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Analysis of the effect of initial hemostasis resuscitation with recombinant human coagulation factor VII a on the treatment of postoperative hemorrhage in cardiac surgery

Yan Yu[1], Maomao Liu[1], Xuran Lu[1], Li Yu[1] and Nan Liu[1*]

Abstract

Objective To investigate the effectiveness of initial hemostatic resuscitation(IHR) on the treatment of bleeding with recombinant human coagulation factor VIIa after cardiac surgery.

Methods The clinical data of patients who received rFVIIa hemostatic treatment after cardiac surgery at Beijing Anzhen Hospital, Capital Medical University, from January 1, 2021, to December 31, 2021 were retrospectively collected. A total of 152 cases were included in the study. In this study, initial hemostatic resuscitation was defined as a platelet count > 50,000 per μL and fibrinogen > 1.5 g/L when rFVIIa was used. Based on whether initial hemostatic resuscitation was completed during the application of rFVIIa, patients were divided into an initial hemostatic resuscitation group and an un-initial hemostatic resuscitation group. Baseline information, medical history, surgery-related data, postoperative bleeding volume, transfusion product volume, and overall mortality data were collected for each patient, and the postoperative bleeding volume, transfusion volume, and overall mortality rate were compared between the two groups, thus evaluating the effectiveness of initial hemostatic resuscitation on the treatment of postoperative bleeding with recombinant human coagulation factor VIIa in cardiac surgery.

Result In this study, patients in the initial hemostasis resuscitation group received a lower dose of recombinant activated factor VII (rFVIIa) [29.41 (26.23, 34.63) μg/kg vs. 36.04 (28.57, 59.27) μg/kg, $P=0.002$], had lower blood product requirements [41 (40.2%) vs. 31 (62%), $P=0.011$], received fewer units of packed red blood cells within 24 h postoperatively [0 (0, 2) U vs. 2 (0, 6) U, $P=0.018$], had a lower volume of plasma transfusion [0 (0, 0) ml vs. 0 (0, 400) ml, $P=0.021$], exhibited a lower peak value of D-dimer after surgery [756 (415.5, 2140.5) ng/ml vs. 1742.5 (675.25, 3392) ng/ml, $P=0.003$], experienced fewer postoperative neurological complications [4 (3.92%) vs. 12 (24%), $P<0.001$], had a lower mortality rate [8 (7.84%) vs. 14 (28%), $P=0.001$], and had a shorter duration of mechanical ventilation [17 (12, 60.13) hours vs. 39.5 (15.75, 115.13) hours, $P=0.022$].

*Correspondence:
Nan Liu
ln9102@126.com

Full list of author information is available at the end of the article

Conclusion Initial hemostasis resuscitation can significantly reduce the bleeding volume and blood product requirements in patients with bleeding complications after cardiac surgery who were treated with rFVIIa, thus improving patient prognosis. And it is crucial to closely monitor for symptoms and signs of thromboembolic complications during the application of rFVIIa.

Keywords Hemorrhage, Recombinant activated factor VII, Cardiac surgery, Patient blood management, Intensive care

Introduction

Bleeding is a common complication after cardiac surgery, with approximately 5-7% of cardiac surgery patients experiencing postoperative bleeding exceeding 2 L. Inadequate hemostasis may result in 3.6-4.2% of patients requiring thoracotomy for exploration [1], which is an independent risk factor for mortality after cardiac surgery [2]. The risk of postoperative complications in this type of patient is much higher than that in the normal heart surgery population, with a mortality rate ranging from 19 to 40% [3]. Recombinant factor VIIa (rFVIIa) was initially developed and used to treat clinical condition associated with low FVII, but more recently has been employed in the treatment of various post-surgical and trauma-related bleeding, including post-cardiac surgery bleeding. However, currently, there is a lack of consensus among clinical physicians regarding the application of rFVIIa for the treatment of refractory bleeding after cardiac surgery [4, 5], and its recommended timing are not mentioned in current guidelines. Therefore, the aim of this study was to explore the impact of initial hemostatic resuscitation on the therapeutic efficacy of rFVIIa treatment for bleeding in patients following cardiac surgery. The findings were used to provide a reference for the timing of rFVIIa use.

