Patient Blood Management in Cardiac Surgery

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Editors

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Preface

Patient blood management (PBM) is an evidence-based, multidisciplinary approach that aims for a more conscious practice of hemotherapy, i.e., transfusion of blood products, in clinical medicine. This is, in particular, important for cardiac surgery where a relatively high percentage of blood resources are used. PBM may contribute to a reduction in allogeneic blood transfusion requirements and healthcare costs and furthermore to a reduced number of postoperative complications and improved patient outcome. PBM transcends individual medical disciplines and consists of a chain of care that spans the preoperative, intraoperative, and postoperative period. It, among others, involves the treatment of risk factors for blood transfusions (e.g., preoperative anemia or anticoagulant treatment), maintenance of hemostasis, minimization of blood loss, and conscious reservation of blood transfusions to patients who are at ischemic risk due to acute or chronic anemia.

PBM in cardiac surgery requires teamwork and a multidisciplinary approach. Without involvement of all members of the surgical team, including the surgeon, anesthesiologist, clinical perfusionist, nurses and intensive care specialist, the benefits of PBM cannot be fully exploited. Moreover, the surgical procedures, the unique patient characteristics, and the impact of cardiopulmonary bypass distinguish this discipline from other surgical specialties.

The present book has adopted the interdisciplinary approach of the PBM concept by not only combining the cardiac anesthesiologist's, surgeon's, and intensivist's view but also collecting the best evidence and knowledge for each step in the chain of measures that can be taken in favor of the patient. Using the evidence and experience of the authors, this book shows that PBM has been developed from a more and only blood-saving concept to a treatment concept that is driven by the improvement of the overall patient care in cardiac surgery.

We are happy to have the chance to edit and contribute to this book that comprises a large number of focused topics that appraise the latest scientific and clinical evidence. The book covers several PBM measures, spanning from the preoperative to the postoperative care of the cardiac surgery patient. When we started this project, we were convinced that only a "practical" PBM book will have the chance to change daily practice in the operation theater or the intensive care unit. We are now proud to present this book that contains various clinical treatment protocols including dosing schemes that were derived from scientific evidence and clinical experience.

We hope in the name of all authors and contributors that our book serves the overall objective of PBM to enhance the quality of care for our patients in cardiac surgery.

Berlin, Germany — Christian von Heymann
Amsterdam, The Netherlands — Christa Boer
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Contents

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Abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ANH	Acute normovolemic hemodilution
aPTT	Activated partial thromboplastin time
AT	Antithrombin
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
CECC	Conventional extracorporeal circulation
CI	Confidential interval
COX	Cyclooxygenase
CPB	Cardiopulmonary bypass
CT	Clotting time
DAPT	Dual antiplatelet therapy
DDAVP	Desmopressin
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
EACA	ε-Aminocaproic acid
EACTA	European association of cardiothoracic anaesthesiology
ECC	Extracorporeal circuit
ECMO	Extracorporeal membrane oxygenation
EuroSCORE	European system for cardiac operative risk evaluation
FFP	Fresh frozen plasma
FIBTEM	Rotational thromboelastometry test for fibrinogen levels
GFR	Glomerular filtration rate
Hb	Hemoglobin
Hct	Hematocrit
HES	Hydroxyethyl starch
HIT	Heparin-induced thrombocytopenia
HR	Hazard ratio
ICU	Intensive care unit
INR	International normalized ratio
IPC	Intermittent pneumatic compression stockings

LD	Leukocyte depleted
LMWH	Low molecular weight heparin
MI	Myocardial infarction
MiECC	Minimally invasive extracorporeal circulation
MUF	Modified ultrafiltration
NOAC	Non-vitamin K oral anticoagulants
OAC	Oral anticoagulation
PAI-1	Plasminogen activator inhibitor 1
PBM	Patient blood management
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
PFA	Platelet function analyzer
PMEA	Poly2-methoxyethylacrylate
POC	Point-of-care
PRBC	Packed red blood cells
PT	Prothrombin time
RAP	Retrograde autologous priming
RCT	Randomized clinical trial
ROTEM	Rotational thromboelastometry
RR	Relative risk
TEG	Thromboelastography
TF	Tissue factor
t-PA	Tissue plasminogen activator
TRALI	Transfusion-related acute lung injury
TRAP	Thrombin receptor-activating peptide
TXA	Tranexamic acid
UF	Ultrafiltration
UFH	Unfractionated heparin
VKA	Vitamin K antagonists
VTE	Venous thromboembolism
vWF	von Willebrand factor

Team Approach

1

Benjamin Porter and Harjot Singh

Case Vignette

It is approaching the end of the day shift when a nurse informs the intensive care doctor about an excessive loss in the chest drains of a patient that was admitted to the intensive care unit 45 minutes earlier following aortic valve surgery. The unit intensive care doctor, who is busy attending to another patient, instructs the nurse to contact the cardiothoracic surgical registrar (trainee surgical doctor). Instead of calling the registrar who assisted with the case, the nurse contacts the on-call registrar. The on-call registrar is informed that during surgery, there were some concerns raised that the patient was excessively "oozy" despite normal coagulation. This fact was not documented in the surgical operation notes. The on-call registrar assumes that the operating registrar knows about the problem and is at the bed side. The case remains unattended for a further 25 min before the surgical registrar arrives. At this point the chest drain output has increased to an alarming level. The nurse in-charge of the shift escalates the matter to the senior surgeon but there is a confusion about which consultant is on-call and during this delay and the distraction of discussions, the patient progresses to have a cardiac arrest which requires emergency resternotomy.

Why Is It Important?

Cardiac surgery has always required the collaboration of experts, but regardless of this longstanding use of teams, outcomes are not always favorable. It is unreasonable to assume that all adverse outcomes are preventable, but the majority of clinical staff will recognize that avoidable harm does occur.

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The United Kingdom Department of Health's "*An Organisation with a Memory*" published in 2000 [1] and the US Institute of Medicine's report "*To Err Is Human*" published in 1999 [2] both highlighted the frequency with which failures in teamworking and non-technical skills led to adverse outcomes and near misses. Both these national publications have raised awareness internationally of the need for a better understanding, and improved training, in system design and non-technical skills as a method of reducing harm and improving quality. This chapter will discuss the definition of teamwork in the context of adult cardiac surgery and outline the wider topics of system ergonomics and non-technical skills. It will discuss practical ways to improve outcomes through specific interventions to enhance teamworking in your own environment.

Definition of Teamwork

Salas et al. define teamwork as "*a distinguishable set of two or more people who interact, dynamically, independently, and adaptively toward a common and valued goal, who have each been assigned specific roles or functions to perform, and who have a limited lifespan of membership*" [3]. The importance of this definition is twofold: firstly, that the team members must interact and communicate with each other, and secondly that they must share and believe in a common goal.

Contemplate the typical make up of a cardiac surgical team. The knowledge and skills of this team are vast, and it becomes easy to see how having a shared mental model becomes very difficult. The overall goal of a positive patient outcome is likely to be shared, but when specific aims are identified, not everyone's targets are aligned. Consider the common scenario of fluid balance in the post-operative patient. The intensivist may feel that the patient is hypovolemic and requires fluid to optimize cardiac output, while the cardiac surgeon may wish to increase the inotropes to help improve myocardial function. Neither strategy is wrong because fluid management in this patient population can be extremely difficult, and both members want the best for the patient, yet without a shared mental model, conflict arises. This is where non-technical skills really come into play, and it is helpful to look at models of teamworking to understand how to get the performance outcomes desired. Team briefings, handovers, and verbalization of decision-making processes are particularly useful methods of establishing a shared mental model. Rhona Flin, in her seminal text on non-technical skills, "*Safety at the Sharp End*" describes four elements of teamworking: support others, manage conflicts, exchange information, and coordinate activities (Fig. 1.1) [4].

These four elements are the processes that lead to performance outputs, but there are many factors that influence them, for example, leadership, individual attitudes and biases, team structure, culture, available resources, environment, and norms (comfortable unconscious ways of working).

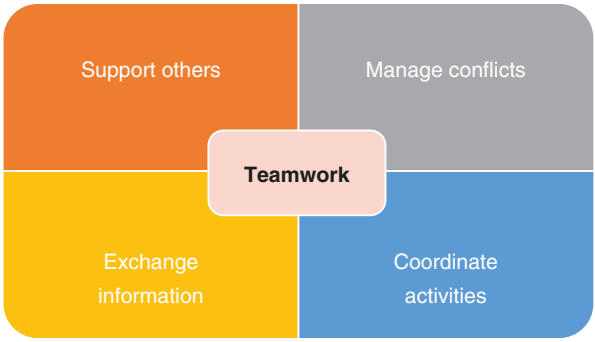

Fig. 1.1 Elements of teamworking

Supporting Others

Team members must pay attention to the workload of others in their team and support them by recognizing cognitive overload and offloading their colleagues when appropriate. Cognitive overload is often sighted as a causative factor in critical incident analysis. It is important to remember that people become overloaded at different levels and in different circumstances. Fatigue, stress, and hunger all affect our ability to work efficiently. It is part of the team's function to identify cognitive overload and allocate adequate resources to optimize performance.

Education of team members is a vital part of providing support. Adequate training in interpretation of routine lab and point of care blood results, resuscitation, and efficient preparation of patients for theater will enhance the care that the bleeding post-cardiac surgery patient receives. Prompt and effective resolution to coagulation problems and optimization of physiology will reduce secondary organ dysfunction.

Social support is also vital to effective teamwork. Individual personalities and attitudes need to be compatible to help develop working relationships, and team members must be open and tolerant of others viewpoints and previous experiences. An open culture and integrity among members will vastly improve the team's performance. Members must take ownership of their tasks and support others in completing theirs. Team members must ensure their own competence to undertake their role; otherwise, credibility is lost and conflict may arise. It was Belbin's conclusion in 1970's that it was the non-technical skills and behaviors that affected outcomes far more than the knowledge or intellect of the team [5]. Belbin went on to describe the nine team roles, which must be fulfilled in order for a team to be successful. Equally the balance of roles was found to be important, with too many members in one role and insufficient of another resulting in less successful teams. The fundamental idea that Belbin highlights is that it is as crucial to understand the strengths and weaknesses of other team members as it is to understand your own and facilitate discussion about it.

Managing Conflict

Perhaps counterintuitively, conflict among team members is vital to ensure creativity and optimum team performance, but this conflict must be managed. Conflict occurs because one section of a team holds behavioral preferences or attitudes which are incompatible with another, or because a mutually desired resource is limited. It is important for individuals to consider the knowledge, skills, and previous experience of other team members prior to embarking on a decision. A useful skill when making complex team decisions is to ask the rest of the team to give reasons why following a particular course or action is not a good idea. As an example, the cardiac surgeon wishing to take a bleeding post-operative patient back to theater for re-exploration could ask, "Give me two reasons why I should NOT take this patient back to theater?" The team is then empowered to offer their mental model of the situation. These perceptions will often deliver new information or a different perspective that had not been anticipated previously, which may or may not influence the situation. Most importantly it also allows the verbalization of the decision-making process, thereby enhancing the whole team's understanding of the situation. In this example team members may announce a newly received abnormal blood result that could be corrected (such as a coagulation deficit or heparin rebound) or ask if administration of an antifibrinolytic has been considered.

Members of any cardiac surgical team will possess overlapping skills and responsibilities, and this can often be a source of conflict. This concept of role blurring, as described by Marino [6, 7], can lead to team member disengagement and bitterness. Providing an opportunity to clarify expectations and renegotiate roles will help reduce this conflict. Junior staff should have a low threshold to raise concerns or discuss arising conflict with senior members of the team. Explicit trigger points and clear escalation pathways are helpful in facilitating this. Senior members of the team should have a willingness to seek external expert help for difficult decisions in complex patients, for example, through second opinions or involvement of other specialties such as hematology. Specialist involvement becomes even more important in patients that have non-cardiac comorbidity.

Dealing with conflict can be difficult. In 1979 Rahim and Bonoma elaborated on 5 previously identified conflict management strategies (Fig. 1.2) [8]. They highlighted the importance of the difference of conflict resolution versus conflict management: Conflict resolution implies elimination of the conflict, whereas conflict management infers that a negotiated and shared understanding is the aim of the conflict handling process. Conflict management, therefore, aims to utilize arising conflict to improve the team's performance rather than eliminate the creativity that conflict can provide to a team.

