who underwent cardiac surgery more than once, chronic haemodialysis patients, patients with haematological diseases, patients with diseases such as pneumonia, chronic obstructive pulmonary disease were excluded from the study.

2.4. Data Collection Method

Data of the patients were obtained from computer, operating theatre records, perfusion follow-up records, intensive care follow-up cards and file records. The obtained data were recorded and entered into the computer. Descriptive data of the patients (age, gender, height, weight, body surface area (BSA), flow, ejection fraction percentage (EF%), aortic cross clamp time, total perfusion time and type of surgery (CABG counts)); prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), activated partial thromboplastin time (APTT), calcium (factor 4), platelets, haemoglobin, haematocrit, The bleeding rate/amount, transfusion rate/amount, reoperation due to bleeding, extubation time, intensive care unit (ICU) stay and hospital stay were recorded.

2.5. Formation of Groups

The patients included in the study were divided into two groups based on tubing line lengths. Those with shorter tubing line lengths were defined as Group 1 and those with longer tubing line lengths than the first group were defined as Group 2.

2.6. Lengths of Tubing Lines

Lengths of Group 1 tubing lines: Arterial line total length: 220 cm, pump artery head line length: 160 cm, venous line total length: 170 cm, aspirators total length: 380 cm, vent line total length: 390 cm. Other equipment was the same in both groups (Figure 1).

Figure 1

Group 1 tubing set scheme

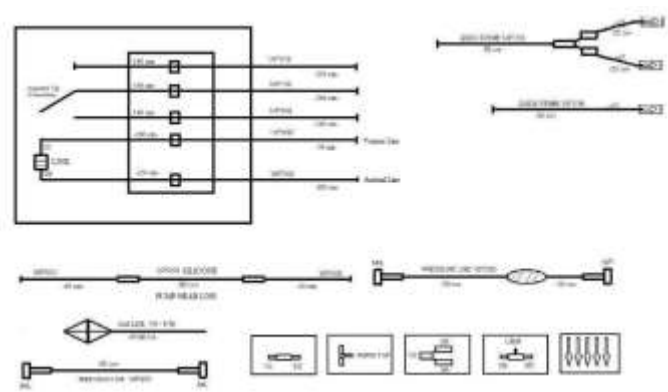
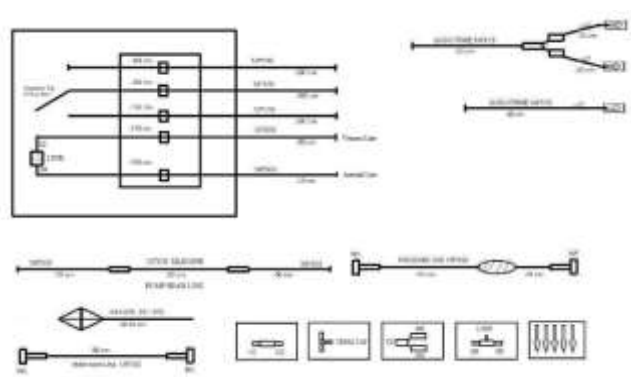


Figure 2

Group 2 tubing set scheme



Lengths of Group 2 tubing lines: Arterial line total length: 250 cm, pump artery head line length: 180 cm, venous line total length: 190 cm, aspirators total length: 410 cm, vent line total length: 430 cm. Other equipment was the same in both groups (Figure 2).

2.7. Cardiopulmonary Bypass (Perfusion) Technique

Standard coronary surgery techniques were applied in all patients. After midline sternotomy in coronary heart surgery patients, arterial cannulation was performed from the ascending aorta and venous cannulation was performed from the right atrium with a single venous cannula (two stage venous conduit). Left mammary artery graft was used in all cases. Saphenous vein graft was applied to other coronary grafts. Complete revascularisation was performed in all patients.

Blood flow rates (flow) of the patients included in the study during extracorporeal circulation (while connected to the heart-lung machine) were determined nonpulsatile according to their body surface areas (2.4 L/min/m2). Oxygenators and tubing sets suitable for the patient's weight and cannula diameters suitable for body surface areas were used. Membrane oxygenator/tubing sets with integrated arterial filter were used. Tubing set venous line diameter was 1/2 and arterial line diameter was 3/8. All patients were subjected to 32oC hypothermia during extracorporeal circulation.

