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# Excessive Bleeding After Cardiac Surgery in Adults: Reasons and Management

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**Summary**
Postoperative bleeding is a concern for all patients undergoing cardiac surgery. In patients exposed to cardiopulmonary bypass, bleeding following surgery is excessive in up to twelve percent of patients in whom subsequent re-exploration is required. Several studies have evaluated main reasons, prevention of excessive postoperative bleeding and impact of patients outcomes. This article contains a literature review on excessive bleeding and re-exploration following cardiac surgery, main surgical and medical sources, prevention and management of bleeding.
**Key words:** re-exploration, bleeding, cardiac surgery.

## INTRODUCTION

Excessive bleeding is common after cardiac surgery and it remains a major source of morbidity and mortality. There have been many studies analyzing the haemostatic derangements caused by cardiopulmonary bypass (CPB) and others have evaluated the various strategies of blood conservations. The incidence of re-exploration during early postoperative period after open heart surgery in the literature is ranging from 2% to 6% (31). The first cause for early mediastinal re-exploration after open heart surgery is the bleeding.

In studies held before 1990, re-exploration rates were as high as 14%, whereas they dropped down to 3% in recent studies. Reasons for this could be follows: shortening of the duration of the operations and more advanced technology, construction of extracorporeal circuatory and oxygenator lines that causes less heamatological trauma, better evaluation of patiens perioperatevly, transfusions of autologus blood components.

Excessive bleeding may result in patients receiving massive blood transfusions or suffering of life-threating complications such as miocardial infarction, low cardiac output sindrome, respiratory failure and pneumonia, severe arrhythmia, deep sternal wound infections, hepatic and renal insufficiency and need for hemofiltration, cardiac tamponade and increased mortality.

Mortality rates seen after revisions for bleeding are between 8–26% in literature, but incidence of wound infections after re-explorations is approximately 2% (15).

Major risks factors for bleeding are summarized in Table 1.

There have been several studies investigating genetic role of developing coagulopathy after cardiac surgery (14). Duggan and coworkers measured Plasminogen Activator inhibitor -1 (PAI-1) gene expression after cardiac surgery and its relation to perioperative morbidity. PAI-1 gene expression decreased after cardiopulmonary bypass in all patients. A larger reduction in PAI-1 gene expression was observed in homozygous carriers of the 5G allele. They are also more likely to receive transfusion of coagulation blood products.

**Re-exploration rates due to bleeding**

In literature need for re-exploration with bleeding revision was evaluated while investigating series of large numbers (Table 2).

**Excessive bleeding reasons after cardiac operation in cardiopulmonary bypass**

The main reasons are categorized as surgical or medical in nature.

**Surgical**: Excessive postoperative bleeding is from surgical sources in the majority of patients. In prior studies surgical causes of bleeding necessitating re-exploration were found to range from 35-100% (19,20,24).

It is usually related to: anastomotic sites (suture lines), side branches of arterial or venous conduits, substernal soft tissues, sternal suture sites, bone marrow, periosteum, raw surfaces caused by previous surgery, pericarditis.

**Medical**: That kind of bleeding usualy is persistent noted after complex operations frequently associated with abnormal coagulation. It is hard to diagnose if bleeding is due to coagulopathies. They have a greater extent, are exposed to greater amounts of inotropes with alpha effect and has greater incidence of low cardiac output syndrome. Also hospitaly stay and mortality rate in higher (19). Therefore for patients in the ICU with unexpected high chest tube output, the goal is to normalize the patients coagulation profiles within 4 hours (19).

There are many risk factors causing medical related bleeding. First of all these ar **preoperative factors** such as low body surface area with small blood circulation volume. It is significant risk factor for bleeding and masive blood transfusions because of greater hemodilution of using higher total volums in the CPB circuit (23).

Qualitative platelet defects are a major concern with the liberal use of antiplatelet medications in patients with acute coronary sindromes. Preoperative platelet dysfunction may result from antiplatelet medications. Most frequently used antiagregant is Aspirin. Clopidogrel also is significant risk factor who causes higher rate of re-exploration (9).