Method

Information and definition

This study has been reviewed by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (IRB2023205X), and was conducted under the supervision of the Ethics Committee. A retrospective observational analysis was conducted on the clinical data of 152 patients who received rFVIIa hemostatic treatment after cardiac surgery at Beijing Anzhen Hospital, Capital Medical University, from January 2021 to December 2021. According to the definition of IHR, a total of 102 patients in the IHR group and 50 patients in the non-IHR group. All patients will be rewarmed to above 36 °C before leaving the operating room and closely monitored for temperature upon returning to the CICU. In this study, the lowest postoperative temperature for all patients was above 36 °C.

When patients continue to bleed after surgery, clinical physicians will treat according to the center's hemostasis process (as shown in Fig. 1). If bleeding persists after completing this treatment process, rFVIIa therapy will be initiated. The dosage of rFVIIa, in our center, is usually 20–40 μg/kg after referring to previous studies. However, the specific dosage also depends on the severity of the patient's condition and the clinical experience of the attending physician. In this study, initial hemostatic resuscitation (IHR) was defined as achieving a platelet count > 50,000 per μL and fibrinogen > 1.5 g/L prior to the administration of rFVIIa. Patients were divided into two groups: the IHR group, which met these criteria before receiving rFVIIa, and the non-IHR group, which did not meet these criteria but still received rFVIIa based on clinical judgment and emergent bleeding conditions. The decision-making algorithm for each group was guided by the patient's bleeding severity, coagulation parameters, and clinical status.

The following patient characteristics were collected for analysis: demographic information (gender, age), medical history (hypertension, diabetes mellitus, smoking, alcohol use, renal dysfunction, coagulation abnormalities), preoperative laboratory values (hemoglobin and platelet counts, liver function tests), surgical details (elective or emergency surgery, type of surgery, operation time, cardiopulmonary bypass time), and postoperative data, including laboratory results, ICU duration, mechanical ventilation time, and length of hospital stay. Additional relevant clinical information was also included as necessary. Notably, except for demographic and surgery-related data, all other indicators in this study were collected during the ICU phase.

In this study, we defined renal dysfunction as serum creatinine (Scr) levels exceeding 111 μmol/L in males and 81 μmol/L in females. Coagulation abnormalities are defined as prothrombin time (PT) of more than 3 s or more and activated partial thromboplastin time (APTT) of more than 10 s or more in the most recent coagulation function test prior to surgery. Early neurologic complications were defined as the occurrence of stroke (i.e., thrombosis) or hemorrhage within 72 h after the completion of surgery.

Statistical analysis

Statistical processing was performed using SPSS 26.0(https://www.ibm.com/cn-zh/spss). For normally distributed metric data, the mean ± standard deviation (x ± s) was used to express the data. Independent samples t tests were conducted for between-group comparisons. For nonnormally distributed metric data, the median and interquartile range [mean (25%ile, 75%ile)]were used to