Table 1

Comparison of descriptive and intraoperative data of the groups

Variables		Group 1 (n=108)	Group 2 (n=123)	P
Age (year) (Mean±SD)		64.88±8.20	62.94±9.65	0.235[a]
Gender (n, %)	Female	43, %39.8	50, 40.7%	0.797[b]
	Male	65, %60.2	73, 59.3%	
Type of surgical procedure (n, %)	CABGX1	6, %5.6	6, 4.9%	0.850[b]
	CABGX2	16, %14,8	18, 14.6%	
	CABGX3	32, %29.7	38, 30.9%	
	CABGX4	34, %31.5	38, 30.9%	
	CABGX5	20, %18.5	23, 18.7%	
Height (cm) (Mean±SD)		166.05±10.05	165.15±8.89	0.116[a]
Weight (kg) (Mean±SD)		74.12±15.63	81.42±58.14	0.347[a]
BSA (Mean±SD)		1.81±0.21	1.86±0.18	0.104[a]
Flow (L) (Mean±SD)		4.32±0.53	4.47±0.44	0.126[a]
Preoperative % EF (Mean±SD)		49.44±10.69	44.79±11.77	0.077[c]
Aortic cross clamp time (minutes) (Mean±SD)		70.90±33.27	81.91±36.68	0.682[c]
Total Perfusion Time (minutes) (Mean±SD)		106.81±38.01	115.15±46.18	0.694[c]
Intraoperative Bleeding Rate / Amount (mL)		133.56±107.67	124.34±113.13	0.324[c]
Intraoperative Transfusion Rate / Amount (unit)		1.05±1.09	1.30±1.10	0.070[c]

a: Mann Whitney U tests, b: Chi Square test, c: Student t test, Mean±SD: Mean±Standard Deviation, n: Frequency, %:Percent, CABG: Coronary Artery Bypass Graft, BSA: Body Surface Area, EF: Ejection Fraction.

Table 2

Comparison of preoperative coagulation and haematological factors of the groups

Variables	Group 1 (n=108) (Mean±SD)	Group 2 (n=123) (Mean±SD)	P
PT (seconds)	12.01±1.53	11.75±1.36	0.281[c]
PTT (%)	89.38±16,33	88.18±16.13	0.530[c]
INR (INR)	0.99±0.09	1.01±0.10	0.375[a]
APTT (seconds)	23.53±3.31	23.13±3.05	0.061[c]
Factor 4 (Calcium) (mg/dL)	8.99±0.94	9.15±0.59	0.296[c]
Platelets (10^3)	234.82±48.98	250.63±165.08	0.839[a]
Haemoglobin (g/dL)	13.66±1.76	14.03±1.97	0.061[a]
Haematocrit (%)	39.79±6.05	40.10±6.58	0.692[a]
Erythrocyte (10^6uL)	4.50±0.67	4.64±0.64	0.107[c]

a: Mann Whitney U tests, c: Student t test, Mean±SD: Mean±Standard Deviation, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, INR: International Normalized Ratio, APTT: Activated Partial Thromboplastin Time.

