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Review Article

Consequences of Blood Loss in Cardiothoracic Surgery

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Abstract

Efforts to minimize perioperative blood loss in surgery in order to improve short and long- term outcome should be made, as implications extend considerably beyond the perioperative period. Minimally invasive approaches are associated with less bleeding. However, it is all the more important that the personnel involved with the procedure should be familiar with the maneuvers required, so as to be able to prevent and respond in a swift manner when bleeding does occur.

List of Abbreviations

ACA - aminocaproic acid
CABG - coronary artery bypass graft
CT surgery - cardiothoracic surgery
Cox regression - standardized coefficients in the regression model
DAPT - dual anti-platelet therapy
DIC - disseminated intravascular coagulopathy
EBL - estimated blood loss
EuroSCORE - European System for Cardriac Operative Risk Evaluation
HR - hazard ratio
IBL - intraoperative blood loss
MACE - major adverse cardiovascular event
MIE - minimally invasive esophageal surgery
NOACs - new oral anticoagulants
RAMIE - robotic-assisted minimally invasive esophageal surgery
RATS - robotic-assisted thoracoscopic surgery
RBCs - red blood cells
RR - relative risk
TXA - tranexamic acid
VATS - videoscope assisted surgery

Introduction

One of the key factors contributing to an increase in postoperative morbidity and mortality during cardiothoracic surgery is the large amount and rapid loss of blood [1]. During the cardiothoracic surgeries, the risk factors of blood loss are complex and diverse [2]. In some cases with moderate to severe bleeding, blood transfusion may be needed, but it comes with some risks like transfusion reactions, infectious diseases and allergic reactions [3,4]. Therefore, a wise perioperative identification of risk factors for bleeding is necessary for development of a treatment plan in order to avoid severe complications as hypovolemic shock, abnormal blood coagulation, even disseminated intravascular coagulopathy (DIC), multiple organ dysfunction syndrome (MODS) and possible death. Factors associated with higher incidence of bleeding in different cardiothoracic surgeries (CTS) and reported consequences are summarized in Table 1. Reduction of blood loss probably shortens hospital stay, decreases cancer recurrence, reduces morbidity and mortality and could be of benefit to cardiothoracic surgical patients [5,6].

***Table 1:** Factors associated with higher incidence of bleeding in different cardiothoracic surgeries, consequences and prevention/reduction methods*

	Causes	Consequences	Prevention/Reduction
General causes	Bleeding diathesis Anticoagulants use Reintervention Vessel injury Diabetes Neoplasia	Need for transfusion Hypovolemia Anemia Shock Death	Proper tissue handling/ hemostasis Search for bleeding sites Antifibrinolytics use
Lung surgery	Pulmonary vessel injury Extracorporeal membrane oxygenation (ECMO) Stapler failure	Hemothorax	Proper tissue handling/ hemostasis Search for bleeding sites
Cardiac surgery	Great vessel injury Heparin induced thrombocytopenia Duration of CPB Deep Circulatory Arrest	Tamponade Hemothorax	Use of cell saver Proper tissue handling Search for bleeding sites Antifibrinolytics use
Esophagectomy	Stapler failure Varices Anastomotic leak Vessel injury	GI tract necrosis Hemothorax Hemoperitoneum	Proper tissue handling/ hemostasis Search for bleeding sites
Thymectomy	Innominate vein injury Thymic vein injury	Tracheal compression	Proper tissue handling/ hemostasis Search for bleeding sites
Chest wall resection	Bone injury Vessel injury	Hemothorax	Proper tissue handling/ hemostasis Search for bleeding sites

CPB: cardiopulmonary bypass, **GI:** gastrointestinal

Blood Loss in Lung Surgery

There is no consensus whether blood transfusions are associated with worse outcomes after resection in lung cancer [7,8], including a systemic review of 19 studies [9]. However, some reports in literature showed how perioperative blood transfusions worsen the prognosis of patients with lung cancer, as the poorer prognosis was attributed to immune suppression [5,10].