Preoperative trombocytopenia < 100 x $10^9$L is a serious risk factor for bleeding and for masive blood transfusions in postoperative period (35). Be aware that reason for trombocytopenia also can be Heparin-induced trombocytopenia (HIT). Up to 8% of heparinized patients develop the antibody associated with HIT and approximately 1–5% of patients on heparin progress to develop HIT.

Patients with hepatic dysfunction, residual Warfarin effect, vitamin K-dependent clooting factors deficiencies, von Willebrand's disease and also thrombolytic therapy is more likely to have excessive bleeding after CPB.

**Intraoperative factors**

The main source for bleeding intraoperatively is CPB. Prolonged cardiopulmonary bypass period is an independent risk factor for higher mortality and morbidity rate after cardiac surgery and it is the best predictor of microvascular bleeding. The risk for bleeding increases if CPB period is more than 120 minutes (34).

Patients undergoing cardiac surgery in CPB acquire some degree of platelet dysfunction. Cardiopulmonaly bypass circuit induce platelet dysfunction because of release of alfa granule and alteration of platelet membrane receptors. How to predict excessive microvascular bleeding due to platelet dysfunction after CPB remains an elusive goal. More sensitive and specific compareble to routine laboratory coagulation tests in predicting blood loss are Thromboelastogram (TEG) and Platelet-Activated Clotting Test (PACT). However some authors report, that TEG have better predictive value than PACT (16).

Thrombocytopenia will be progressive as the duration of CBP lengthens. Also administration of Protamine transiently reduces the platelet count by about 30%.

Hemodilution on CPB reduces most factors by 35-50% and factor V by 80% (8). This is most pronounced in patients with small blood volume and they are more likely to have dilution coagulopathy thereby also higher risk for excessive bleeding (23). Loss of clotting factors also results from use of intraoperative cell-saving devices.Clotting factor degradation and platelet dysfunction causes also fibrinolysis due to plasminogen activation during CBP and heparinization itself induces a fibrinolytic state.

Hypothermia – it could reduce platelet and enzime function. Platelet agregation and adhesion decrease when body temperature is $33^0$C and less.

**Postoperative factors**

The phenomen of „heparin rebound" has been considered to be the most common cause of bleeding in the postbypass period. The phenomen is the best defined as the reappearence of hypocoagulability of blood after adequate neutralization of heparin has been accomplished (30). This is more common in patients receiving large amounts of heparin, especially obese patients. The incidence of the „heparin-rebound prhenomen" have been investigated by many studies (29). Reappearence of heparin in circulation usually occur in 1-8 hours after neutralization with Protamine. Heparin effect was detected in 43% of patients studied at 2h, 31% at 4h, and 37% at 8h.

Number of reasons have been attributed to the appearence of heparine in the circulation. It may be either due to reabsorption of heparine into the blood stream from extravascular depots or it may be due to the faster degradation of Protamine. Also application of Cell saver system after Protamine administration may reintroduce unreversed heparine, but several studies have been reported that Cell saver system with separated red blood cells washed in physiological saline were totaly free of heparine, partly small remains of heparine could be found.

**Anticoagulation for cardiopulmonary bypass**

It is essential during CPB. The main anticoagulant is heparin. Its inhibits the coagulation system by binding to antithrombin III. Dose approximately is 3-4mg/kg of heparin prior to cannulation of CPB. Efficiency of heparin is performed in 3-5 minutes measuring active coagulation time (ACT). During cardiopulmonary bypass ACT must be maintained over 480 seconds. Because of individual patient respons to heparin and the effects of hemodilution and hypothermia on the ACT, anticoagulation can also be assessed by Medtronic Hepcon system. In few cases heparin resistance occure. It is present when heparine dose of 5 mg/kg fails to raise the ACT to an adequate level. More commonly it s noted in patients on preoperative heparin, IV nitroglycerin. It is usually related to antithrombin III deficiency.