Managing conflict so that it is a healthy part of the cardiac surgery team requires team members to identify when conflict has arisen by understanding the relationship between their concern for others balanced against their own self-interest. Management of conflict is perhaps best understood through game theory modeling commonly used in economics and psychology. Zero-sum styles, where if someone takes more, someone else has to have an equal amount less (the total resource must

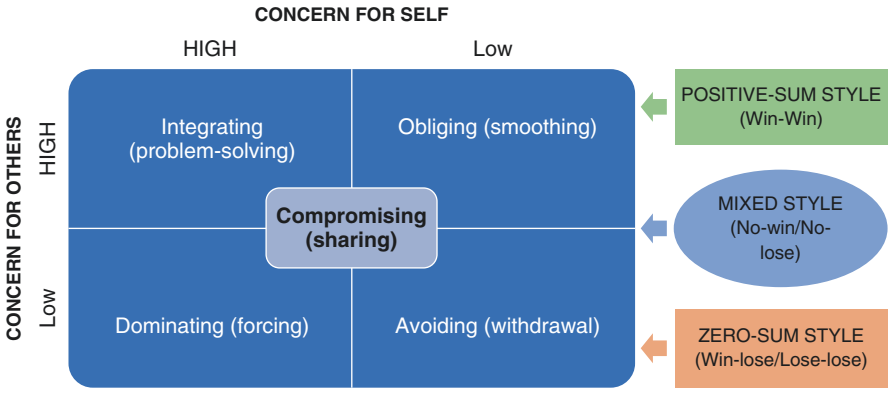

Fig. 1.2 Conflict management styles—replicated with permission from the publisher [8]

always add up to 1), are sometimes useful; for example, when you are certain the other party is incorrect in their assumptions or are unsure your own view point is correct (*forcing or withdrawing styles*). The withdrawing style can also be used when somebody wishes to sacrifice something now for a potential gain in the future. Non-zero sum styles are where both parties involved in the conflict can gain (*problem-solving or smoothing styles*) or where no one loses out (*sharing*).

The teams should have a working knowledge of these when there is a root cause analysis of a return to theater for bleeding to aid or enhance team performance. Such aspects are applicable to all morbidity and mortality analyses.

Exchanging Information

The exchange of information through both verbal and non-verbal means is a fundamental part of teamworking. Communication has the largest impact on clinical safety and outcomes of all the non-technical skills [1, 2, 9–11]. These aspects are demonstrated throughout the management of a patient undergoing cardiothoracic surgery.

Communication failure has been categorized by James Reason (most famous for his Swiss cheese model of organization accident causation) into system failures, message failures, and reception failures [12]. System failures occur when there is no communication between two parties, for example, someone who requires information is not on an e-mail distribution list or has no mobile phone reception. When a patient deteriorates in the night after cardiac surgery the on-call surgeon may be informed but the operating surgeon may be subject to a system failure of communication. In this instance it is possible the operating surgeon has a key piece of information that the on-call team taking the patient back to theater need in order to provide the best outcome. Clear escalation pathways should exist both to minimize conflict and appropriately communicated with all involved parties.

Message failures occur when the transmission is possible but where missing or incorrect information is sent, and *reception failures* occur when the message is misunderstood or do not arrive on time. These failures may be due to: cultural or language barriers, bias or previous experience affecting expectations, emotional state, fatigue and stress, cognitive workload, and physical barriers such as deafness or a noisy environment. Instructing colleagues to order investigations or blood products without explaining the rationale behind these decisions can lead to misinterpretation and message failure. Strong paths of communication from the laboratories and blood bank should be established to ensure rapid and effective communication during time critical bleeding emergencies. This may involve having the bed side presence of laboratory staff to ensure blood products are managed and replenished in a timely manner. Standard operating procedures for the availability, and timely delivery of blood products to the bedside should be robust to allow for times of extraordinary demand. Rhona Flinn describes several methods for improving communication within and between teams, namely, explicitness, timing, assertiveness, and active listening. Some examples are shown in Table 1.1 [4].

Coordination

Good coordination of a team requires three things: effective leadership, a comprehensive shared mental model, and effective communication.

Table 1.1 Methods for improving communication within and between teams, namely, explicitness, timing, assertiveness, and active listening

Method	Rationale	Examples
Explicitness	• Avoids ambiguity • Improves clarity	• Declare responsible individual to liaise with blood bank • Use a succinct message to avoid cognitive overload of receiver
Timing	• Avoids interruptions • Information is given at the relevant time • Reduces distraction and task interruption	• Ensure the surgeon is ready to listen by either waiting for a pause in concentration or draw their attention prior to delivering important information • Deliver the correct information as it is required, for example, state the ACT prior to cannulation of the aorta
Assertiveness	• Avoids passive communication approach • Helps overcome hierarchy	• Use a staged and proportional increase in verbal and non-verbal cues to ensure the message is received
Active listening	• Acknowledges understanding • Consolidates information received	• Avoid completing others sentences • Avoid interruptions during the WHO team brief • Ask questions to clarify ambiguity, for example, to ensure the correct replacement valve is chosen • Paraphrase information to demonstrate understanding

In 2017 the Faculty of Medical Leadership and Management published the *Leadership and Management Standards for Healthcare Teams*, which encompasses four main domains applicable to effective leadership and teamwork [13]. These four domains encompass culture, vision and strategy, management, and people and relationships. This document provides some fundamental principles about how to effectively coordinate a high functioning team and allow it to control variance, improve quality, and enhance the shared mental model. The faculty also produces a self-assessment tool for healthcare teams which allows teams to reflect on their collective performance and quickly identify areas of strength or improvement goals [14].

Leadership requires many skills including the use of assertiveness, providing and maintaining standards, planning and prioritization, and managing workload and resources [4]. Some decisions are rule-based and simple to implement, for example, delivering defibrillation. These rule-based decisions are useful for life-threatening emergencies, but under stress or unfamiliar circumstances can be incorrectly applied or fail to consider other factors which require thought and understanding. Junior rotational staff are likely to be familiar with the standard adult resuscitation guidelines but may not be aware of the alterations made to these guidelines in the management of the post-cardiac surgery patient. Training and education in cardiac advance life support for all staff will improve coordination among team members who, during an emergency, will have a common understanding of the management pathway. The common language used as part of adult cardiac life support training will allow rapid and coordinated escalation to resternotomy when required in an exsanguinating patient.

The majority of decisions that are made by teams, however, are not dire emergencies and there is usually a minimum of a few minutes to think. This is where models or tools can improve the decision-making process and facilitate the best choice of action with the resources and time available. One example of a decision-making tool for more complex decisions is t-DODAR (see Table 1.2), an

Table 1.2 The t-DODAR system, a decision-making tool for more complex decisions

	Task	Description
t	Time	Assess how much time is available to reach the decision
D	Diagnose	Consider possible diagnoses and avoid confirmation bias by asking the other team members what they feel the diagnosis is rather than asking for confirmation of your own diagnosis
O	Options	Consider the options available to manage the situation given the time and resources available and the diagnosis
D	Decide	The team leader needs to lead on making a decision and get agreement from the team. If agreement cannot be found the team leader is responsible for explaining their decision choice to the team. If the team feel the decision is dangerous they must clearly communicate this
A	Assign Tasks	Assign roles to team members to facilitate the plan that has been made
R	Review	Undertake frequent reviews until the task is complete to allow changes to be made to the plan and to maintain situational awareness

acronym taught to airline pilots, but applicable to cardiac surgery [15]. It provides a framework to help reduce cognitive biases and encourages a team approach to decision-making.

Within cardiac surgery the team leader will vary depending on the situation. In the theater environment the team leader is often a senior member of the nursing team, who has the expertise to coordinate the team's activities, liaise with external departments, and promote a positive culture within the operating theater. It is the team leader's role to help ensure a shared mental model. For example, during the World Health Organization's team brief they will need to collaborate with the whole team in order to ensure that the operating surgeon, anesthesiologist, perfusionist, and scrub team have the opportunity to vocalize their plans and any anticipated risks for the cases that day. It is vital to avoid planning, briefing, and checklists during periods of high stress and workload as the risks of error increase. It is also extremely difficult for the theater team to function effectively if the individual members do not understand why particular aspects of patient care might deviate from expectation. A team with a shared mental model will have a far better ability to adapt to unanticipated events, by behaving in a more appropriate and predictable fashion.

During critical incidents the leadership role may move toward another member of the team. For example, on intensive care it may be the consultant anesthesiologist or lead intensive care nurse. These individuals are likely to have better situational awareness and can help to reduce the surgeon and nursing team's cognitive load and allow then to focus on their allocated roles and tasks.

Improving Teamwork in Cardiac Surgery

James Reason classifies the factors leading to medical errors as: team factors, task factors, situational factors, and organization factors [16].

Team Factors

In healthcare teams often come together for only short periods of time. The team will be made up of individuals with very specific skill sets, performing a specific task, but the people performing these skills may vary from day-to-day. This has its own challenges, but having standardized ways of working, a robust education program and ensuring closed-loop communication will improve performance. The behaviors and attitudes that team members need to develop include adaptability, sharing situational awareness, coordination, and communication. Introducing briefings and simulations to prepare for common or serious cardiac surgical emergencies (for example, advanced cardiac life support, massive hemorrhage, expedient return to bypass or resternotomy) improves teamworking. Team members checking and communicating with each other during periods of high workload heightens alertness

Table 1.3 Situational awareness levels

Level	Description	Example
Perception	Perception of data and the environment	Looking at the monitor and noticing the blood pressure is very low and the chest drain output has been minimal for the past hour when previously it had been high
Comprehension	Comprehension of the meaning and significance of the data relevant to the situation	Recognizing that this could be cardiac tamponade and needs immediate action
Projection	Perception and anticipation of future states and events	Anticipate that the patient may require blood products or need to return to theater urgently

and improves situational awareness, ensuring not just perception, but comprehension and projection (Table 1.3).

Task Factors

Taskwork reflects the skills and behaviors that team members must have in order to complete their role. Recognizing and adjusting tasks that are susceptible to failure, misinterpretation, or repeated errors are crucial steps in mitigating risk. For example, instead of someone copying down blood tests results into the medical records, which is prone to transcription error, redesign the task to mitigate this. For instance, ensuring the order in which the tests are listed on the pro forma mimics the sequence of the results as shown on the screen or the development of an electronic system which would negate the need for transcription. This might be pertinent to the perfusionist or anesthesiologist documenting blood gas results in theater.

Cross training is also a useful way to promoting better teamworking. This is where a team member shadows or undertakes another team member's role to improve their understanding of others roles and responsibilities. For example, the critical care nurse may spend time in theater with the scrub nurse and surgeon to help understand the process of resternotomy.

Situational Factors

During his research Reason identified situational factors that most commonly led to error. These included unfamiliarity with the task, time limitation, poor human–system interface, misunderstanding of the task, and inadequate checking. Many of these can be avoided with engaged briefings, and adequate staffing and resources. Ensuring effective handover between shifts by reducing cognitive overload and utilizing electronic or written communication tools will benefit the team and the patient. Task training either through supervised activity or simulation should be offered to all those staff who may be working as part of the team to ensure familiarity with common and critical tasks. Other factors such as sleep disturbance, a hostile

environment (both psychologically such as aggression, and physically such as too hot), and boredom also contribute to an increase in risk. The case that comes out of theater shortly before a change of staff is particularly prone to adverse outcomes if handover is not robust.

Organizational Factors

The development of a positive culture for incident and excellence reporting will allow improved teamworking and should focus on learning from previous system failures and successes rather than apportioning blame to individuals. A contemporary, candid, and multidisciplinary clinical governance program will be fundamental to any cardiac surgery center looking to deliver safe and quality patient care. Encouraging the team to embrace diversity, listen to other's thoughts, and value different perspectives will all be developed through promoting an open organizational culture. Improvements in quality and safety through meaningful audit and quality improvement projects will enhance teamworking through development of team self-awareness and interdependence. Participation in research programs and collaborative working between local and national cardiac centers will lead to the sharing of best practice and the development of a dependable evidence base. Enrolment and contribution to national and international registries using appropriate quality indicators should allow early identification of deviations of practice, and rapid resolution of inadequate care, through support and collaboration.

Implications for Daily Practice

In summary, while the expert clinical knowledge and skills shared in this book are fundamental to the management of bleeding in the pre-, intra-, and peri-operative periods of cardiac surgery, the non-technical skills underpin the safe, efficient, and quality outcomes that we are all striving to achieve. Improving non-technical skills through effective quality improvement programs and by developing a positive culture to learn, we can develop cardiac services that we can be proud of.