Nakamura *et al.* [11] studied the long-term survival of patients according to the intraoperative blood loss (IBL). Firstly, IBL differed according to the operative choice, which is closely linked to the extent of lung cancer progression. The greatest amount of IBL was observed in combined resection, followed by pneumonectomy, lobectomy and sublobectomy ($p<0.0001$). They further analyzed the lobectomy group and noticed a significant difference in survival according to the volume of IBL (≥ or < 318ml) ($p<0.0001$), gender ($p < 0.0001$), pathologic stage ($p<0.0001$), histologic type (adenocarcinoma or non-adenocarcinoma) ($p < 0.0001$), and year of operation (1983-2002 and 2003-2012) ($p < 0.0001$) [11].

Effect of Different Surgical Techniques on Blood Loss in Lung Surgeries

A potential advantage of the introduction of minimally invasive surgery, like video-assisted thoracoscopic surgery (VATS), in controlling blood loss is performing smaller incisions compared to thoracotomy [12]. A meta-analysis by Wu *et al* [13] showed an advantage of VATS over thoracotomy in the management of chest trauma with regard to reduction of postoperative complications (relative ratio (RR: 0.47, $p <0.001$)), even more, smaller chest tube drainage volume, less amount of bleeding, shorter duration of tube drainage, hospitalization and operation time ($p<0.001$). Another meta-analysis [14] described similar results for Non-Small-Cell Lung Cancer (NSCLC). Robotic-assisted thoracoscopic (RATS) vs VATS is still controversial, according to two studies done comparing both techniques [15,16] which indicated the superiority of VATS in terms of less blood loss, less operative time ($p = 0.0362$) and less procedure cost by 44%. On the other hand, RATS may have a better mortality outcome [17]. Further studies are needed to assess whether (RATS) is equivalent, better or worse than VATS [18].

After VATS was introduced, further development of this procedure reduced the number of ports used, from multiple to single port in an attempt to reduce complications. Different recent meta-analyses studied possible advantages of one technique over the other as far as bleeding concerns, but controversies still persist. The biggest meta-analysis [19] with 39 included studies, showed less blood loss for single-incisional VATS vs. multi-incisional VATS (pooled standardized mean difference (SMD): -40, $p = 0.006$). However, other two smaller meta-analyses [20,21] with 11 included studies reported no significant difference between the two groups.

In lung transplantation recipients, it was acknowledged that blood transfusion can cause series of complications. In addition to the ordinary complications reported like transfusion reaction, transmission of infectious disease, it can cause transfusion related acute lung injury, allograft dysfunction and increase mortality [22,23]. A study by Triulzi and colleagues [24] showed that single lung transplantation required less blood products compared to double lung transplantations, attributed to higher surgical complexity. They also found that transplantations on cardiopulmonary bypass (CPB) needed more transfusions. Wang *et al.* [25] also found a higher use of blood products in patients with Eisenmenger syndrome and cystic fibrosis undergoing lung transplantation, as these patients need more frequently double lung transplants or because they had already undergone surgery, which is a risk factor for increased blood loss.