**Prevention of perioperative bleeding**

Antifibrinolytic therapy have been demonstrated to reduce perioperative blood loss in cardiac operations. **Aprotinin**. It is serine protease inhibitor that has been demonstrated in numerous studies to be extremely effective in reducing perioperative bleeding and also in producing an antiinflammatory effect (32). In 2006 Mangano and coworkers (28) published an observational, multicenter, score adjusted study on 4,374 patiens. They demonstrated that patients receiving aprotinin had a double risk of acute renal failure, 55% increased risk of myocardial infarction and 181% increased risk of stroke. Aprotinin reduces bleeding but it is also a significant link to increased risk of morbidity and mortality. It has been stoped for using in many countries. But for example in Japan they continue to use it in cases of endocarditis because in this type of operations its efficiency is undisputable. Moreover the impact of patients morbidity and mortality using Aprotinin is still under discussion.

**Tranexamic acid.** During CPB releases plasmin and activates fibrinolysis. Tranexamic acid prevents plasmin formation and inhibits fibrinolysis**.** It has been shown to reduce perioperative blood loss in on-and off-pump surgery (3,6). Some studies have shown it to be as effective as aprotinin (7). Postoperative thrombotic

complications such as miocardal infarction, acute renal failure, stroke, pulmonary artery trombemboly where not founded when Tranexamic acid was administrated (26,27).

In several studies have shown topical use of tranexamic acid in the pericardial space to significantly reduce perioperative bleeding (1,2,12). Barica and coworkers (11) report of topical application of tranexamic acid in pericardial cavity. It was single-center prospective, randomized, double-blind trial, with 300 adult cardiac patients who were randomized into three groups. One group receive one million IU of Aprotinin, second group - 2.5 g of Tranexamic acid and third group - placebo topically before sternal closure. Bleeding rates values were significantly higher in placebo group. There were no found statistical differences between Tranexamic acid and Aprotinin groups. Also difference of blood product requirements was not statistically significant.

**Autologus blood withdrawal** – it has been shown to reduce allogen transfusion requirements and preserve red cells. However its efficacy in reducing perioperative bleeding is controversal (18).

**Rewarming of patient** till normothermia before the end of CPB. It could significantly improve coagulation function and prevent of postoperative bleeding.

**Cardiopulmonary bypass consedirations**

There are many factors for prevention of perioperative bleeding associated with cardiopulmonary bypass. One of that is using of heparin – coated circuit during bypass allows for a reduction in heparin dosing. It has been associated with reduced perioperative blood loss. Hematocrit level < 20% during CPB is a strong predictor of packed cell transfusions and higher mortality rate after surgery (22) however low intraoperative hematocrit levels dont predict excessive postoperative hemorrhage (13). In some studies retrograde autologus priming of the extracorporeal circuit has been shown to minimize hemodilution, thus maintaining a higher hematocrit and colloid oncotic pressure on pump (25).

Aviodance of cardiotomy suction also may reduce perioperative blood loss. Blood aspirated from the pericardial space has been in contact with tissue factor and contains high levels of factor VIIa, procoagulant particles and activated complement proteins and exhibits fibrinolytic activity. Blood aspirated from pericardial space consist very high concentration of inflalmmatory mediators, such as Il-6, however there were no data of Il-6 and TNF-alpha rising on patient's plazma after re-infusion.

It is unadvised to aspirante blood directly from pericardial space, it could be better to pump this blood via cell saver to wash it from activated components. Limitation of blood suction, reduces thrombin formation, platelet activation and sistemic inflammatory reaction.

Sirvinskas *et al.* (35) reports efficacy of collected and re-infused autologous shed mediastinal blood on a patient's in cardiac surgery. They concluded that re-infused shed mediastinal blood dont increase bleeding tendency and systemic inflammatory response. Conversely to this opinion there are also few studies reporting increased bleeding tendency after re-infusion of shed mediastinal blood.