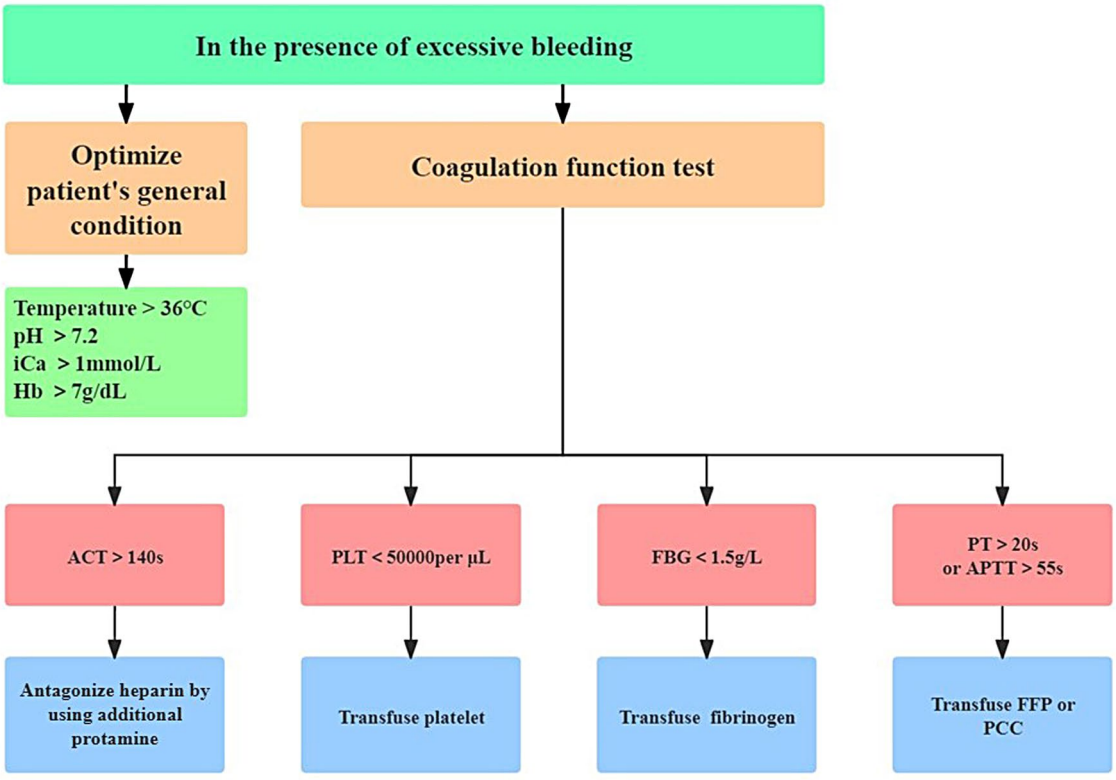

Fig. 1 The hemostasis process: This is the center's hemostasis management process: when a patient has persistent bleeding after surgery, the first step is to optimize the patient's general condition including body temperature, PH value, Ca concentration and Hb level. Coagulation tests are performed at the same time, and further management is carried out according to different test results: protamine antagonist heparin for anticoagulant effect if ACT is > 140 s, platelet transfusion if platelet count < 50,000 per μL, fibrinogen replacement if fibrinogen is less than 1.5 g/L, FFP or PCC if INR > 1.5 or APTT > 55s

Table 1 Baseline characteristics and the information about operation

	IHR group($n=102$)	non-IHR group ($n=50$)	*p*-value
Age, years	61.5(51.0,68.3)	62(52.8,67.3)	0.83
Male, n(%)	40(39.2)	21(42.0)	0.74
Hypertension, n(%)	13(12.8)	7(14.0)	0.86
Diabetes mellitus, n(%)	21(20.6)	12(24.0)	0.63
Smoking, n(%)	32(31.4)	15(30.0)	0.86
Drinking, n(%)	21(20.6)	12(24.0)	0.63
Renal dysfunction, n(%)	9(9.0)	7(14.0)	0.35
Coagulation abnormalities, n(%)	22(21.6)	13(26.0)	0.54
Emergency, n(%)	14(13.7)	7(14.0)	0.96
Hb, g/L	136.5 ± 18.7	137.2 ± 16.5	0.82
Platelet, $\times 10^9$/L	197.5(148.0, 241.5)	190(145.5, 225.5)	0.55
ALT, U/L	17(12.0, 23.0)	18.5(11.8, 24.0)	0.8
AST, U/L	18.5(16.0, 22.8)	19(15.0, 24.3)	0.73
Aortic surgery, n(%)	24(23.5)	18(36.0)	0.11
OPCABG, n(%)	16(15.7)	3(6.0)	0.09
CPB time, min	147(97.0, 204.5)	175.5(111.0, 257.0)	0.06
Arrest time, min	95(16.5, 129.5)	98(53.3, 133.0)	0.79

represent the data, and the Mann–Whitney U test was employed for between-group comparisons. For repeated measures data, repeated measures analysis of variance was employed. Count data are presented as frequencies and percentages, and between-group comparisons were conducted using the chi-square test or Fisher's exact test, considering a ***p-value*** less than 0.05 to indicate statistical significance.