Table 3

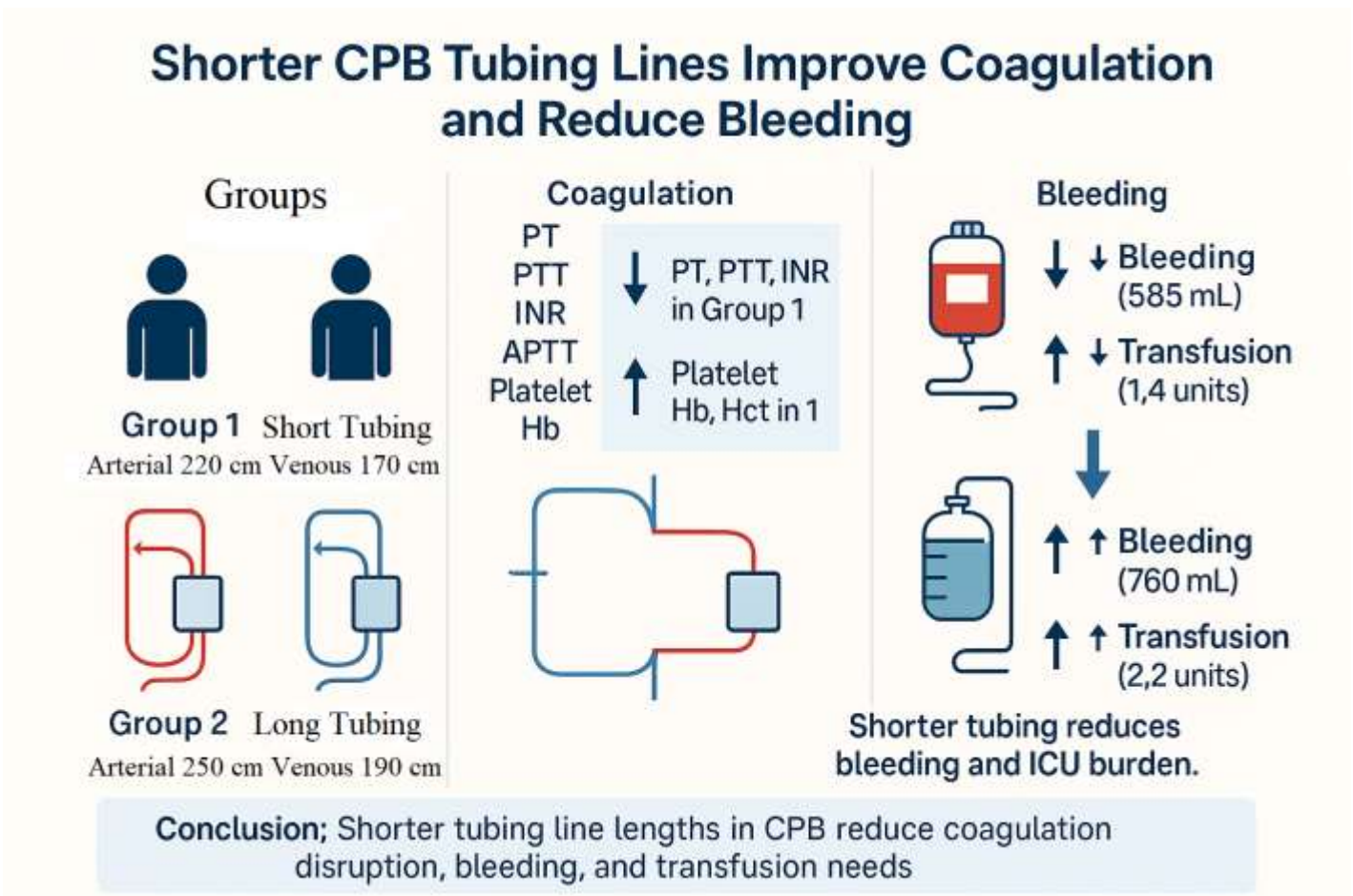
Comparison of postoperative day 1 coagulation factors and early clinical outcomes of the groups

Variables	Group 1 (n=108) (Mean±SD)	Group 2 (n=123) (Mean±SD)	P
PT (seconds)	13.00±0.95	14.33±0.73	<0.0001[c]
PTT (%)	93.44±5.81	106.67±9.88	<0.0001[c]
INR (INR)	1.05±0.08	1.14±0.12	<0.0001[a]
APTT (seconds)	25.25±3.23	27.38±4.57	0.001[c]
Factor 4 (Calcium) (mg/dL)	9.08±0.64	8.88±0.56	0.018[a]
Platelets (10^3)	216.64±43.40	203.03±45.46	0.002[a]
Haemoglobin (g/dL)	11.76±2.11	10.60±2.02	<0.0001[c]
Haematocrit (%)	35.07±8.39	30.54±5.61	<0.0001[c]
Erythrocyte (10^6uL)	4.09±0.87	3.42±0.47	<0.0001[c]
Postoperative Bleeding Rate / Amount (mL)	586.48±355.87	760.44±372.13	0.001[c]
Postoperative Transfusion Rate / Amount (unit)	1.44±1.32	2.21±1.42	<0.0001[c]
Reoperation for bleeding	0.02±0.16	0.03±0.17	0.834[c]
Intubation Duration (hours)	7.50±3.06	8.08±6.03	0.001[c]
Duration of ICU stay (days)	1.99±1.80	1.98±1.05	0.027[c]
Duration of hospital stay (days)	5.11±3.52	5.57±2.43	0.708[c]

[a]: Mann Whitney U tests, [c]: Student t test, Mean±SD: Mean±Standard Deviation, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, INR: International Normalized Ratio, APTT: Activated Partial Thromboplastin Time, ICU: Intensive Care Unit.