**Management of mediastinal bleeding in ICU**

Excessive bleeding amount and time for re-operation in literature is defined variously. Excessive bleeding is defined as chest tube drainage greater that 3ml/kg/h in the first 3hours, continued bleeding of more that 200ml/h (10) or more that 200ml/h in the first 4 hours(19). Persistend bleeding must be treated immediately and agressively based on the suspected cause of hemorrhage. Management include:

1. Check of chest tube patency. Ongoing bleeding wihout drainage leads to tamponade.
2. Warm the patient to 37°C. Hypothermia produces a generalized suppression of the coagulation mechanism and also impairs platelet function.
3. Coagulation studies (PT, PTT, platelet count), ACT, also D-dimers, fibrinogen level, thromboelastography if necessary.
4. Maintenance of normothension and control agitation if the patient is awake and control shivering.
5. Increased level of positive and expiratory pressure (PEEP) to augment medistinal pressure has been shown to reduce bleeding.
6. Blood components should be based on suspection of the hemostatic defect, but transfuzion of allogeneic blood products is associated with many adverse affects. Patients needing surgical re-exploration have a significantly higher blood loss and need significantly higher amounts of fresh frozen plasma, packed red blood cells and platelet concentrates (31). **Fresh frozen plasm**a – contains all clotting factors except platelets. It is usefull if patient have hemodilution after CPB and there is progressive loss of coagulation factors during ongoing bleeding. Dose 10-15 ml/kg. **Cryoprecipitate** – it contains VIII and von Willebrand's factor and is also a source of fibrinogen (factor I) and XIII. It is usefull for patients with hypofibrinogenemia and von Willebrand's disease. **Platelets** – Should be given to the bleeding patient if the platelet count is less than 100,000/mkl. It is usefull when patient has platelet dysfunction after using of antiplatelet medications and IIb/IIIa inhibitors and following long duration of CPB. Platelet function is also impaired when hematocrit is less that 30%. **Packed red blood cells** – amount of packed red cell transfusion still is the main determinant of morbidity and mortality for patients requiring re-exploration due to bleeding. Hematocrit must be greater then 26-28% for patient who is bleeding to ensure tissue oxygen delivery. Dial and coworkers (13) found that strong predictor of packed red cell transfusion is severe intraoperative anemia (hematocrit < 19%). Blood transfusions more than 4 units increases risk of infections and operative mortality rate after on-pump surgery (15) and longer stay in ICU. Risk of development of infection is 3,9% in cases with 2 units whole blood transfused, 6,9% in cases with 3-5 units transfused and 22% in cases with 6 and more units of whole blood transfused.

**Medical treatment** in intensive care unit – include such kind of drugs: **Protamine**, should be given in a

dose 25-50 mg if the ACT is elevated. ACT should return in baseline after CPB but heparin rebound may occur in ICU and patient may start to bleed. ACT and rebound heparine can be assessed by Medtronic Hepcon system.
**Desmopressine** – Laupacis and coworkers (26) report that Desmopressine in dose 0,3mkg/kg i/v does not affect on bleeding rate and does not decrease rate of allogeneic transfusion rate as well, but it could be effective in patients who is taking Aspirin. Conversely to that in literature are few reports, that Demopressine should be given for patients who have tendency to bleed. It is usefull for patients with uremia and von Willebrand's disease as well. **Novoseven** – Recombinant Activated Factor VII. There are many studies approve its efficacy to decrease blood loos after on-pump cardiac surgery (21). But we should be also carefull with Novoseven because some of studies have been shown that Novoseven can increase risk of thrombosis. Therefore in cardiac surgery Novoseven could be recommended for patients with isolate VII factor deficiency. **Octoplex** – Prothrombin complex concentrate contains II, VII, IX, X factors and C and S proteins. It is efficacious and safe in immediate correction of dosage-dependent INR in patients who need rapid reversal of anticoagulant effect from the use of vitamin K antagonists (33). But we should be aware to use it on cardiac patients because Octoplex increases oncotic pressure and circulation volume and can produse heart failure.
**Urgent re-exploration must be done** when is presence of untapering mediastinal bleeding despite correction of coagulopathies, sudden massive bleeding, obvious signs of cardiac tamponade, cardiac arrest of a patient who continues to bleed urgent mediastinal reexploration must be done.
Re-exploration for bleeding is associated with increased operative mortality and morbidity. Ranucci and coworkers (31) demonstrated that patients who underwent a surgical reexploration had a higher moratlity rate 14,2% versus 3,4% who did not have re-exploration. The mean timing for surgical reexploration was 6,2 hours. Karthik and coworker (24) in 2004 published that patients needing re-exploration have a worse outcome in terms of morbidity but not a significantly higher mortality rate and the median time to reexploration was 8,5 hours.
Re-explorations very often is delay. Recently, Choong and coworkers (10) showed delaying surgical reexploration after 12 hours from the end of operation results in a longer stay in ICU, a higher need for intra-aortic balloon pump support, and increased mortality in a population of patients having undergone coronary revascularization. Conversely to this averment Ranucci and coworkers found that timing of the re-exploration was not associated with increased morbidity and mortality (31).