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Part I

Identification of Patients at High Risk for Bleeding

Definition and Risk Factors of Bleeding

2

Michael I. Meesters and Christa Boer

Case Vignette

A female patient of 74 years was scheduled for aortic valve and coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass. Her medical history included previous myocardial infarction and a percutaneous coronary intervention. She received aspirin, simvastatin, and metoprolol. The patient had a preoperative hematocrit of 40% and a normal platelet count. Due to her low body surface area she dealt with severe hemodilution from the circuit prime.

After weaning from bypass, cell salvaged blood was retransfused, and the patient received fibrinogen concentrate and one unit of packed red blood cells. However, upon admission to the intensive care unit chest tube production remained high, and this continued for the first hours. Based on the assumption that the bleeding problem was caused by hemodilution issues, the attending team treated her with procoagulants and allogeneic blood transfusions to maintain hemodynamic stability.

Due to the continuation of high chest tube production she was scheduled for re-exploration 6 h following surgery, and a surgical bleeding due to a leaking anastomosis was found. After surgical repair, the patient returned to the intensive care unit without further requirements for blood transfusion. The postoperative course was uneventful with discharge at one week after surgery.

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Why Is It Important

Major hemorrhage and blood product transfusion in cardiac surgery is highly variable among centers [1]. Although the definition of major blood loss is controversial, it is assumed that bleeding and the transfusion of even a single packed red blood cell may be associated with reduced outcome [2]. Therefore, it is warranted to reduce blood loss. Patient blood management (PBM) has been developed to decrease blood loss and subsequent unnecessary blood product transfusion [3].

Patients undergoing cardiac surgery may suffer from bleeding complications with a surgical or non-surgical cause. The first step in patient blood management is to identify patients at high risk for transfusion as these individuals may benefit most from PBM interventions. By addressing their specific risk factors patient-tailored interventions can be applied to optimize patients' red blood cell volume and reduce coagulopathy. In this manner blood loss is better tolerated and decreased, leading to reduced morbidity and mortality. The purpose of this chapter is to discuss different definitions and predictors of bleeding in cardiac surgery.

Surgical and Non-Surgical Bleeding

Cardiac surgery with cardiopulmonary bypass (CPB) is known to be associated with a high risk of bleeding and blood transfusions. This is mainly caused by the size of the surgical wound and the need for full anticoagulation during the use of CPB. While perioperative bleeding is associated with adverse clinical outcomes, patient blood management (PBM) strategies are increasingly implemented to reduce the risk for bleeding.

Bleeding can have a surgical origin due to tissue injury or trauma, and this usually requires rapid mechanical control by the surgeon to limit the volume of blood loss. In a recent meta-analysis, it was shown that in two-thirds of patients requiring re-exploration for bleeding following cardiac surgery, a surgical site bleeding is discovered. The main sites of bleeding were the body of the graft, the sternum, vascular sutures, and anastomoses and the internal mammary artery harvest site [4].

The cause for non-surgical or microvascular bleeding (oozing) is more complex, and frequently comprises a combination of tissue injury, coagulation factor deficiency, hemodilution, body temperature, and anticoagulation strategies. It requires a multimodal diagnostic and therapeutic approach to stop microvascular bleeding, which is described in subsequent chapters.

Estimation of Perioperative Blood Loss

The volume of perioperative blood loss or postoperative allogeneic transfusion requirements are the most commonly used estimators for bleeding. In patients undergoing coronary artery bypass graft surgery, it was shown that the total blood volume of patients reduces by 18%, while the red blood cell volume reduces by

38% [5]. The use of blood saving techniques, like cell salvage, however limits the relative loss of red blood cell volume significantly, and intraoperative measurements of blood loss are therefore less frequently reported.

With respect to postoperative blood loss, chest drainage volume and allogeneic blood transfusions are the most commonly used estimates, but variations from bleeding volume corrected for body weight and duration to number of allogeneic transfusions can be found in the literature. Postoperative chest tube drainage or transfusion requirements are easily quantifiable, and are used as an outcome measurement in clinical trials [6]. However, it is difficult to define which cut-off values for blood loss or transfusion rates are related to adverse outcomes. While definitions may vary, the final estimate of the severity of bleeding should also include the individual patient characteristics, underlying diseases and the capacity of the patient to deal with blood loss.

Risk Factors for Postoperative Bleeding

Risk factors can arbitrarily be divided into different categories such as patient-related vs. procedure-related or surgery-related vs. anesthesia-related. However, for clinical purposes it can be more useful to distinct modifiable and non-modifiable risk factors. Modifiable risk factors can be adjusted in order to reduce blood loss in (general) clinical practice. Non-modifiable risk factors on the other hand are useful to identify patients at increased risk for bleeding. In these high-risk patients, additional measures (e.g., higher dosage of antifibrinolytic treatment, the change of the type of antifibrinolytic, the use of a device for heparin titration or a mini extracorporeal circuit, etc.) can be taken to reduce blood loss. These measures can include a higher vigilance, and more aggressive and prompter treatment of coagulopathy.

Modifiable Risk Factors

Modifiable risk factors for bleeding and transfusion are listed in Table 2.1. As mentioned, these factors can be useful to change practice for all patients, especially in high-risk patients, in order to improve outcome. Preoperative anemia is a major risk factor for blood product transfusion and preoperative optimization of red cell volume is assumed to improve outcome, which is extensively described in this book. The management of preoperative anticoagulants is more complex. It is clear that discontinuation of anticoagulants reduces bleeding; however, the thrombosis risk and general outcome should be kept in mind as a reduction in blood loss and transfusion should not be the sole goal. For example, it is advised to continue acetylsalicylic acid prior to CABG surgery as this leads to better graft function, while the effect on blood loss is minor.

It might seem contradictory that the transfusion of large volumes of cell saver blood increases the risk of blood transfusion. However, transfusion of large amounts of cell saver blood leads to the dilution of coagulation factors and platelets as these are

Table 2.1 Modifiable and non-modifiable risk factors for bleeding

Modifiable risk factors
• *Preoperative anemia*
• *Preoperative continuation of anticoagulants*
• *Increased salvaged blood transfusion*
• *High protamine dosing*
• *Lack of antifibrinolytic use*
• *Low intraoperative core temperature*
• *Lack of a transfusion and hemostasis algorithm*
Non-modifiable risk factors
• *Age*
• *Female sex*
• *Low body surface area/body mass index*
• *Coagulopathy*
– Low platelet count
– Platelet dysfunction
– Low fibrinogen level
– Reduced thrombin generation
– Other congenital or acquired bleeding disorders
• *Poor left ventricular function*
• *Co-existing diseases*
– Renal impairment
– Diabetes mellitus
– Vascular disease
– Liver failure
• *Type of surgery*
– Non-CABG
– Complex surgical procedures
– Emergency surgeries
– Rethoracotomy
• *Duration of cardiopulmonary bypass*

washed out during the cell salvage process. The transfusion of solely cell saver blood, in large quantities (>1 L), thereby leads to dilution coagulopathy and bleeding. Therefore, it is advised to restrict the amount of cell saver blood transfusion to a maximum of 1 L [3] or to concomitantly treat the resulting dilution of coagulation factors and platelets with therapeutic plasma, factor concentrates, and platelet transfusions.

Recently it has become more apparent that high protamine dosing is associated with increased bleeding. Protamine, a highly cationic molecule, irreversibly binds and inactivates the anionic heparin. However, when in excess protamine may also bind other anionic compounds such as the negative phospholipid layer of thrombocytes and coagulation factors [7]. This may lead to coagulopathy and causes increased blood loss and transfusion. On the other hand, underdosing of protamine may cause a residual heparin effect which also deteriorates hemostasis. Therefore, protamine dosing should be optimized to minimize postoperative bleeding. The final modifiable risk factor is the lack of a transfusion and hemostasis algorithm. Many studies found that the introduction of such an algorithm leads to reduced transfusion requirements. When point-of-care hemostasis monitoring techniques are added, guiding therapy, a further reduction in blood loss and transfusion was found [8].

Non-Modifiable Risk Factors

Non-modifiable risk factors for bleeding and transfusion are listed in Table 2.1. For many of the non-modifiable risk factors the association with increased bleeding and transfusion is evident, although the exact pathophysiological mechanism is unknown. The hypothesis for the association between a low body surface area (BSA) and blood loss is the relatively large contribution of hemodilution by prime volume of the extracorporeal circuit leading to dilutional coagulopathy. The reason for increased bleeding in (inherited) coagulopathic patients does not need further explanation, also explaining the bleeding risk in patients with hepatic (reduced synthesis of coagulation factors) and renal impairment (uremia induced platelet and endothelium dysfunction).

Although a study on the prophylactic administration of fibrinogen did not show better outcome, there is a clear correlation between a low fibrinogen level and bleeding [9, 10]. Therefore, patients with a preoperative fibrinogen level below 2.5 g/L may require correction in order to reduce blood loss [11]. While classical or point-of-care coagulation test cannot predict which patient will bleed [12, 13], the addition of viscoelastic tests to transfusion algorithms is associated with improved outcome [8]. In contrast, deviating platelet function test results are predictive for patients at risk for bleeding [14], although it remains questionable to what degree of preoperative platelet dysfunction is safe to perform surgery and when and how platelet inhibition should be treated in order to prevent excessive bleeding. These aspects of a patient blood management program will be discussed in subsequent chapters. In clinical practice it is difficult to identify patients at high risk for bleeding based on individual risk factors. Hence, several attempts have been made to quantify the bleeding risk by the use of risk models.

Risk Scores for Postoperative Bleeding in Cardiac Surgery

In a greater attempt to predict which patients are prone to postoperative bleeding, several risk scores for cardiosurgical cases have been developed (Table 2.2). Some models are very complex while others are easy to use and require only basic patient demographics. The predictive value of a model is usually described by the area under the curve (AUC) of a receiver operating curve (ROC). This is a method to quantify and combine the sensitivity and specificity of a test [15]. An AUC of 0.5 suggests the inability to predict which patient will bleed, 0.7–0.8 is considered an acceptable discriminative value, between 0.8 and 0.9 suggests excellency, and an AUC above 0.9 is considered as an exceptionally good predictive ability. A problem of these risk scores is that they frequently lack external validation, or show a low external validity [16]. Moreover, most scores have an excellent predictive value for patients who are not going to bleed, but a low predictive value for patients prone for bleeding.

In a comparison of two newly developed risk scores for transfusion and bleeding with the transfusion risk and clinical knowledge score (TRACK), transfusion risk understanding scoring tool (TRUST), and Papworth bleeding risk score (BRiSc) it

Table 2.2 Risk scores for bleeding in adult cardiac surgery

Bleeding risk score	Type of surgery	Definition	Risk factors for bleeding
Papworth bleeding risk score (BRiSc) [21]	Mixed	Postoperative blood loss >2 mL/kg/h for 3 consecutive hours The score gives a low, medium, or high risk for bleeding, resulting in 3%, 8%, and 21% risk on major blood loss	Low body mass index Older age Emergency surgery Non-CABG or single valve surgery Non-isolated surgery
WILL-BLEED [22–24]	CABG	Transfusion of >4 units of red blood cells or reoperation for bleeding AUC for model 0.73	Preoperative anemia Female gender eGFR <45 mL/min/1.73 m^2 Antiplatelet drugs discontinued <5 days Critical preoperative state Acute coronary syndrome Use of heparin or fondaparinux
Anesthesie Réanimation COeur THOrax VAisseaux (ARCOTHOVA) [1]	CABG	Postoperative blood loss >1.5 mL/kg/h for 6 consecutive hours	Low body mass index
UDPB/E-CABG [6, 18, 24] Universal definition for postoperative bleeding	Mixed	<1000 mL 12-h chest tube volume, 2–4 PRBC and FFP units, PLT/cryoprecipitate/PCC	EUROSCORE Preoperative hematocrit Cardiopulmonary bypass time
Transfusion risk understanding scoring tool (TRUST) [25]	Mixed	Any blood transfusion Model AUC 0.80	Older age Low weight Female gender Low hemoglobin Non-elective surgery High serum creatinine level Previous cardiac surgery Non-isolated surgery
Transfusion risk and clinical knowledge score (TRACK) [26]	Mixed	Any blood transfusion Model AUC 0.71	Older age Low body mass index Female gender Low hematocrit Complex surgery
Goudie [17]	Mixed	Transfusion of >4 units of red blood cells Model AUC 0.77	Older age Low weight Female gender Low preoperative hemoglobin Diabetic on medication EUROSCORE parameters

Table 2.2 (continued)

Bleeding risk score	Type of surgery	Definition	Risk factors for bleeding
Karkouti [27, 28]	Mixed	Transfusion of >4 units of red blood cells The score classified patients in low, intermediate, or high risk, corresponding with a 5%, 27%, and 58% risk for transfusion	Older age Low body surface area Low platelet count or hemoglobin Duration of bypass, lowest temperature Prior surgery, complexity of surgery The surgeon

was shown that all scores have a moderate predictive value measured by the area under the receiver operating characteristics curve (AUC) between 0.69 and 0.80 [17]. Similarly, the BRiSc and universal definition of postoperative bleeding (UDPB) were compared, both showing a low ability for discrimination [16]. Moreover, both models had a high predictive value for patients not going to bleed, but a low predictive value for excessive bleeding.