Figure 3

The relationship between tubing length and bleeding and transfusion



Arterial line pressures were maintained between 150-180 mmHg on average during CPB. Active clotting time (ACT) was kept at 480 seconds and above by providing adequate anticoagulation. As prime solution; 1200 mL balanced solution (isolayte), 150 mL 20% mannitol, 5 thousand units heparin and 2 g cefazolin were used. Blood cardioplegia solution was used in all patients. In patients in whom isothermic blood cardioplegia solution (32oC) was used, the initial amount of cardioplegia solution was administered as kgx15mL (full dose) and the maintenance dose was administered as half dose (1/2) every 20 minutes.

2.8. Statistical Analyses

In our study, statistical analyses were performed using SPSS® 17.0 computer programme (version 17.0, SPSS, Chicago, IL, USA). Means and standard deviations were calculated for continuous and ordinal data. Kolmogorov Smirnov test and Shapiro-Wilk test were used to evaluate normality distribution. Student t test and Mann Whitney U tests were used to evaluate normal and non-normally distributed data, respectively. Frequency and percentage analyses were performed for nominal data and Chi Square test was used for comparison. A 'p' value less than 0.05 was considered statistically significant.

3. Results

Demographic and descriptive data including age, gender, surgical procedure, height, weight, BSA, flow, preoperative EF%, aortic cross clamping time, total perfusion time, intraoperative bleeding rate and intraoperative transfusion interval were similar (p>0.005) (Table 1).

PT, PTT, INR, APTT, APTT, factor 4, platelet, haemoglobin, haemotocrit and erythrocyte levels were similar and there was no statistically significant difference (p>0.005) (Table 2).

PT, PTT, INR, APTT, APTT, factor 4, platelets, haemoglobin, haematocrit, erythrocytes, postoperative bleeding rate, postoperative transfusion rate, postoperative intubation time and ICU length of stay (p<0.0001; p<0.0001; p<0.0001; p=0.001; p=0.018; p=0.002; p<0.0001; p<0.0001; p<0.0001; p=0.001; p<0.0001; p=0.001; p=0.027) (Table 3). However, there was no significant difference between the groups in terms of reoperation due to bleeding and length of hospital stay (p=0.834; p=0.708, respectively) (Table 3) (Figure 3).

4. Discussion

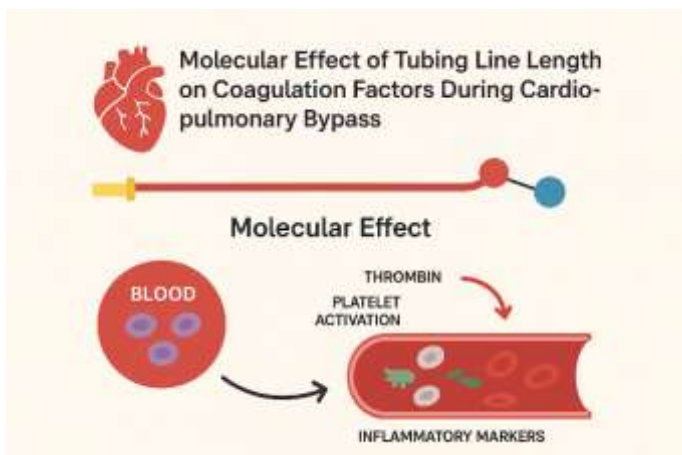
In CPB-guided cardiac surgery, blood is transferred outside the body via artificial tubing lines for an immobilised and bloodless heart.[8] Contact of blood with these lines may lead to various consequences. Components of CPB tubing line circuits may cause systemic inflammation, haemolysis and various complications including multiple disorders of coagulation and fibrinolytic systems.[9,10] In addition, haemorrhage and transfusion are common in cardiac surgery and are associated with worse outcomes. It has been reported that bleeding is frequently caused by coagulopathy caused by a complex interaction between CPB, major surgical trauma, anticoagulation management and perioperative factors.[11] However, prolonged exposure of blood to tubing lines may also affect coagulation factors, bleeding and transfusion rate. In this study, we aimed to evaluate the effect of tubing line lengths on coagulation factors and the effect of these effects on bleeding and transfusion rates and early clinical outcomes in patients who underwent CPB-guided cardiac surgery. One of the advantages of our study is that the negative effects of longer tubing lines on coagulation factors, haematological parameters, bleeding and transfusion rates were determined.