Blood Loss in Cardiac Surgery

Poorer outcomes were associated with large amount of blood loss that require re-exploration [26,27] and frequently these bleedings were treated with large amounts of blood transfusion [28]. Moreover, blood loss and replacement were very critical in pediatric patients especially with the use of CPB due to several contributing factors as the immaturity of the hemostatic system, cyanosis induced polycythemia causing hemodilution (low clotting factors and low platelets number) and low fibrinogen level. All of these made bleeding prediction important to improve survival [29]. Several risk scores showed that post-surgical blood loss can be predicted by a set of demographics, surgical characteristics, and medication use in cardiac surgery [30-32]. Cox-regression was used to predict the probability of the time-varying events. The risk for need for red blood cells (RBCs) transfusion was decreased if preoperative hemoglobin was more than 13 grams per deciliter (Hazard Ratio (HR) 0.89; p<0.001), intraoperative temperature more than 33.8 degrees Celsius (HR 0.88; p<0 .001), the use of aprotinin (HR 0.04; p<0.001) and the use of cell salvage (HR 0.15; p<0.001). On the other side, the risk of RBC transfusion was increased with increased fluid balance at 6 hours after surgery 0.52L (HR 1.20; p<0.001) and EuroSCORE (European System for Cardiac Operative Risk Evaluation) wasn't predictive (HR 1; p=0.68) [33]. A recent meta-analysis [27] studied the cardiac surgical sites of bleeding: blood loss in cardiac positions was identified in 40.9% of cases and mediastinal/sternal bleedings in 27.0% of cases, suggesting that two thirds of patients undergoing cardiac surgery will develop a surgical site bleed. The most frequent site of hemorrhage was the body of the coronary artery bypass graft (CABG) (20.2%), followed by the sternum (17.0%), vascular sutures (12.5%), the internal mammary artery harvest site (13.0%) and anastomoses (9.9%). The individual surgeon's impact on the risk of re-exploration seems to correlate with the amount of post-operative blood loss [34], therefore, suggesting that an accurate hemostasis during the intervention may reduce bleeding complications.

Table 2: *Risk factors that may have impact on the need for transfusion*

Type of surgery/drug	Procedure	Method	Risk factors that may have impact on need for transfusion & survival rate
Cardiac surgery	CABG especially ON-pump	Thoracotomy, VATS and RATS	Preoperative Hemoglobin Euroscore Intraoperative temperature* Cell salvage* Use of aprotinin* Fluid balance* Bleeding site
Lung surgery	Lung resection for cancer Lung transplantation	thoracotomy VATS Single port (less blood loss)* Multiple ports RATS	Extent of cancer progression* Intraoperative blood loss* histologic type* The use of CPB Single or double lung transplantation Type of disease in patient
Esophageal surgery	Esophagectomy	Open MIE RAMIE	Estimated blood loss MIE & RAMIE showed less blood than open* EBL is less in RAMIE compared to MIE in some trials

Thymic surgery	Thymectomy	Median sternotomy VATS RATS	Estimated blood loss VATS show less EBL than open technique* No difference between VATS to RATS
Chest wall surgery	Neoplasia Deformity	Nuss technique (less blood loss than Ravitch)* Ravitch techniques	Blood loss*
Oral Antico-agulants	------	------	DAPT*

* Statistical significance

CABG = coronary artery bypass graft, DAPT = dual anti-platelet therapy, DIC = disseminated intravascular coagulopathy, EBL = estimated blood loss, EuroSCORE = European System for Cardriac Operative Risk Evaluation, IBL = intraoperative blood loss, MIE = minimally invasive esophageal surgery, RAMIE = robotic-assisted minimally invasive esophageal surgery, RATS = robotic-assisted thoracoscopic surgery

Blood Loss in Esophageal Surgery

Esophagectomy is one of the most challenging surgeries to perform worldwide, and the open approach is associated with elevated complication rates, including significant blood loss [35,36]. Minimally invasive esophageal esophagectomy (MIE), as video-assisted surgery, was therefore developed and studied in order to provide evidences for the best surgical choice. A more recent robotic-assisted technique (RAMIE) is now being developed. A recent meta-analysis [37] study indicated a similar safety and feasibility of RAMIE and MIE in patients with esophageal cancer. No significant difference between the two techniques was observed regarding in-hospital mortality rate, postoperative complications (pneumonia, arrhythmia, chylothorax, empyema or anastomotic leakage), operation time and length of hospital stay. However, the meta-analysis showed that RAMIE was associated with a significantly fewer estimated blood loss (EBL) (p = 0.0075). Moreover, the vocal cord palsy rate was lower in the RAMIE group compared to MIE (p = 0.0447) [37]. As far as EBL concerns, only few of the included studies showed a significant difference between RAMIE and MIE. In the others, blood loss was shown to be less in RAMIE than MIE, but this was not statistically significant. Currently, Robotic-assisted Esophagectomy vs Video-Assisted Thoracoscopic Esophagectomy (REVATE): a randomized controlled trial protocol was published and estimated blood loss is one of the secondary outcomes [38].