Result

According to the definition, there were a total of 102 patients (67.1%) who qualified as the early resuscitation group. The baseline characteristics and the information about operation of the patients in the IHR group ($n=102$) and the patients in the non-IHR group ($n=50$) are presented in Table 1.

Among all 152 patients, a total of 42 patients underwent aortic surgery. The surgical methods included simple Bentall procedure, Bentall procedure+sun's procedure, Bentall procedure+partial arch replacement, Bentall procedure+CABG procedure, Bentall procedure+valve replacement, ascending aortic replacement, ascending aortic replacement+sun's procedure, ascending aortic replacement+partial arch replacement,

Wheat's operation, David's operation, Carbrol's operation. There were 30 cases of simple coronary artery bypass grafting, with surgical methods including CABG and OPCABG. The remaining 80 patients underwent various surgical methods including valve replacement, valve repair, heart tumor resection, MORROW procedure, VSD repair, congenital heart disease correction surgery, hybrid surgery, etc.

Compared with the un-initial hemostatic resuscitation group, the initial hemostatic resuscitation group had significantly lower dosages of rFVIIa [29.41 (26.23-34.634) μg/kg vs. 36.04 (28.57–59.27) μg/kg, $P=0.002$]. In addition, we observed a lower rate of re-application of rFVIIa in the IHR group compared with the non-IHR group [18 (17.6%) vs. 18 (36%), $P=0.012$], as shown in Table 2.

In terms of treatment effectiveness, compared with the patients in the un-initial hemostatic resuscitation group, the patients in the initial hemostatic resuscitation group had a lower rate of blood product use within the first 24 h after surgery [41 (40.2%) vs. 31 (62%), $P=0.011$], lower fluid intake volume [2612.5 (2051.25, 3337.5) ml vs. 3395 (2537.5, 4395) ml, $P<0.001$], lower amount of red blood cells infused [0(0,2) U vs. 2(0,6) U, $P=0.018$], and a lower volume of plasma infused [0(0,0) ml vs. 0(0,400) ml, $P=0.021$]. In addition, the drainage volume of the patients in the initial hemostatic resuscitation group was lower than that of the patients in the un-initial hemostatic resuscitation group at 6 h [315(150,762.5)ml vs. 690(400,1162.5) ml, $P<0.001$], 12 h [600(300,1062.5)ml vs. 1075(600,1560)ml, $P<0.001$], and 24 h [875(500,1340) ml vs. 1500(990,2300)ml, $P<0.001$] after surgery. Furthermore, the lowest platelet count within 3 days after surgery was higher in the initial hemostatic resuscitation group [74.5(58,115) ×109/L vs. 33.5(20.75,59.25) ×109/L, $P<0.001$], and the highest value of D-dimer was lower [756(415.5,2140.5) ng/ml vs. 1742.5(675.25,3392) ng/ml, $P=0.003$], as shown in Table 2; Fig. 2.

In terms of prognosis-related factors, longer mechanical ventilation time [17 (12, 60.13) h vs. 39.5 (15.75, 115.13) h, $P=0.022$], postoperative re-exploration [13 (12.75%) vs. 17 (34%), $P=0.002$), application of CRRT [10 (9.8%) vs. 15 (30%), $P=0.002$], and all-cause mortality [8 (7.84%) vs. 14 (28%), $P=0.001$] were more common in the un-initial hemostatic resuscitation group, as shown in Table 3.