In many studies, the effects of the minimally invasive method on bleeding and coagulation factors in CPB-guided cardiac surgery have been mentioned, but heart-lung machine (tubing set, etc.) equipment, which is inevitable equipment in both methods, has not been mentioned much.[12-14] In addition, there is no definite standard regarding the optimal lengths of CPB tubing line lengths. When all these components are evaluated, the answer to the question 'what should be the ideal length of tubing line lengths?' is not yet clear. In addition, regarding the effect of tubing line lengths on coagulation factors, haematological parameters, bleeding and transfusion rate, most clinicians/perfusionists intuitively agree that tubing line lengths should be minimised in CPB because the adult literature supports their negative effects on patient outcomes after cardiac surgery.

The study by Cheng et al. supports our study results.[15] They reported that the reduced size of the CPB circuits exhibited favourable effects on haematological outcomes, possibly as a result of the reduced size of the CPB circuit, which minimised haemodilution and thus increased haematocrit levels during surgery. They noted that another contributing factor may be the lower mean postoperative blood losses and surgical re-exploration rates for bleeding. They also noted a lower platelet requirement, which may reflect reduced activation of coagulation cascades. They stated that minimising perioperative and postoperative transfusion rates reduces the burden on blood banks and limits associated risks and complications.[15,16] However, there is no study directly evaluating the relationship between tubing line lengths and coagulation factors in the literature. In our study, it was observed that shorter aortic, venous and aspirator lines had positive results on coagulation factors, haematological factors and bleeding transfusion rates.

Figure 4

Tubing Line Length and Molecular Activation of Coagulation Pathways



In our study, the group with longer tubing sets demonstrated poorer coagulation parameters and a higher need for blood transfusion/transfusion in the postoperative period. This clinical picture is consistent with the triggering of coagulopathy at the molecular level through increased platelet activation, thrombin

production, and increased complement/inflammatory markers due to increased contact time with tubing surfaces (Figure 4). Considering that the literature reports less haematological impairment in minimal circuit/microcircuit studies, our results suggest that reducing tubing length may preserve postoperative haemostasis not only haemodynamically but also molecularly. Although this perspective requires the measurement of molecular markers such as IL-6, TNF-α, vWF, or thrombin-antithrombin complexes in future studies, current clinical evidence provides strong support for the existence of a molecular mechanism.

The limitations of this study include the retrospective and single-centre nature of the study. Although the results of the study are at a generalisable statistical level, we think that multicentre and more patient populations would give more comprehensive results.

5. Conclusion

The primary outcome of this study was the release of coagulation biomarkers (PT, PTT, INR, APTT, calcium (factor 4)). Secondary outcomes were transfusion requirement and postoperative bleeding volume. In this study, we found that tubing line lengths in CPB-guided cardiac surgery have effects on coagulation factors and also increase the postoperative bleeding rate and consequently increase the transfusion rate. Consequently, CPB tubing lengths are not merely a technical preference; they influence coagulation and inflammatory responses at the molecular level through blood-biomaterials interactions, thereby affecting clinical outcomes. Therefore, tubing lines should be kept short, and it is recommended that this mechanism be validated in the future through the measurement of molecular markers.

Statement of ethics

In this study, approval was obtained from the institution and the local ethics committee before the study (Date: 29.04.2024 - Approval no: HRÜ/24.05.23). The study was conducted following the principles of the Declaration of Helsinki. Since only anonymized patient data was used and there was no risk or impact on patient care, informed consent was not required. This consent waiver was approved by the Institutional Review Board and Ethics Committee and complies with regulatory and ethical guidelines for retrospective studies.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

BA and MZB is the major contributor to the writing of the manuscript. BA, MZB and ME are involved in the design, conception, data collection and analysis of the study. All authors read and approved the final version of the manuscript.

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