Many meta-analyses [39-43] focused their attention on comparing the open technique to MIE. In particular, they all showed how MIE was associated with less bleeding compared to the standard approach. High heterogeneity was reported despite some patients matching for age and sex in some studies, highlighting how blood loss may be a very surrogate outcome, significantly dependent on surgeon and neoplasia features. Tumor characteristics matching was not performed in all studies, implying that patients with more advanced stage may have not undergone MIE, thereby favoring clinical heterogeneity between the groups [39-43].

Blood Loss in Thymic Surgery

The gold standard for treating thymic neoplasm is complete surgical resection through median sternotomy [44,45]. However, minimally invasive approaches are receiving growing interest as means of decreasing perioperative mortality and morbidity rates [45]. Progressive adoption of techniques like VATS or the more recent RATS in thymic surgery have prompted many surgeons to explore the use of these approaches for the resection of thymic tumors [46]. Unfortunately, no randomized controlled trial (RCT) has been designed to address the issue due to the rarity of the condition.

Recent meta-analyses have investigated blood loss outcomes comparing open thymectomy to VATS thymectomy [47,48], to RATS thymectomy [49] or both [50]. The results showed that minimally invasive techniques were associated with less bleeding compared to the open approach. When analyzing VATS vs. RATS, the meta-analysis by Fok *et al* [51] reported no significant difference between the two techniques.

Blood loss in Chest Wall Resection

Chest wall deformity, either for congenital or pathologic, may eventually require resection. Prior study [6] analyzed the outcomes of primary malignant chest wall tumors and showed that higher rates of blood loss (p=0.003) was an independent predictor of worse disease-free survival on multivariable Cox regression analysis.

Moa *et al*. compared two surgical techniques (the Nuss and Ravitch procedure) [52] in their pectus excavatum repair meta-analysis. The overall analysis revealed that patients in the Nuss group had less blood loss (pooled standardized mean difference = -1.68, 95% CI = -2.28 to -1.09, p < 0.001) than the Ravitch group.

Anticoagulants

The meta-analysis by Siller-Matula *et al*.[53] showed that patients in treatment with aspirin + clopidogrel (dual anti-platelet therapy [DAPT]) undergoing CABG was associated with a 2.5-fold increased risk of reoperation for bleeding (95% CI: 1.92–3.25; p<0.001) and a 1.47-fold increased risk of death (95% CI: 1.25–1.72; p<0.001). In addition, it did not diminish the risk for myocardial infarction (risk ratio (RR): 0.96; 95% CI: 0.75–1.25; p=0.18) or MACE (major adverse cardiovascular event) (RR: 1.16; 95% CI: 0.90-–1.50; p=0.30).

A recent meta-analysis by Columbo *et al*. [54] sought to determine the effect of perioperative bleeding risk associated with aspirin vs. DAPT in adults undergoing non-cardiac surgery. They reported that RR of transfusion in Aspirin was 1.14 (95% CI= 1.03-1.26, p=0.009) and in clopidogrel was 1.33 (95% CI=1.15-1.55, p=0.001). The RR of bleeding requiring reintervention in aspirin was 0.96 (95% CI=0.76–1.22, P = 0.76); 1.84 (95% CI=0.87-3.87, P = 0.11) in clopidogrel and 1.51 (95% CI=0.92–2.49, P=0.10) in DAPT. They concluded that at the time of non-cardiac surgery, antiplatelet therapy conferred minimal bleeding risk with no difference in thrombotic complications.