Discussin

In recent years, the use of recombinant activated Factor VII (rFVIIa) has emerged as a significant therapeutic strategy for managing intractable bleeding following cardiac surgery, especially when conventional hemostatic approaches are inadequate [6]. The therapeutic action of rFVIIa is mediated by two principal mechanisms [7]. Initially, it operates via the tissue factor (TF) pathway, also known as the third coagulation pathway. Damage to vascular endothelium triggers the activation of TF, which then complexes with rFVIIa, catalyzing the activation of Factor X and the subsequent transformation of prothrombin into thrombin. Additionally, rFVIIa can induce coagulation through a TF-independent route by directly activating Factor IX, which initiates the intrinsic coagulation cascade, further facilitating the conversion of prothrombin to thrombin. It's important to underscore that these mechanisms illustrate the therapeutic utility of rFVIIa in addressing bleeding complications, extending its coagulative efficacy beyond the innate coagulation processes found in healthy individuals. A study on bleeding in patients with nonhemophilia demonstrated that rFVIIa treatment for bleeding requires at least 60,000 per μL of platelets and adequate fibrinogen [8].

Patients after cardiac surgery, due to the use of extracorporeal circulation, experience significant consumption or loss of platelets and coagulation factors. Low body temperature reduces the activity of coagulation factors. Previous studies have shown that low temperatures (34 °C–31 °C) may increase the ability of platelets to respond to activating stimuli. This may only one step in increasing the consumption of platelets during cardiac

Table 2 Evaluation of Hemostatic effects

	IHR group($n=102$)	non-IHR group ($n=50$)	*p*-value
Dosage of rFVIIa, μg/kg	29.41 (26.2,34.6)	36.04(28.6,59.3)	0.002
Re-application of rFVIIa, n(%)	18(17.6)	18(36.0)	0.012
Percentage of patients needing blood product, n(%)	41(40.2)	31(62.0)	0.011
Fluid volume administered in 24 h, ml	2612.5(2051.3,3337.5)	3395(2537.5,4395.0)	<0.001
RBC transfusion in 24 h, U	0(0,2)	2(0,6)	0.018
Plasma transfusion in 24 h, ml	0(0,0)	0(0,400)	0.021
Chest tube drainage in 6 h, ml	315(150.0,762.5)	690(400,1162.5)	<0.001
Chest tube drainage in 12 h, ml	600(300.0,1062.5)	1075(600.0,1560.0)	<0.001
Chest tube drainage in 24 h, ml	875(500.0,1340.0)	1500(990.0,2300.0)	<0.001
PLTmin, $\times10^9$/L	74.5(58.0,115.0)	33.5(20.9,59.3)	<0.001
D-Dmax, ng/ml	756(415.5,2140.5)	1742.5(675.3,3392.0)	0.003

PLTmin: lowest platelet count; D-Dmax: The highest value of D-dimer

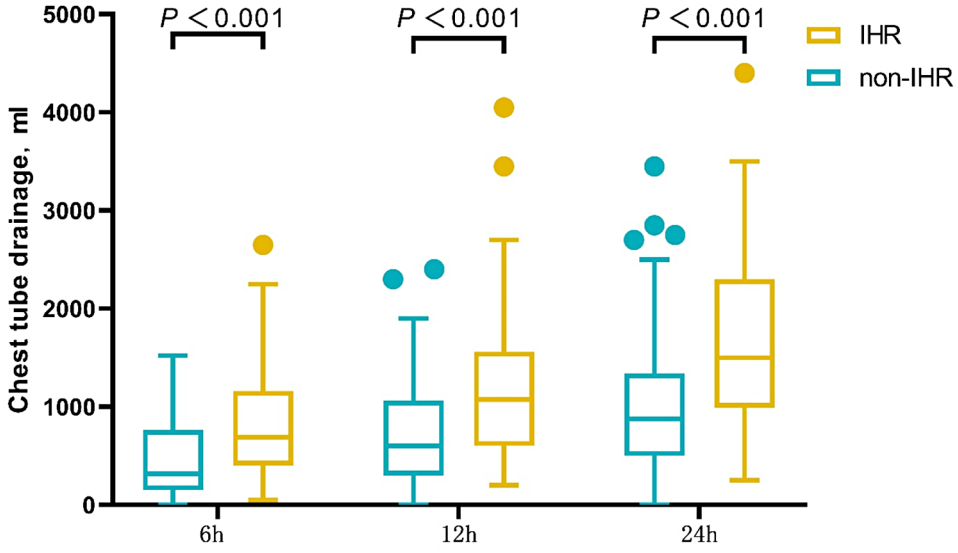

Fig. 2 Chest tube drainage: The figure shows the total volume of Chest tube drainage to patients in the IHR group and the non-IHR group at 6, 12, and 24 h post-surgery. There are statistically significant differences in the total volume of fluids administered at each of the three time points between the two groups of patients