The UBPD and E-CABG [18] bleeding severity grade were compared in a substudy of the Transfusion Avoidance in Cardiac Surgery (TACS) trial, showing a significant difference in the classification of severe bleeding for the E-CABG (12.4%) and UDPB (23.8%) [19]. These findings suggest that discrimination of patients at high risk for bleeding highly depends on the choice of bleeding risk score, thereby limiting their generalizability. Another comparative evaluation showed that risk scores that were particularly designed for the prediction of bleeding in cardiac surgery were superior over scores that were particularly used to estimate the impact of drugs on bleeding risks [20]. Risk prediction scores are, due to low positive predictive value and lack of external validation, mostly used to stratify study outcomes and allow risk-adjusted benchmarking [3].

Implications for Daily Practice

As described, several attempts have been made to develop preoperative risk models for the bleeding risk in cardiac surgery. Although, in general, these risk scores have not been implemented in daily practice their use can be practical to warrant the clinician which patients are at high risk for bleeding and/or transfusion. Unfortunately, studies comparing the different risk scores are scarce. Nevertheless, all models are restricted by several individual limitations, including the population on which the scores are based, the number of included centers, the sample size, baseline patient characteristics in the study centers, and the available parameters. Several studies were externally validated, improving the generalizability of the model where others only performed internal validation. Moreover, the definition of major hemorrhage and/or transfusion has great impact on the model and is highly variable.

More importantly, it is unclear whether preoperative risk scores are clinically valuable, as the decision to return to the operating room for a reoperation due to bleeding is more important for patient outcome. In particular, it has been shown that a threshold of severe bleeding in the first hours following surgery (200 mL/h in any of the first 6 h after intensive care unit admission) is associated with worse outcomes [2]. A diagnostic and therapeutic algorithm to detect and treat bleeding early (including redo surgery) might result in better outcomes, and further studies in this direction are warranted [29].

As there are many, relative equivalent, risk scores it can be difficult to choose the optimal score for an individual practice. However, there is a large overlap in the risk factors included in the scores. Most scores use: advanced age, low BSA (or BMI), female gender, complex (e.g., more invasive) surgery, preoperative anemia, renal impairment, and urgent procedures (Fig. 2.1). These are powerful predictors for bleeding and/or transfusion and when kept in mind can give direction which patients will be at risk for bleeding and blood transfusion.

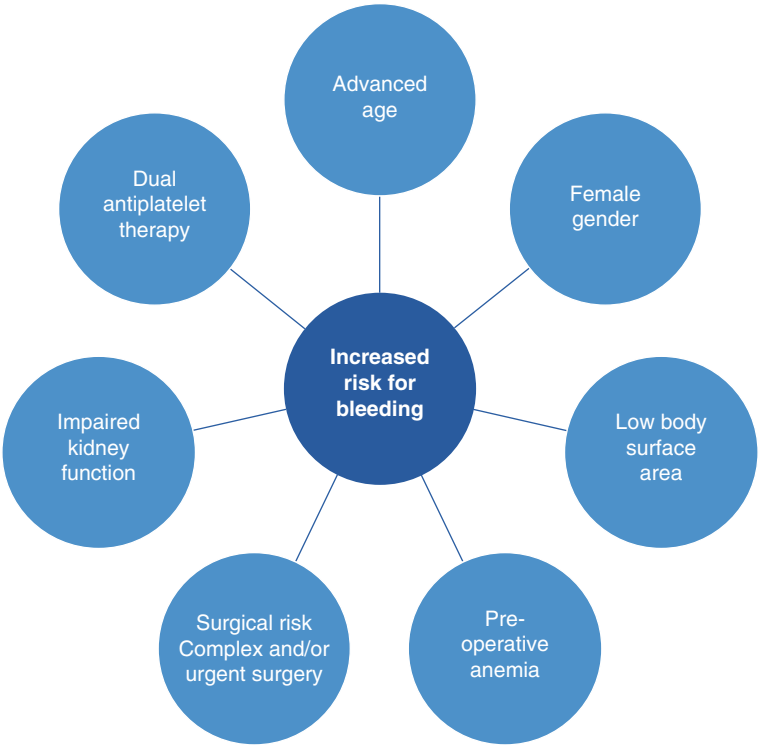

Fig. 2.1 Patient-related factors associated with an increased risk for bleeding in cardiac surgery

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Relevance of Blood Loss and Economic Impact

3

Felix Balzer and Henning Uden

Case Vignette

A 62-year-old male patient was presented for CABG surgery due to left main stem coronary artery disease. Comorbidities include arterial hypertension, hyperlipidemia, chronic kidney disease grade 2, non-insulin dependent diabetes mellitus, and obesity with a body mass index of 34 kg/m^2.

The patient undergoes an uncomplicated procedure and is admitted to the cardiac postoperative care unit. Increased chest tube drainage is observed exceeding 900 mL in 12 h. Even after the transfusion of four units of packed red blood cells (PRBCs), the patient becomes hemodynamically more unstable. Subsequently, a decision to undertake surgical re-exploration is made and the patient is taken back to the operating room.

After surgical control of the bleeding and perioperative transfusion of an additional two units of PRBCs and two units of fresh frozen plasma (FFP), no more bleeding is observed and he is readmitted to the cardiac ICU. On day three the patient can be taken off mechanical ventilation, but due to acute renal failure, continuous veno-venous hemodialysis needs to be started for 5 days and the patient develops a postoperative delirium. He is discharged from the ICU after nine days. His hospital stay is further complicated by a superficial wound infection.

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In the end, his length of stay is 15 days longer than the mean time for CABG patients at the hospital. The case cost is more than double the average case due to extra staff and material costs. The reimbursement scheme of the universal public health care provider is insufficient to cover the costs, and the excess must be covered by the hospital.

Why Is It Important?

Major blood loss has been reported as one of the main challenges in cardiac surgery [1]. As a result of the demographic change and a rising number of comorbidities seen in patients presenting for cardiac surgery, there has been a considerable increase in perioperative treatment costs [2]. The true cost of transfusion is hard to estimate as not only the direct acquisition has to be considered, but also indirect costs such as blood collection, testing, distribution, storage, and expenses for staff handling the blood products [3]. Moreover, there is strong evidence that allogenic blood transfusion is associated with longer hospital stay, which significantly increases case costs, with hospital stays accounting for more than half of all transfusion-related costs [4], while evidence shows non-inferiority of restrictive transfusion triggers on patient outcome [5, 6].

In this chapter, we will approach the discussion on blood loss and its economic impact in cardiac surgery from three different dimensions. Firstly, bleeding and costs can be considered from a resource perspective, given that allogenic blood products to manage blood loss are a limited resource. Secondly, it can be seen from a patient outcome centered perspective. Finally, it can be approached in terms of the economic impact resulting from the first two dimensions (Fig. 3.1).

Fig. 3.1 The three dimensions that are considered in the discussion on blood loss in cardiac surgery

Blood Products as Limited Resource

The proportion of blood products of the total blood supply used in association with cardiovascular surgery has been reported to be 5% in the UK and up to 10–15% in the USA [7, 8]. As a consequence, there is a considerable pressure on health care budgets caused—among others—by allogenic blood products. While there has been an overall decline in the use of allogenic blood products in the USA since 2013, which is mainly attributed to patient blood management strategies and surgical innovations, this has also been followed by a decline in blood collection [9]. Therefore, even if blood supply may currently be relatively stable, allogenic blood continues to be of limited availability from a resource perspective.

The number of PRBC transfusions is reported to vary widely between different hospitals, even to the extent that the institution itself has been identified in one study as an independent risk factor for transfusion [10]. When a liberal rather than a conservative transfusion regimen was followed, the odds ratio for PRBC transfusion in those institutions was 6.5 (95% CI 3.8–10.8). In an observational study that included roughly 100,000 patients from 798 institutions, the rate of PRBC transfusion even ranged from 8% to 93%, showing the need for an evidence-based and more standardized approach to blood transfusion [11].

Patient Outcomes

The second dimension of blood loss considers its relevance in terms of patient outcomes. The lack of a universally agreed definition of blood loss means that different studies have used different criteria when defining major or massive perioperative blood loss. Several studies have found a strong association between major blood loss and increased mortality. Defining massive blood loss as having received at least five units of PRBCs within one day of surgery with cardiopulmonary bypass, Karkouti et al. demonstrated an eightfold increase in mortality in their study of 9215 patients [12]. A study by Ranucci et al. of 16,154 patients showed an increase in relative risk of operative mortality of 12% for every 100 milliliters (mL) blood loss in the first 12 postoperative hours [13]. Major postoperative bleeding in this study was defined as the upper 10th percentile of the overall bleeding distribution, which corresponded to 900 mL within 12 h, or to have needed surgical revision due to postoperative bleeding. Patients in the study that suffered from a major bleeding had a fivefold risk of operative mortality. Additionally, preoperative anemia and PRBC transfusion were identified as independent risk factors multiplying the adverse effect of major bleeding. Christensen et al. have showed similar results in their study that included 1188 patients undergoing surgery requiring cardiopulmonary bypass [14]. Patients with increased chest tube drainage in the first six postoperative hours defined as $\geq$200 mL/h or $\geq$2 mL/kg/h for two consecutive hours showed a higher 30-day mortality. Nonetheless, high-risk patients undergoing major surgery under a restrictive transfusion strategy are also at a higher risk for complication including higher mortality [15].

Clinical studies also indicate higher morbidity in patients suffering from major blood loss. Both of the last two mentioned studies showed higher rates of strokes, while others demonstrated higher rates of myocardial infarction in addition to higher rates of acute kidney injury and sepsis [13]. Christensen et al. found higher rates of re-exploration and stay in an ICU >72 h, which was corroborated by Ranucci's results that also showed a longer stay at the ICU [13, 14]. Recently developed standards for the definition of major blood loss have been positively validated and higher scores shown to be associated with increased mortality [16–18]. This hopefully will lead to a better comparability of future research.

The Economic Impact of Blood Loss

The economic impact of blood loss, resulting from the previous two dimensions, constitutes the third dimension needing consideration. Stokes et al. investigated the impact of bleeding-related complications in 103,829 heart surgery patients in the USA [19]. In their study, the mean total adjusted hospital costs for patients with bleeding complications was US$ 39,050 compared to US$ 28,771 for patients without this complication. Bleeding complications in this study were defined as having an international classification of disease code related to either hemorrhages or hematoma complicating a procedure, interventions to control for bleeding or transfusion of blood products. Patients with and without bleeding complications also significantly differed in terms of the length of stay (11 days compared to 6 days, respectively) and number of days in ICU (5 days versus 2 days, respectively) [19].

In an analysis that included 463,734 cardiac patients, Zbrozek et al. reported that 51.5% received RBC transfusions, 36.4% fresh frozen plasma (FFP), and 27.7% platelets [20]. Per transfused patient, the mean cost for RBC was $1034, for FFP $323 and for platelets $1281. In a multivariate analysis, the total costs (including expenditures for agents used for bleeding control) increased by 133%. This may be partly explained by a more than fourfold risk of bleeding patients being admitted in an ICU and also to be readmitted for bleeding within 30 days [20].

Christensen et al. conducted a retrospective analysis on the economic impact of postoperative hemorrhage in cardiac surgery [21]. In patients affected by this condition, they found an incremental cost of €6251 on average. Compared to patients without postoperative hemorrhage, univariate analyses demonstrated that bleeding was associated with an increase of €1844 for surgical re-exploration, €639 for blood products, and €3432 for ICU treatment. The authors highlight, however, that additional costs apply to the initial hospitalization with further costs expected for follow-up and rehabilitation care for complications such as stroke and myocardial infarction not considered in this calculation. The overall impact is hence expected to be higher [21].