He *et al.* [55] in their meta-analysis analyzed the safety of new oral anticoagulants (NOACs) by comparing it with warfarin therapy in different surgeries. Compared to warfarin, NOACs have similar effects on embolism events (RR 0.85, 95% CI 0.65-1.16, P = 0.32). Dabigatran increased the risk of major bleeding (RR 1.37, 95% CI 1.06–1.78, P = 0.02) compared to warfarin, while Apixaban, on the other hand, reduced thrombotic events (RR 0.63, 95% CI 0.40-0.99, P = 0.04). NOACs therapy decreased thrombotic events in patients undergoing non-cardiac surgery (RR 0.68, 95% CI 0.50-0.92, P = 0.02), but not in cardiac surgery (RR 3.50, 95% CI 0.81-15.04, P = 0.09). Therefore, the authors concluded that patients undergoing non-cardiac surgery might benefit more from perioperative NOACs therapy. No difference in the risk of perioperative major bleeding (RR 1.00, 95% CI 0.76-1.32, P = 0.59) or all-cause mortality (RR 1.09, 95% CI 0.83-1.44, P = 0.53) between NOACs and warfarin was observed. Risk factors that may have an impact on the need for transfusion are shown in Table 2. Causes, sequelae, and prevention of blood loss are shown in figure 1.

Antifibrinolytics

Treatment for significant bleeding, both surgical and pharmacological, is not trivial and may result in further blood loss and large amount of blood transfusions. The use of antifibrinolytics can reduce blood loss in cardiothoracic surgery, trauma, liver surgery, solid organ transplantation, obstetrics and gynecology, neurosurgery and non-surgical diseases [56]. Antifibrinolytics are now the standard practice in cardiac and non-cardiac surgeries for perioperative blood loss prevention [57].