Table 3 Prognosis-related factors

	IHR group($n=102$)	non-IHR group ($n=50$)	*P* value
Ventilation hours, hours	17(12,60.13)	39.5(15.75,115.13)	0.022
ICU length, hours	44.5(20.5,116.5)	63.5(25.75,157.25)	0.12
Neurological complications, n(%)	4(3.92)	12(24)	<0.001
Re-exploration, n(%)	13(12.75)	17(34)	0.002
CRRT, n(%)	10(9.80)	15(30)	0.002
ECMO, n(%)	3(2.97)	4(8)	0.167
IABP, n(%)	9(8.82)	7(14)	0.329
Death, n(%)	8(7.84)	14(28)	0.001

surgery [9, 10]. The use of heparin and excessive activation of the fibrinolytic system during surgery greatly increases the risk of postoperative bleeding in patients [11]. At present, the hemostasis process for patients with postoperative bleeding after cardiac surgery is usually as follows: monitoring ACT to adjust the dose of protamine to antagonize the application of intraoperative heparin; fresh frozen plasma (FFP), prothrombin complex (PCC), and fibrinogen (FBG) are given according to coagulation function; platelet transfusion, suspension of red blood cells; and secondary thoracotomy exploration [12]. However, postoperative transfusion of blood products in large quantities significantly increases the mortality rate, incidence of complications, mechanical ventilation time, and ICU stay time after cardiac surgery, severely affecting patient prognosis [13].

In the guidelines of the Cardiovascular Anesthesia Society, it is recommended that when bleeding complications occur after cardiac surgery, after correcting the patient's general vital signs, the platelet count should be corrected to >50,000 per μL and FBG>1.5 g/L [12]. This goal-oriented initial resuscitation for patients with bleeding means that a certain amount of coagulation and hemostatic materials are supplemented for patients. Therefore, in this study, we defined a platelet count greater than 50,000 per μL and FBG greater than 1.5 g/dL as initial hemostatic resuscitation. The optimal dose of rFVIIa is unclear, as there are no current guidelines mentioning the dose of rFVIIa for use in cardiac surgery. In previous studies, rFVIIa was used to treat bleeding after cardiac surgery at doses ranging from 12 μg/kg to 90 μg/kg [14–16]. In our study, patients who underwent initial hemostatic resuscitation had lower doses of rFVIIa, with a median dose of 29.41 μg/kg. Since the determination of whether to achieve initial hemostatic resuscitation was performed before the first application of rFVIIa, patients with non-IHR were also observed in this study to have higher re-application of rFVIIa. This study is a single-center retrospective study, and the physicians who initiated rFVIIa therapy had a similar treatment philosophy, that is, the corresponding therapeutic dose was given at the initiation of treatment. Higher doses of rFVIIa were applied in the non-IHR group that were observed subsequently, and we believe this is related to the re-application of rFVIIa. This suggests that in clinical practice, for patients with postoperative bleeding after cardiac surgery, initial hemostatic resuscitation can not only reduce the use of blood products and improve patient prognosis but also reduce the dose of rFVIIa and reduce the economic burden on patients. This result is similar to the recent proposal of using a low dose (i.e., <40 μg/kg) rFVIIa to treat postoperative bleeding after cardiac surgery [17]. In addition, in this study, it was found that

patients who underwent initial hemostatic resuscitation needed fewer blood products, produced less drainage, and had a better prognosis, which is similar to previous research results [18].