As evidence on the risks associated with transfusions in cardiac surgery patients has become clearer, structured patient blood management programs have started to be implemented. In order to study the effect of this type of program, Ternström et al. did a prospective study looking at the difference in the year before and after the

implementation of one such program in 2010 at the department of cardiothoracic surgery at a Swedish university hospital [22]. The authors found a reduction of transfusion of any blood product by 20.7%, with no evidence of compromised medical safety. This constituted a cost reduction for blood products of 12.4%. To achieve this, the implemented program consisted of three different components, being education, a revision of transfusion guidelines, and a transfusion log.

The probable cost savings from an educational intervention to reduce bleeding-related complications was calculated in a study by Ravyn et al. [23]. The authors developed a model to assess the impact of continuing medical education on the prevention of bleeding-related complications and reoperation for bleeding. Their results suggest that there is a high potential for relevant cost savings by implementing respective educational strategies.

Implications for Daily Practice

In conclusion, there is broad evidence in the literature that transfusion as a consequence of bleeding in cardiac surgery is associated with poor outcomes from a patient and financial perspective. However, the effects of blood loss, transfusion, and the causes leading to transfusion (comorbidities of the patient, hemodynamic instability, acute anemia due to blood loss, etc.) are tightly related and the weight of each component is not yet fully understood. Given the fact that blood transfusions may be life-saving and that studies comparing blood transfusions with placebo in clinical settings are unethical, the estimation of the real clinical impact of transfusion is very difficult. This dilemma also indicates that calculating the real costs of transfusion is complex, as the patient may have died without a transfusion. From an economic point of view, the prolonged length of stay, especially in the ICU, may account for a large portion of case costs. Given that the treatment of bleeding associated complications may be required also after hospital discharge, total costs that result from blood loss are expected to be higher than figures quoted in this chapter. The long-term impact of efficient blood patient management on health resource utilization may thus become considerably more important. Future research may include studies that investigate the impact of a targeted anemia treatment prior to cardiac surgery versus standard of care and the impact of designated treatment algorithms for increased blood loss in the ICU. These studies should include the meticulous prospective sampling of economic data of, e.g., transfusion requirements and ICU treatment to better estimate the costs of blood loss and its required treatment.

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Part II

Preoperative Measures to Reduce Anemia

Risk of Anemia

4

Christian von Heymann and Lutz Kaufner

Case Vignette

A 76-year-old female is scheduled for elective aortic valve replacement for severe aortic valve stenosis. From her history the patient complained of progressive shortness of breath for the last 12 months. Past medical history included a 10-year history of orally treated diabetes mellitus and chronic obstructive pulmonary disease associated with an ongoing longstanding nicotine abuse. Additionally, she suffered from chronic anemia that was treated with a course of oral iron about 1 year ago, but it was discontinued due to gastrointestinal discomfort. The patient is stable without symptoms of disease or complaints on low intensity physical exertion. Blood screening on admission reveals a hemoglobin of 10.1 g/dL (6.3 mmol/L), a hematocrit of 31%, a mean cellular volume (MCV) of 75 fL, and a mean corpuscular hemoglobin of 25.9 pg. No further anemia studies have been ordered yet. Does anemia increase the risk of the patient suffering adverse outcomes including mortality after cardiac surgery?

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Why Is It Important?

According to the WHO about 1.93 billion people—27% of the world's population—suffered from anemia in 2013 [1].The age-adjusted prevalence of anemia was 19,748 per 100,000 inhabitants in developed countries. Prevalence by age shows a marked increase (up to 30,000 per 100,000) in the elderly population > 65 years of age [2].

In cardiac surgery, between 20% and 45% of patients present with anemia of any cause prior to surgery [3–7]. Preoperative anemia has been identified as a risk factor for a variety of adverse outcomes in different surgical specialties [8] and is frequently the reason for blood transfusion in various settings [9].

Patient blood management (PBM) is a multidisciplinary concept that aims to tailor the administration of blood products to the need and clinical situation of each particular patient. Furthermore, PBM intends to sharpen the consciousness for the reasons underlying the need for blood transfusions. Within the first pillar of the clinical concept of PBM the detection and treatment of preoperative anemia plays a prominent role [10].

Cardiac surgery continues to use a high percentage of the national blood supply [11] and anemia either pre- or perioperative as well as acute or chronic is the major underlying cause. For this reason, the assessment of the impact of preoperative anemia in patients undergoing cardiac surgery is warranted. In this context the impact of perioperative transfusion on postoperative outcomes and the interaction with causative factor anemia has to be acknowledged.

The purpose of this chapter is to review the data of the impact of preoperative anemia on the outcome of patients scheduled for cardiac surgery. A second chapter of this book will focus on diagnostics and treatment of preoperative anemia.

Evidence

A literature search using the following query (((Cardiac surgery) NOT (Children OR Pediatric))) AND (anemia AND (preop* OR pre-op* OR before OR prior)) was performed, to identify studies investigating the impact of preoperative anemia on the clinical outcome of patients undergoing cardiac surgery. Sixty-one publications on preoperative anemia in adult cardiac surgery published between 2001 and January 2017 were identified. After the exclusion of case reports, editorials, studies investigating postoperative anemia, or the treatment of anemia that did not report the risk associated with preoperative anemia, 48 studies reporting patient outcomes remained. Of these, 21 studies were observational, one was a national audit, 5 were matched cohort, and 21 retrospective studies in design.

Forty-five of these 48 studies reported that preoperative anemia was associated with worse outcome after on-pump or off-pump cardiac surgery. Worse outcomes ranged from the need for blood transfusions and acute kidney injury to mortality. In contrast, only 3 studies did not describe preoperative anemia as a risk factor for adverse clinical outcomes after cardiac surgery [12–14].

Without assessing the quality of evidence from each study of this literature search, these numbers suggest that preoperative anemia seems to be a risk factor for adverse clinical outcomes after cardiac surgery rather than it conveys no risk for the patient. These results are in line with data from non-cardiac surgery that also indicated the independent impact of preoperative anemia on adverse outcomes [15, 16]. The remaining question is whether preoperative anemia is simply a surrogate for the severity of comorbidities of the patients or a risk factor that is independent of other factors conveying a risk for the cardiac surgery patient? This question is difficult to answer, but the literature provides data suggesting that anemia is an independent risk factor in cardiac surgery.

The study by Williams and colleagues collected data from more than 180.000 isolated coronary artery bypass graft procedures and reported that preoperative anemia, as defined by a hematocrit <33%, was an independent predictor of perioperative mortality, renal failure, and deep sternal wound infection [3]. These results were confirmed by other large and more recent analyses from different countries [4, 6, 7, 17].

Hence, some national and international guidelines have addressed preoperative anemia as a risk factor in cardiac surgery: The 2017 Patient Blood Management Guideline of the European Association of Cardiothoracic Anaesthesiologists (EACTA) in conjunction with the European Association of Cardiothoracic Surgery (EACTS) acknowledges preoperative anemia as a significant risk factor for cardiac surgical procedures and recommends preoperative treatment according to the underlying cause of anemia (Class IIb and IIa recommendations) [18].

Moreover, the increased risks of preoperative anemia in patients undergoing surgery were acknowledged by the British Committee for Standards in Haematology Guidelines [19] which recommend that healthcare pathways should be structured to ensure anemia screening and correction before surgery (Grade 2b).

In addition, the first update of the European Society of Anaesthesiology (ESA) Guideline on the Management of Severe Perioperative Bleeding states that preoperative anemia in adults and children is a strong risk factor for perioperative blood transfusion in different surgical specialties and may be associated with adverse outcomes (B) and recommends anemia assessment in patients with a risk of bleeding within 3–8 weeks before operation (1C).

Furthermore, adapted to the results of the blood work up, a causal treatment is recommended (strong recommendation either 1B or 1C depending on the treatment option and the quality of evidence for the treatment modality) [20].

The recently published German Guidelines on Preoperative Anemia investigated the risk of anemia before cardiac and non-cardiac surgery using the GRADE system to assess the published evidence until early 2015 [21]. This guideline attempted to quantify the risk with preoperative anemia for different outcome variables and patient groups. The included meta-analysis showed that preoperative anemia increased the risk for mortality by a factor 2.72 [95%CI: 2.28, 3.24] (Fig. 4.1, panel (**a**)), the risk to be transfused by 1.97 [95%CI: 1.59, 2.44] (panel (**b**)), and the hospital stay after cardiac surgery to be in median prolonged by 2.3 days [95%CI: 0.39, 4.24] (panel (**c**)). The confidence intervals indicate that all results were statistically significant [21].

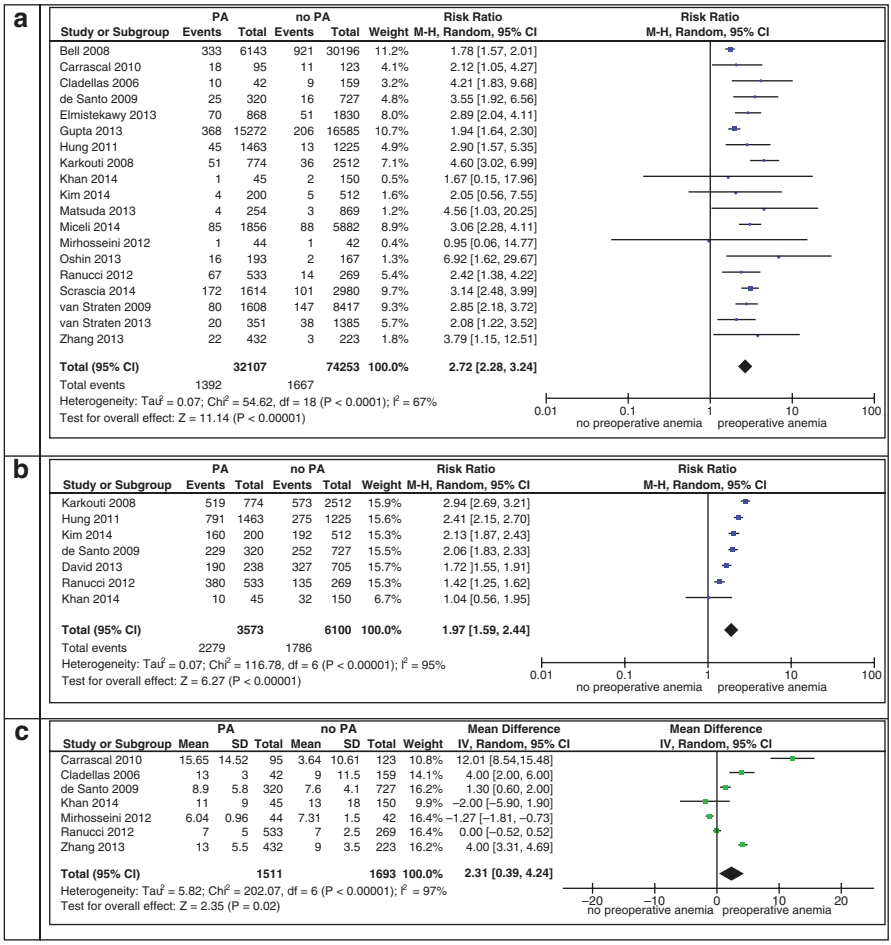

Fig. 4.1 The risk of mortality (panel (**a**)) and perioperative red cell transfusion (panel (**b**)) with anemia before cardiac surgery and the impact of preoperative anemia on hospital stay (panel (**c**)) are shown as forest plots of observational studies [21]

The guideline group, including representatives of 18 different medical societies, stated that the abovementioned risks of preoperative anemia refer to the untreated preoperative anemia in cardiac and non-cardiac surgery irrespective of the underlying cause of anemia as the causes were mainly not investigated in the studies included in the meta-analysis.

Risk of Anemia in Certain Patient Populations

Cardiac surgery with CPB induces hemodilution which is usually more pronounced in women due to a lower body weight and circulating blood volume. This increases the risk to be transfused for women during or after cardiac surgery, especially when

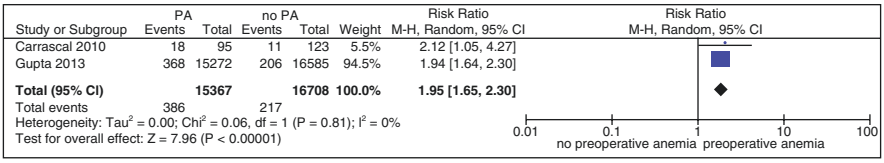

Fig. 4.2 The impact of anemia in patients >65 years of age on mortality [21]

patients are anemic preoperatively. Until 2015, only one study in gynecological surgery investigated the risk of preoperative anemia. This study showed a 4.7 times higher risk to be transfused in patients with preoperative anemia [22]. However preoperative anemia was not identified as an independent risk factor for other clinical outcomes such as the rate of complications or length of hospital stay. Perioperative transfusion, however, was significantly associated with a higher risk in the adjusted analysis, so that the authors concluded that patients should be systematically screened for preoperative anemia and treated according to the results [22].