## CONCLUSIONS

More aggresive management and early reexploration is one of the most important factor in cases of mediastinal bleeding. It may reduce the requirement for homologus transfusions, reduce the risk of respiratory and renal insufficiency and may also lower the wound infection rate associated with an undrained mediastinal hematoma (24,17). Eventually it may reduce rate of mortality.
Careful monitoring of mediastinal bleeding is essential in ICU in first 30 minutes, in each hour during first 4 hours as well as in 24 hours and 48 hours from the end of operation. Evaluation of coagulation studies and in some cases thromboelastography if necessary.
Cardiac off-pump surgery could be significant way how to decrease incidence of bleeding and re-exploration rate. Risk factors associated with CPB undergoing on-pump cardiac surgery should be minimized as possible. It is poosible to use smaller volumes for priming of the extracorporeal system and to use close system as well as circuit oxygenator lines that causes less heamatological trauma.
Cooperation, understanding and co-decision making between ICU staff, anaesthesiologists and surgeons is essential. Moreover, clinical protocol for mediastinal bleeding and re-exploration management in cardiac surgery must be formed.

**Conflict of interest:** None

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**Table 1. Major risk factors for bleeding requiring revision**[a]

| |
|---|
| - Small body surface area |
| - Older patients |
| - Previous cardiac operations |
| - Previous cerebrovascular event |
| - Continuation of preoperative use of Aspirin, Clopidogrel and oral anticoagulants (Warfarin) |
| - Renal and/or hepatic insufficiency |
| - Prolonged cardiopulmonary bypass period |
| - Increased numbers of distal anastomoses and use of internal thoracic artery |

[a] (10,13,31)

**Table 2. Re-exploration rates**

| **Author of study** | **Re-exploration rate due to bleeding, reasons** |
|---|---|
| Choong, C.K., et al. Cambridge, United Kingdom[a] | Re-exploration rate – 5,9% |
| Hall, T.S., et al. Univeristy of California[b] | Re-exploration rate after coronary artery bypass grafting (CABG) – 3.6%<br>• Surgical bleeding 66%: from the graft – 39% and from the chest wall – 34.5%.<br>• Coagulopathic – 34%. |
| Hirose, H. and A. Takahashi Shin-Tokyo and Kobari General Hospital[c] | Re-exploration rate – 0.7%<br>• Bleeding from the chest wall - 82.5%, bleeding, from the graft -17.6% |
| Karthik, S., et al. Liverpool, United Kingdom[d] | Re-exploration rate – 3,1%.<br>• Graft anastomosis – 43%, sternal/left internal mammary artery – 26%,<br>• Unspecified – 18% |
| Kinduris, S., et al. Kaunas University of Medicine, Lithuania[e] | Re-exploration rate – 4,3% |
| Ranucci, M., et al. Milan, Italy[f] | Re-exploration rate – 2,2% |
| Wolfe, R., et al. Monash University, Australia[g] | Re-exploration rate – 4,9% |

[a] (10), [b] (19), [c] (20), [d (24), e (25), f (31), g (39)]