In contrast to previous studies, in this study we applied platelet count and fibrinogen as criteria for determining whether a patient has completed initial hemostatic resuscitation, in order to determine the timing of rFVIIa administration. When bleeding occurs, hemostasis is critical. The hemostasis process can be divided into primary hemostasis and secondary hemostasis, which involve platelet plug formation and coagulation processes, respectively [19]. Platelets are key players in primary hemostasis. When activated, a conformational change in the most abundant membrane receptor of platelets, αIIbβ3, increases its affinity, allowing fibrinogen and vWF factors to form bridges between platelets [20, 21]. The involvement of the Src family leads to irreversible platelet aggregation and clot contraction [22, 23]. It has been shown that rFVIIa can activate platelets by binding to the glycoprotein Ibα on the platelet surface, and the presence of the platelet surface glycoprotein Ibα contributes to the production of thrombin, a non-tissue factor-dependent pathway of rFVIIa [24]. In addition, the presence of endothelial protein C receptor (EPCR) on activated platelets is also an important site for rFVIIa to bind to platelets [25, 26]. A decrease in platelet levels or impaired platelet function after cardiopulmonary bypass surgery is one of the risk factors for postoperative bleeding in cardiac surgery [27]. Fibrinogen, or coagulation factor I, plays a key role in hemostasis. In animal experiments and in vitro studies, fibrinogen supplementation has been shown to counteract thrombocytosis caused by thrombocytopenia-induced dilution of coagulation dysfunction and impaired hemostasis [28]. Research shows that low levels of fibrinogen during the perioperative period and low platelet levels before surgery are important predictors of postoperative bleeding after cardiac surgery [29]. In a study by Martin Karlsson and others, the preoperative level of fibrinogen was found to be an independent predictor of postoperative bleeding and transfusion after cardiac surgery. For patients undergoing CABG, preoperative prophylactic infusion of fibrinogen can reduce postoperative bleeding [28]. In the study by Caroline Shams Hakimi et al., increasing platelet and fibrinogen levels in patients with bleeding after cardiac surgery can improve platelet and coagulation in patients [28, 30].

In the two pathways that play a role in hemostasis after rFVIIa administration, activated platelets are two key products in the activation process of the coagulation system, namely, the tenase complex and the prothrombinase complex, which provide a phospholipid surface to activate downstream fibrinogen, thus completing the hemostasis process. Therefore, a certain level of platelets and fibrinogen provide sufficient raw materials for postoperative bleeding in patients treated with rFVIIa. In addition, in this study, the lowest platelet count and highest D-dimer value in the recovery group of patients were relatively low, which may be due to the better correction of the patient's coagulation system function after initial hemostatic recovery with the use of rFVIIa, thus preventing continued platelet consumption and excessive activation of the fibrinolysis system.

This study has several limitations. First, as a retrospective study, it is subject to selection bias, particularly in the classification of IHR and non-IHR groups, as rFVIIa administration decisions may have occasionally preceded laboratory results. Second, thrombotic events were not systematically screened in all patients; only those with abnormal clinical signs or laboratory values were evaluated, limiting the assessment of thrombotic safety following rFVIIa-based initial hemostatic resuscitation. Furthermore, the absence of 24-hour thromboelastography (TEG) testing and detailed data on preoperative antiplatelet or anticoagulant use may have influenced the findings. Future studies will aim to address these limitations with more comprehensive data and stricter group classifications to validate our results.

Conclusion

In conclusion, when using rFVIIa to treat postoperative bleeding in cardiac surgery patients, although there are recommendations on its timing of use in current guidelines, the findings of this study suggest that for the effective use of rFVIIa, it may be beneficial to first ensure initial hemostatic resuscitation of patients, which includes correcting platelet counts to exceed 50,000 per μL and fibrinogen levels to be above 1.5 g/L. Initial hemostatic resuscitation can significantly reduce postoperative bleeding and blood product requirements and improve patient prognosis. However, it is crucial to closely monitor for symptoms and signs of thromboembolic complications, as well as relevant laboratory tests, during the application of rFVIIa.

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Author contributions
YY and MML designed the research study, YY and LY performed the research, YY and XRL analyzed the data, NL* reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
This study has been reviewed by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (IRB2023205X), and was conducted under the supervision of the Ethics Committee.

Human ethics and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Cardiac Surgery Critical Care Center Inpatient Ward 1, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

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