Another group at risk are elderly patients undergoing cardiac surgery, in whom the prevalence of anemia is already increased [1, 2]. Pooled data from 2 studies show that the risk of mortality is increased by the factor 1.95 in anemic patients >65 years of age undergoing cardiac surgery (Fig. 4.2) [21]. Another study showed that elderly and anemic patients stayed longer in the hospital and the ICU than non-anemic elderly patients, although these results did not reach significance (median hospital stay 15.6 ± 14.5 vs. 3.6 ± 10.6 days, $p = 0.23$, and ICU stay 7.2 ± 10.7 vs. 4.9 ± 8.0 days, $p = 0.069$) [23].

The Independent Impact of Anemia

Preoperative anemia is frequently associated with a higher demand of intra- or perioperative blood transfusions as demonstrated in the majority of studies. Blood transfusions themselves are considered a risk factor for adverse outcomes after cardiac surgery [24, 25] and so it is difficult to estimate the independent impact of preoperative anemia. Three studies confirmed that there is an interaction between anemia and transfusion and described an almost two-fold higher risk of mortality anemic in patients who were transfused [6, 7], although in one study the risk associated with blood transfusions seemed to be stronger than that with anemia [8].

The authors of all studies suggested that the treatment of preoperative anemia as a modifiable risk factor should be considered as it may also influence the risk associated with blood transfusions in cardiac surgery.

Implications for Daily Practice

A large body of literature and separate analyses from different national guidelines show that preoperative anemia is a risk factor for adverse outcomes after cardiac surgery. Preoperative treatment may not only improve anemia, but also reduce

allogenic transfusion requirements, which show a significant interaction with anemia on outcome after cardiac surgery. However, it needs to be proven in a pragmatic and prospective randomised, sufficiently powered trial whether preoperative anemia treatment is superior to blood transfusion.

Answering the question of the case vignette, current evidence from a large number of studies and some recent meta-analyses and guidelines suggest that this lady with an isolated aortic stenosis has an increased risk for mortality (by factor of 2) and other adverse outcomes associated with her anemia. Due to her stable clinical condition, the attending clinicians should consider to identify the cause of anemia and treat the patient accordingly.

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Therapy of Anemia

5

Lutz Kaufner and Christian von Heymann

Case Vignette

A 76-year-old female is scheduled for elective aortic valve replacement due to third degree aortic valve stenosis. Beside an orally treated diabetes mellitus known for the last 10 years and a chronic obstructive pulmonary disease associated with a long standing and still ongoing nicotine abuse, the patient reports a chronic anemia that has been treated with a course of oral iron about 1 year ago, but was discontinued due to gastrointestinal discomfort. Blood screening on admission reveals a hemoglobin of 10.1 g/dL (6.3 mmol/L), a hematocrit of 31%, a mean cellular volume (MCV) of 65 fL, and a mean corpuscular hemoglobin of 25.9 pg. Further anemia studies showed a ferritin of 20 µg/L and a transferrin of 450 mg/dL. Other parameters have not been ordered. Which type of anemia is this female patient suffering from? Should anemia be treated preoperatively? What kind of treatment is indicated?

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Why Is it Important?

Iron deficiency and a functional disorder in iron metabolism are the most common causes of preoperative anemia [1]. However, anemia due to renal disease or anemia based on chronic disease/inflammation has to be considered routinely when anemia is diagnosed before cardiac surgery [1]. Furthermore, both causes of anemia should be distinguished from tumor-related anemia with or without combined iron deficiency [2], hemolytic anemia, or nutritional forms of anemia, for instance, caused by vitamin B_{12} and/or folic acid deficiency [1]. As a matter of principle, any anemia in the perioperative setting should be diagnosed based on a differentiated blood screening and treated individually according to their cause [2]. If anemia cannot be reliably ruled out preoperatively, diagnostic test should be used before elective cardiac surgery to identify anemia and to determine the cause [2]. If preoperative anemia is diagnosed, differential blood screening should be performed timely, usually 4–6 weeks before elective cardiac surgery [2]. This long-term window is necessary to treat the cause of preoperative anemia properly. It is recommended to establish a diagnostic–therapeutic algorithm for preoperative anemia in advance [2]. This algorithm should be consented with the cardiac surgeons and all clinicians involved working in the perioperative setting, such as anesthesiologists, hematologists, and internal medicine doctors [2].

The purpose of this chapter is to give a summary of the current state of preoperative anemia treatment modalities before elective cardiac surgery according to the most common causes of anemia.

Therapy with Iron

Besides the risk of preoperative anemia, the recently published German guidelines on preoperative anemia investigated the therapeutic strategies of anemia before elective cardiac and non-cardiac surgery using the GRADE system to assess the published evidence until early 2015 [2]. One of the major results of these guidelines was that in almost all studies in cardiac and non-cardiac surgery, preoperative anemia was mainly treated without any preoperative diagnostic testing. For a causal and successful treatment of anemia, the guideline group stated that a reasonable therapy has to be based on the underlying cause of anemia after a preoperative differential diagnostic test [2].

Iron deficiency is one of the leading causes for anemia in the world, which can be treated by substituting iron, either by oral or intravenous preparations. The German guidelines stated that no recommendation could be made for or against treatment of preoperative anemia with iron (oral or intravenous) prior to elective cardiac surgery with respect to the outcomes “transfusion” and “hemoglobin” [2]. This is related to the small number of studies on preoperative patients and low quality of the evidence [2]. These findings are well in line with a recently published Cochrane review on iron therapy of preoperative anemic patients [3]. The authors could neither find any effects of iron therapy with regard to the reduction of allogenic blood transfusion nor

identify any other evidence for the effectiveness of preoperative iron therapy [3]. International guideline recommendations from the American Society of Anesthesiologists (ASA) refer to preoperative treatment with iron in case of proven iron deficiency only if the time frame to elective cardiac or non-cardiac surgery allows for the treatment of preoperative anemia [4]. If there is a proven absolute or functional iron deficiency in the preoperative period, the British Committee for Standards in Haematology guidelines recommend the initiation of preoperative oral iron therapy [5]. Intravenous administration of iron is only recommended if the preoperative time interval for oral therapy is too short, or if there is an intolerance or resorption disorder for oral iron [5]. An international consensus advises the preoperative diagnosis of anemia [6]. In case of iron deficiency, substitution therapy with oral iron or, in case of resorption disorders, with intravenous iron is recommended [6]. The European Society of Anaesthesiology (ESA) guidelines for the Preoperative Evaluation of Patients for Elective Non-Cardiac Surgery recommend intravenous iron therapy in case of existing iron-deficiency-based anemia (1A recommendation) [7]. It remains unclear if the recommendations are transferable to cardiac surgery, but the ESA follows the earlier recommendations for the management of severe perioperative bleeding, where diagnosis of anemia 3–8 weeks preoperatively should be followed by intravenous iron treatment in the presence of iron deficiency anemia [8]. The recently published guidelines on Patient Blood Management for Adult Cardiac Surgery of the European Association of Cardiothoracic Anaesthesiology (EACTA) and the European Association for Cardio-Thoracic Surgery (EACTS) also recommended intravenous iron in preoperative mildly or severely anemic patients with iron deficiency (Class IIb, Level C) [9].

All guideline recommendations are based on results from only a few prospective randomized trials (RCTs). Both the German guidelines [2] and the Cochrane review [3] consistently identified two trials in non-cardiac surgery [10, 11], but without any significant effects of iron therapy on the reduction of allogenic blood transfusion. In both studies, no diagnostic test for the presence of anemia was performed before the onset of iron therapy. Therefore, it remains unclear what the proportion of patients with iron deficiency anemia was. Furthermore, the effect of iron treatment in iron deficient patients was not assessed. The low level of evidence for iron therapy in iron deficient patients is therefore mainly attributed to methodological flaws of the available prospective randomized studies, rather than a lack of effect.

In a recent review on the impact of anemia and intravenous iron replacement in cardiac surgery, three RCTs and one observational study were identified [12]. However, only one RCT investigated oral and intravenous iron replacement without additive erythropoietin in the period before cardiac surgery [13]. Hundred milligrams of intravenous iron (intravenous iron (III)-hydroxide sucrose complex) given within 24 h before the operation, and daily until discharge, resulted in higher serum ferritin levels at discharge compared to placebo or oral iron replacement (105 mg/day), however, without any impact on blood transfusion requirements [13]. Again, no diagnostic work up to identify the cause of anemia was performed before surgery, and the pre- and postoperative time frame of a low dose intravenous or oral iron therapy selected in these trials was too short to influence intra- and

postoperative transfusion requirements [12, 13]. An ongoing RCT of 214 patients undergoing valve surgery with random allocation to either 1000 mg of intravenous iron isomaltoside (for 3 days pre- and postoperatively) or placebo is more likely to give an answer on the effectiveness of intravenous iron therapy in case of proven preoperative iron deficiency anemia [14].

All of the above-mentioned guideline recommendations are valid for the treatment of preoperative anemia before elective surgery only. However, outside preoperative anemia, there are basic national guideline recommendations for the treatment of proven iron deficiency anemia [15]. Once again, this underlines the need for standardized preoperative anemia testing in order to start adequate and targeted therapy.

Therapy with Erythropoietin

Raising preoperative hemoglobin values is the endpoint of most studies after the initiation of preoperative anemia therapy, mostly in combination with the reduction of anemia-related perioperative transfusion. Regardless of the type of surgery, the German guidelines identified 14 RCTs for the outcome "hemoglobin level" and 13 RCTs for the outcome "transfusion requirements" after treatment of preoperative anemia with erythropoietin [2]. Due to the low or very low quality of the evidence, the guideline group suggested treatment of preoperative anemia with erythropoietin as long as diagnostic tests have confirmed anemia due to chronic disease (e.g., renal insufficiency) [2]. If concomitant iron deficiency is present, therapy with erythropoietin in combination with iron is recommended [2]. In their guideline for the Management of Severe Perioperative Bleeding, the ESA calls for a causal diagnosis of anemia and an appropriate therapy [8]. However, these guidelines disregarded possible non-hematopoietic effects of erythropoietin, e.g., the potential impact on angiogenesis and tumor growth or rare severe cutaneous reactions requiring a differentiated and cautious use of erythropoietin [2]. The guidelines on patient blood management for adult cardiac surgery of the EACTA and EACTS recommended erythropoietin with iron supplementation in preoperative anemic patients with non-iron deficiency anemia (Class IIa, Level B) [9].

Regardless of the onset of anemia, international guidelines recommend the use of erythropoietin to treat chronic renal anemia [16, 17]. The effects of erythropoietin on hemoglobin levels as a marker of increased erythropoiesis in chronic renal anemia are undisputed. However, the conclusions regarding perioperative transfusion-sparing effects in case of preoperative anemia with erythropoietin are inhomogeneous [2]. In addition, the duration of treatment, the severity of anemia, the type of erythropoietin preparation and dosage, and the use with or without concomitant iron substitution are different among the analyzed RCTs [2]. Similar to the studies on iron replacement, most of the investigations on erythropoietin in preoperative anemia were performed without diagnosis of the type and severity of anemia before treatment [2].

In a single-center, prospective trial, 600 patients undergoing cardiac surgery with a preoperative hemoglobin level below 14.5 g/dL (9 mmol/L) were randomly assigned to either 80.000 IU of erythropoietin subcutaneously 2 days before surgery or to control [18]. The hemoglobin value measured on day 4 postoperatively was significantly increased in the treated group compared to the control one [18]. The incidence of perioperative transfusion was reduced for anemic patients with a preoperative hemoglobin below 13 g/dL (8.1 mmol/L) only [18]. These findings underline the need of preoperative diagnosis of anemia as well as the indication of erythropoietin for patients with even mild (hemoglobin <13 g/dL (8.1 mmol/L)) or severe (hemoglobin <10 g/dL (6.2 mmol/L)) in case of preoperative renal anemia or anemia due to other chronic diseases. Additionally, in a meta-analysis of six RCTs it was stated that the preoperative administration of erythropoietin in case of preoperative renal anemia is an important measure in preventing acute kidney injury after cardiac surgery [19].