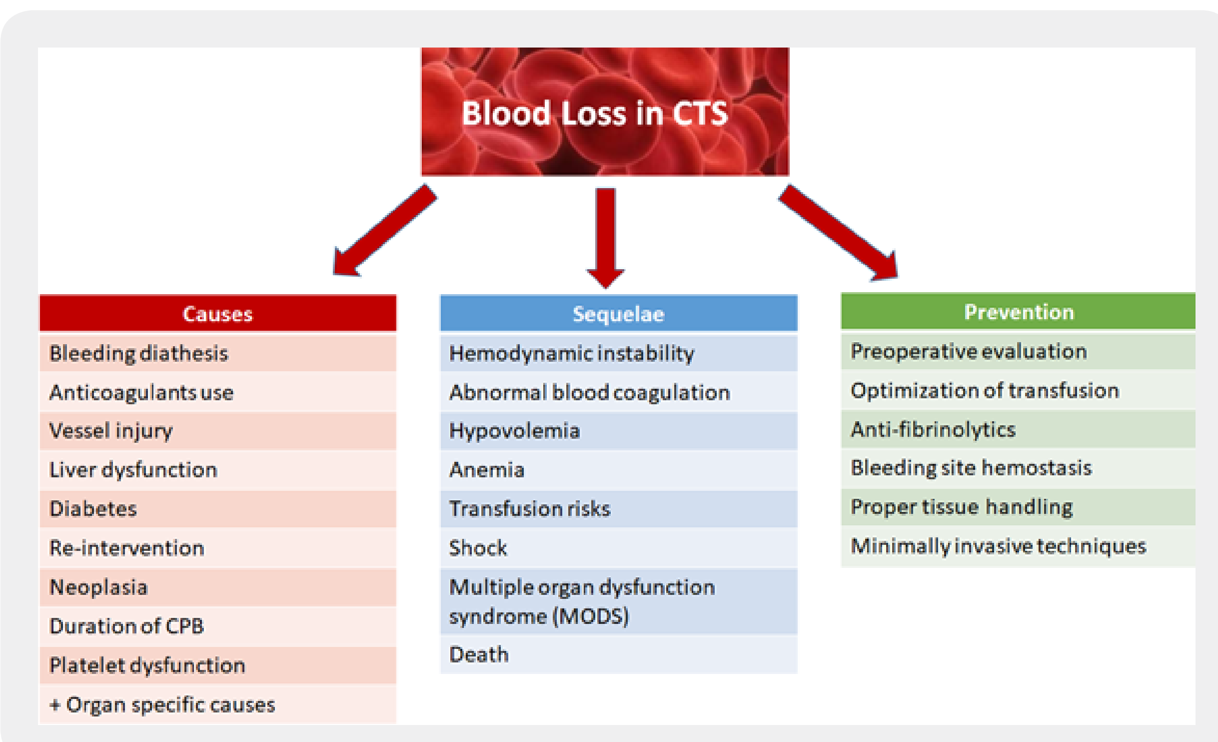

Figure 1: *Blood loss; causes, sequelae and prevention*

Different drugs can be used for this purpose and among these, tranexamic acid (TXA) and aminocaproic acid (ACA), both lysine analogs, and formerly aprotinin (a serine protease inhibitor), firstly withdrawn from the market and now relicensed in Canada and Europe [58]. Aprotinin was shown to be the only anti-fibrinolytic to reduce re-exploration rate [59] and to have reduced chest tube drainage [60] compared to lysine analogs. In fact, aprotinin is the strongest in reducing blood loss, blood transfusion, and possibly, return to the operating room after cardiac surgery, but associated with the highest side effects and mortality. On the other hand , according to a study published in 2011 by Martin *et al*, comparing the aprotinin to ACA in neonates undergoing cardiac surgeries where they found that aprotinin group has less intraoperative blood loss but there was no statistically difference in re-operation for re-bleeding nor number of transfusions [61]. In another study, ACA was the least effective but also the one with the least side effects, while TXA is somewhere in between [62]. In cardiac surgery, different studies [63-66] have reported that TXA inhibits plasmin-induced platelet activation during CPB, thus reducing excessive bleeding even in less invasive procedures like off-pump coronary artery bypass [67,68], which is already associated with less blood loss and transfusions. In the meta-analysis by Ker *et al*. [69], which included 129 RCTs, showed how the antifibrinolytic TXA during surgery reduces the probability of transfusion (RR 0.65, 95% CI 0.60-0.70, $p < 0.001$). TXA did not come without critical side effects. In fact, moderate to high doses were associated with an increased risk of seizure in cardiac surgeries [56-59]. No evidence till the present time to assess that TXA is associated with increased risk of thrombo-embolic events.

Two articles [70,71] showed for the first time the superiority of TXA and ACA over aprotinin, due to its increased potential risk of renal toxicity, cardiovascular and cerebrovascular events and mortality, which then led after numerous following studies (including the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) [72]) to its withdrawal from the market. A number of discussions and arguments have followed this decision. The whole issue was then re-examined and data from the studies re-evaluated in the following years. Given this new analysis and review of the data on aprotinin therapy showed no conclusive safety signal, regulators in Canada and the European Medicine Agency, together with their independent expert panel, agreed to relicense aprotinin for use during cardiac surgery. Despite the beneficial evidence of aprotinin in cardiac and non-cardiac surgery, the totality of the data for the safety of aprotinin was largely derived from randomized placebo-controlled studies performed mainly in patients having myocardial revascularization. Therefore, the current indications for aprotinin are for isolated CABG operations using CPB only.

Conclusion

Prevention and reduction of perioperative bleeding decreases morbidity and mortality in cardiothoracic surgery, and also results in shorter hospital stay, lower treatment cost [26,73]. Efforts to minimize perioperative blood loss in surgery in order to improve long- term outcome should be made, as implications extend considerably beyond the perioperative period. Reviewing the literature for cardiothoracic surgeries, minimally invasive approaches are associated with reduced bleeding compared to open surgery. However, it is all the more important that the personnel involved with the procedure should be familiar with the maneuvers required, so as to be able to prevent and respond in a swift manner when bleeding does occur.

Finally, a paramount aid in reducing blood loss the use of minimally invasive approaches , the cautious use of DAPT in cardiac and non-cardiac patients as they increase the risk of intraoperative bleed without much effect in preventing myocardial infarction and thromboembolic events [53]. Use of anti-fibrinolytics was shown to be effective in different surgeries including cardiothoracic surgery [57,74-77].

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