Studies on the treatment of preoperative anemia with erythropoietin and iron allow a subdivision into two different treatment regimens:

- A short-term therapy of erythropoietin with a daily dosage of, e.g., 500 IU/kg/day for 1–3 days before surgery, and postoperative continuation (usually in combination with iron).
- A long-term therapy of, e.g., 150–300 IU/kg/day over 5–7 days [20] or 40,000 IU two times a week over 4 weeks [2, 21] with an accompanying iron dose.

In view of the literature and the summary of product characteristics (SmPC) of erythropoietin alfa, therapy with 600 IU/kg erythropoietin alfa once a week subcutaneously, or optionally 40,000 IU/week, over a period of 3 weeks (21st, 14th, and 7th day preoperatively), might be indicated when renal anemia or anemia due to chronic diseases has been diagnosed [2]. In the treatment with erythropoietin it has to be considered not to exceed a preoperative hemoglobin value of 12 g/dL (7.5 mmol/L) [2].

The Independent Impact of Anemia

Preoperative anemia is frequently associated with a higher demand of intra- or perioperative blood transfusions as demonstrated in the majority of studies. Blood transfusions themselves are considered a risk factor for adverse outcomes after cardiac surgery [22, 23] and so it is difficult to estimate the independent impact of preoperative anemia. Three studies confirmed that there is an interaction between anemia and transfusion and described an almost twofold higher risk of mortality in anemic patients who were transfused [6, 7], although in one study the risk associated with blood transfusions seemed to be stronger than that with anemia [8].

The authors of all studies suggested that the treatment of preoperative anemia as a modifiable risk factor should be considered as it may also influence the risk associated with blood transfusions in cardiac surgery.

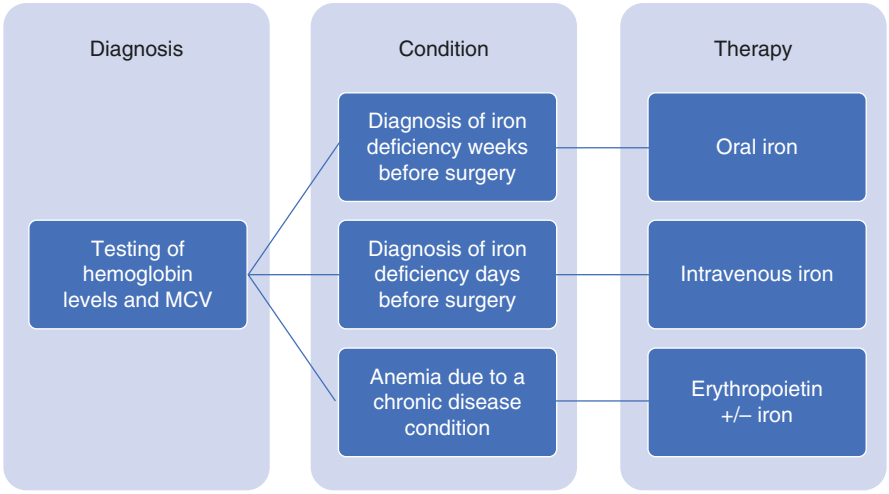

Fig. 5.1 Diagnosis and therapy of anemia are key elements of a patient blood management program

Implications for Daily Practice

A large body of literature and separate analyses from different national guidelines show that preoperative anemia is a risk factor for adverse outcomes after cardiac surgery. Preoperative treatment may not only improve anemia, but also reduce allogenic transfusion requirements, which show a significant interaction with anemia on outcome after cardiac surgery (Fig. 5.1).

Answering the question of the case vignette, this patient suffers from an iron deficiency anemia for which current evidence from a large number of studies and some recent meta-analyses and guidelines suggest that aortic valve surgery has an increased risk for mortality (by factor of 2) and other adverse outcomes associated with her anemia. Due to her stable clinical condition, the attending clinicians should consider to treat the patient with iron and check the effect regularly.

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Part III

Perioperative Drug Management to Prevent Bleeding and Thrombosis

Antiplatelet Drug Management

6

Aamer Ahmed and Adeel Majeed

Case Vignette

A 64-year-old man recently suffered an ST elevation myocardial infarction and underwent percutaneous coronary angioplasty. During the procedure, multiple lesions in all three main coronary arteries were noted. However, only one drug-eluting stent could be placed in the circumflex artery and the patient was started on aspirin and the thienopyridine prasugrel to prevent stent thrombosis. He was then referred for urgent coronary artery bypass grafting to revascularize the remaining affected coronary arteries. The treating physician discussed whether to continue or discontinue aspirin and prasugrel during a multidisciplinary team consult. The team concluded that prasugrel should be discontinued, but there was no consensus regarding the time of discontinuation and whether bridging therapy is required.

Why Is It Important?

Platelets are a vital component of blood involved in hemostasis. They are activated and mediated by a number of mechanisms. Endothelial damage or rupture of an atherosclerotic plaque activates, adheres, and aggregates platelets to allow hemostasis until tissue repair is completed.

Although these processes are part of normal physiological function, amplification and excessive thrombus formation impede vascular flow. Occlusion of blood at regions narrowed by atherosclerotic plaques can lead to tissue ischemia and damage. Antiplatelet agents are a cornerstone of preventing or reducing such events. However, blocking platelet function during surgery delays hemostasis and increases the risk of bleeding. This chapter focuses on the mechanistic action of antiplatelet

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drugs, how to manage these in the perioperative setting and whether to bridge patients in case of antiplatelet drug discontinuation.

Platelet Function

Platelet involvement in coagulation is termed primary hemostasis, whereas secondary hemostasis is mediated by the coagulation proteins leading to fibrin formation. Primary hemostasis involves a number of proteins and interactions and occurs very quickly. However, it can be divided into three stages occurring rapidly in succession.

Initial tissue damage exposes the collagen fibers making up the endothelium. Collagen glycoprotein (GP) Ia/IIa surface receptors anchor passing platelets by interacting through von Willebrand factor (vWF) that is secreted by the endothelium and binds to GPIb receptors forming a complex with GPIX and GPV on platelets.

In the absence of tissue damage, platelets are inhibited by endothelial produced nitric oxide, ADPase, and prostacyclin (PGI_2). Platelet intracellular calcium is maintained at low levels by a cyclic-AMP mediated calcium pump. Activation of platelets occurs from multiple sources:

- ADP binding to the purinergic receptors P2Y1 and $P2Y_{12}$, on the platelet surface.
- Tissue factor (TF) release from endothelial damage activating factor VII and in turn thrombin, which acts directly on platelets.

This increases the net intracellular calcium, which in turn activates the platelet.

Activated platelets increase the production of thromboxane A_2, which activates glycoprotein IIb/IIIa receptors on their own and neighboring platelets, which leads to aggregation. Activated platelets also degranulate, secreting chemotactic agents that attract more platelets to the site of endothelial injury. Activated platelets gather at the site of endothelial injury. The activated glycoproteins IIb/IIIa surface receptors bind to vWF and fibrinogen, thereby anchoring activated platelets to endothelial collagen. The binding to fibrinogen allows platelet cross-linking and hence aggregation.

Mechanisms

Cyclooxygenase Pathway

The enzyme cyclooxygenase (COX) converts arachidonic acid, a fatty acid in cell membranes, to prostaglandins, prostacyclins, and thromboxanes. These are important biological molecules involved in pain, inflammation, and coagulation. There are two forms: COX-1 and COX-2. With COX-1 being a constitutive enzyme that is continuously active and COX-2 being an inducible enzyme that is activated by inflammation or tissue damage (Fig. 6.1).

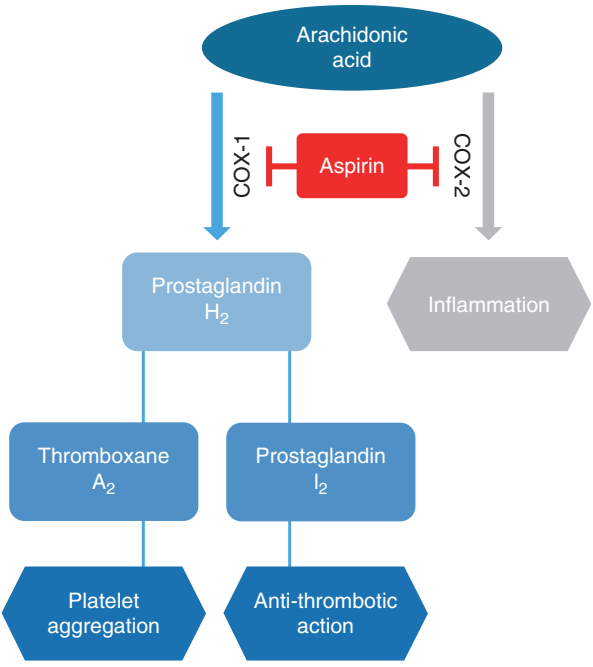

Fig. 6.1 Aspirin inhibits the conversion of arachidonic acid, thereby impacting platelet aggregation, anti-thrombotic mechanisms through the endothelium and inflammation

Aspirin is an irreversible inhibitor of COX-1 and COX-2. By blocking COX-1, the conversion of arachidonic acid to prostaglandin H_2 is blocked, and therefore, its conversion to thromboxane A_2 and prostaglandin I_2 is also hindered. Thromboxane A_2 is the main eicosanoid involved in platelet aggregation as described earlier, while prostaglandin I_2 is produced by endothelial cells and has anti-thrombotic actions [1]. As said, the effect of aspirin on platelets is permanent, and the antiplatelet effect wears off after 7 days once new platelets are synthesized. The antiplatelet effect occurs at low doses (75–150 mg) with mostly COX-1 inhibition, while the anti-inflammatory and analgesic effects, mediated mainly by COX-2 inhibition, occur at higher doses (150–325 mg).

Platelet Surface Receptors

The numerous receptors on the platelet surface are mostly involved in activation, anchoring, and maintenance of platelet aggregation, albeit that not all their functions are yet understood. There are multiple antiplatelet drugs produced that specifically target one or two of these receptors. Receptors not yet targeted continue to provide important potential avenues of research in targeted drug development. The most commonly known receptors are the ADP receptors, glycoprotein IIb/IIIa receptors, phosphodiesterase, and protease activated receptors.

ADP receptors are expressed on the platelet surface, and binding results in platelet activation through a conformational change, platelet aggregation, and interaction with other cell surface and plasma receptors and compounds. Blocking ADP binding to the receptor has antiplatelet aggregation effects [2]. ADP receptors are part of the larger purinergic G-protein couple receptor family, and the specific receptors on the platelet surface are termed P2Y1 and $P2Y_{12}$ receptors. P2Y1 receptors initiate platelet aggregation, whereas $P2Y_{12}$ receptors amplify and complete aggregation. Therefore, both receptors need to be activated for aggregation to occur. Agents developed to block these receptors have focused on the $P2Y_{12}$ receptor and are termed ADP receptor inhibitors or $P2Y_{12}$ receptor antagonists [1]. Drugs currently in clinical use are clopidogrel, prasugrel, ticagrelor, and the more recently approved cangrelor [3].

Glycoprotein IIb/IIIa receptors are the most important receptors on the platelet surface, as they are activated by vWF and fibrinogen. Binding of vWF allows anchorage of platelets to the endothelium and the attraction of other platelets. The binding of fibrinogen allows crosslink formation and platelet aggregation through platelet–fibrin complexes. Activated glycoprotein IIb/IIIa receptors also have effects on thrombin and collagen to continue the prothrombotic effect [4]. Inhibition of these receptors has an antiplatelet effect. The agents currently in use are abciximab, tirofiban, and eptifibatide.

Indications

Antiplatelet drugs are primarily used in the context of prevention of morbidity from coronary artery disease. However, indications for their use differ between agents.

Aspirin

Multiple trials have shown that aspirin as primary prevention taken daily at doses of 75–325 mg reduces the risk of myocardial infarction (MI) by 36–44% [1]. This was questioned from a safety perspective [5], but daily aspirin at low doses (75–150 mg) is still recommended in patients with low risk of gastrointestinal or intracranial hemorrhage.

Aspirin is routinely used after MI and revascularization interventions. Aspirin given within 24 h after a MI reduces the likelihood of reinfarction and mortality. In patients diagnosed with acute coronary syndromes or unstable angina, guidelines recommend that aspirin be given prior to a percutaneous coronary intervention or thrombolysis and continued indefinitely [6]. This reduces the rates of stent thrombosis and mortality. Aspirin is also given as part of a dual antiplatelet therapy (DAPT) regime at low doses. After CABG, the use of aspirin improves graft patency and reduces mortality from MI, stroke, and renal failure [7, 8].

ADP Receptor Inhibitors

In patients presenting with an acute coronary syndrome or unstable angina, ADP receptor inhibitors are recommended by most guidelines. Patients who undergo a percutaneous coronary intervention and have stents are required to take ADP receptor inhibitors in combination with aspirin (DAPT). Recent guidelines have made a number of recommendations in this context [9–12]. Patients who receive bare-metal stents and are at low risk of bleeding should have DAPT for 4–6 weeks, whereas patients receiving drug-eluting stents should take DAPT for 6 months. Where there is increased risk of stent thrombosis, DAPT treatment should be increased to 12 months.

ADP receptor inhibitors tend to be used with low dose aspirin. The CURE trial found that aspirin with clopidogrel is superior to aspirin alone in patients with an acute coronary syndrome. This reduces major cardiac events and also reduces hemorrhagic side effects from higher dose aspirin [13].

ADP receptor inhibitors are also used in peripheral arterial disease to prevent thrombotic events and improve flow. They are also used as alternatives in ischemic strokes associated with carotid or vertebral artery dissections. ADP receptor inhibitors are also used as alternatives to warfarin in atrial fibrillation where warfarin is contraindicated.

Glycoprotein IIb/IIIa Receptor Inhibitors

Glycoprotein IIb/IIIa receptor inhibitors agents are given intravenously to have a quick onset of effect. Therefore, their use is mainly in the context of percutaneous coronary interventions or acute MI. A meta-analysis of 21 studies has shown that the use of glycoprotein IIb/IIIa receptor inhibitors in patients undergoing coronary interventions reduces the combined endpoint of death, non-fatal MI, or urgent revascularization at 30 days [14]. It is therefore recommended to use glycoprotein IIb/IIIa inhibitors in combination with aspirin and heparin for those medically managed or undergoing intervention for acute MI [15]. Specifically, for patients undergoing coronary interventions, initiation of therapy with heparin and abciximab, high-dose tirofiban/eptifibatide [15], or cangrelor, an intravenous and ultra-short acting ADP-receptor blocker is recommended [16].

Risks

Aspirin

Evidence shows that the antiplatelet effect increases up to 75–81 mg dosage, with higher doses increasing the gastrointestinal or intracranial bleeding risk without increasing benefit [17]. In particular, a review of 22 trials found that low-dose

aspirin doubles the risk of gastrointestinal and intracranial bleeding compared to placebo [18]. A meta-analysis of 16 trials showed that aspirin increases the risk of hemorrhagic stroke despite favorable effects on ischemic stroke and MI [19]. In patients undergoing a non-cardiac surgical intervention, aspirin use is not associated with major bleeding events [20]. However, in cardiac surgery, there is increased postoperative bleeding that however does not require reoperation when aspirin is continued [21].

ADP Receptor Inhibitors

ADP receptor inhibitors are associated with an increased bleeding risk, but compared with aspirin the gastrointestinal-related side effects are lower. The addition of clopidogrel to aspirin therapy in patients with coronary syndromes increases the risk of bleeding, but fatal bleeding rates remain similar [13]. More importantly, in patients undergoing CABG surgery, a meta-analysis found that clopidogrel use within 7 days preceding the intervention was associated with an increased risk of major bleeding and related complications, requiring re-exploration and transfusions [22]. In patients with an acute coronary syndrome, ticagrelor reduced the rate of death from prothrombotic causes compared to clopidogrel without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding [23]. However, patients on aspirin with ticagrelor have a stronger trend towards bleeding when ticagrelor is stopped only 1 day prior to surgery than patients on aspirin with clopidogrel [24].

Glycoprotein IIb/IIIa Receptor Inhibitors

Glycoprotein IIb/IIIa receptor inhibitors significantly increase the risk of bleeding compared with placebo [25]. However, the risk of bleeding is comparable to the use of heparin, in particular with respect to the rates of intracranial hemorrhage when used as single antiplatelet therapy [26].

Perioperative Use and Management

The use of antiplatelet drugs during cardiac and non-cardiac surgery increases the risk of perioperative bleeding, as previously indicated. However, the cessation of antiplatelet agents before surgery increases the risk of perioperative MI, stroke, stent occlusion, and even death from rebound pro-inflammatory effects. To ensure minimal risk for bleeding or life-threatening thrombosis, a risk evaluation and interdisciplinary management plan needs to be agreed upon before surgery.

Bleeding Risk

The bleeding risk varies according to the antiplatelet agents used, and whether dual antiplatelet therapy is being used. In a review it was stated that the risk of bleeding with continued use of antiplatelets is 30–50% compared with 2.5–20% in patients without antiplatelet drugs, and a 30% higher transfusion rate [4]. Given these risks, one should outweigh whether it is safe to plan surgery, or to delay surgery such that antiplatelet drugs can be discontinued. Moreover, in case of urgent surgery, the risk of bleeding due to antiplatelet therapy should be quantified. Surgeries are classed as low, intermediate, or high risk of bleeding depending on the vasculature involved and the transfusion requirements.

Cardiac surgery is classified as an intermediate risk of bleeding, but most patients will be on at least aspirin for primary prevention of cardiac ischemia. A sizeable portion of patients will be taking dual antiplatelet agents for secondary prevention after a previous cardiac event or intervention. Other factors that increase the bleeding risk are described in a previous chapter [27].

Recent European guidelines provided multiple recommendations on antiplatelet drug use in cardiac surgery [12, 28]. They recommend continuing aspirin unless the patient is at particularly high risk of bleeding, in which case, aspirin should be stopped at least 5 days before surgery. For patients on DAPT, ticagrelor, clopidogrel, and prasugrel should be stopped 3, 5, and 7 days prior to surgery, respectively. GPIIb/IIIa inhibitors should be discontinued at least 4 h prior to surgery. Obviously, in emergency surgery you should proceed to surgery and anticipate the higher risk of bleeding.

Thrombotic Risk

The thrombotic risk of cessation of antiplatelet therapy before cardiac surgery depends on the initial indication for antiplatelet use and the current cardiovascular status of the patient. Most patients will be taking antiplatelet agents for either primary or secondary prevention of cardiovascular disease, or cerebrovascular disease or peripheral vascular disease. However, patients that will present the greatest challenge will be those taking DAPT for secondary prevention of further ischemic cardiac events, especially following coronary stent implantation. Discontinuing these agents before surgery increases the risk for thrombosis from rebound platelet activation. In the context of coronary stents, thrombosis may occur within stents, leading to potential stent failure and myocardial ischemia. Figure 6.2 shows the considerations that need to be made before DAPT discontinuation. The thrombotic risk of cessation of aspirin is lower than for DAPT.

These factors then need to be considered in those undergoing cardiac surgery. If a stent has not been inserted, surgery will address coronary ischemia. However, if the stented vessels are not being addressed, then the risk of thrombosis from

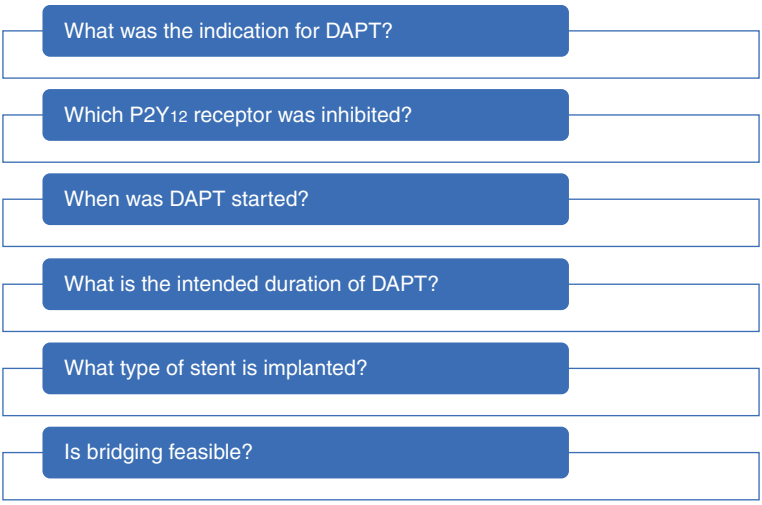

Fig. 6.2 Considerations that need to be made before cessation of dual antiplatelet therapy

discontinuing DAPT needs to be considered. DAPT has also been shown to improve graft patency in patients undergoing coronary artery bypass surgery. Therefore, the ACC/AHA guidelines recommend DAPT postoperatively for 12 months [9].

European guidelines recommend bridging therapy for patients at high risk of thrombosis, including patients with mechanical heart valves, atrial fibrillation with rheumatic heart disease, an acute thrombotic event in the previous 4 weeks, and/or atrial fibrillation with a CHA_2DS_2Vasc score of >4. Most of these patients will be on other anticoagulants, and bridging therapy will therefore consist of unfractionated or low-molecular weight heparins, cangrelor, or glycoprotein IIb/IIIa inhibitors.

Implications for Daily Practice

Antiplatelet drug use is common given the number of indications and the benefit of their use. However, their use perioperatively carries the risk of bleeding if continued intra-operatively and thrombosis if discontinued before surgery. These risks are amplified during dual antiplatelet therapy.

Bridging therapy can include short-acting antiplatelet agents, such as tirofiban and eptifibatide. Antiplatelet agents have transformed the treatment of acute coronary syndromes and the postoperative management of coronary artery bypass graft patients. Appropriate use must be balanced by the risk of thrombosis versus hemorrhage and side effects. Devices such as platelet aggregometry exist to measure platelet inhibition levels, and might be used to assess the risk of individual patients. The correct timing for when to stop and restart therapy is discussed in the next chapters.

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Preoperative Management of Oral Anticoagulants

7

Emma C. Hansson and Anders Jeppsson

Case Vignette

A 73-year-old man with hypertension, paroxysmal atrial fibrillation, and known renal failure (eGFR 40 mL/min) underwent coronary angiography due to stable angina. The patient had not had any thromboembolic episode but is treated with the direct oral anticoagulant dabigatran (150 mg × 2) for stroke prevention. The coronary angiography revealed left main stenosis and a pronounced three vessel disease. Echocardiography shows a moderately impaired left ventricular ejection fraction (45%). The patient is discussed at the heart team conference and accepted for elective CABG within 2 weeks. How should the oral anticoagulant be handled before the elective operation? If the oral anticoagulant is discontinued, is bridging with heparin necessary? How should patients with oral anticoagulation and acute need of surgery be handled?

Why Is It Important?

Oral anticoagulation (OAC), including vitamin K antagonists (VKA), factor Xa-inhibitors, and thrombin inhibitors, is used with increasing frequency among cardiac surgery patients. Current indications for OAC include prevention of thromboembolic complications in patients with atrial fibrillation, venous thromboembolism such as pulmonary embolism and deep vein thrombosis, ischemic stroke, and mechanical valve prostheses [1, 2]. In addition, recent data suggest that selected patients with coronary artery disease may benefit from anticoagulation [3].

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It has been estimated that approximately 300,000 patients in Sweden (3% of a population of ten million inhabitants) are treated with OAC [4]. Extrapolation to the Western European population would mean that approximately 12 million patients receive OAC in this part of Europe. Consequently, a large and increasing number of patients with OAC will be exposed to acute and elective surgery, trauma, and spontaneous bleeding episodes, with ongoing potent anticoagulation. In Sweden, it has been estimated that approximately 0.5–1% of patients on OAC will need acute surgery and 2–3% will have major bleeding annually [5]. A similar study from Denmark showed 3–5% major bleeding rate per annum in patients on OAC [6].

For a long period, VKAs were the mainstay of OAC. This has changed dramatically during the last 5 years with an increasing proportion of patients treated with non-vitamin K dependent oral anticoagulants (NOACs), sometimes referred to as new oral anticoagulants (NOACs) or direct oral anticoagulants (DOAC). Today, the majority of patients on oral anticoagulation are treated with NOACs [4].

Correct perioperative management of patients on OAC, regardless of the type of medication, is essential to reduce perioperative bleeding complications, and subsequent morbidity and mortality.

The purpose of this chapter is to discuss the different oral anticoagulants regarding mode of action, diagnostics, preoperative discontinuation, reversal of the anticoagulant effect, and treatment if bleeding occurs.

Vitamin K Antagonists

Vitamin K antagonists influence all vitamin K dependent coagulation factors, including factors II, VII, IX, and X (Fig. 7.1).

Vitamin K antagonists are the only approved anticoagulant for patients with mechanical heart valves [2, 7], but are also commonly used in patients with atrial fibrillation, venous thromboembolic disease, and ischemic stroke, although NOACs are utilized with increasing frequency for these indications (Fig. 7.2).

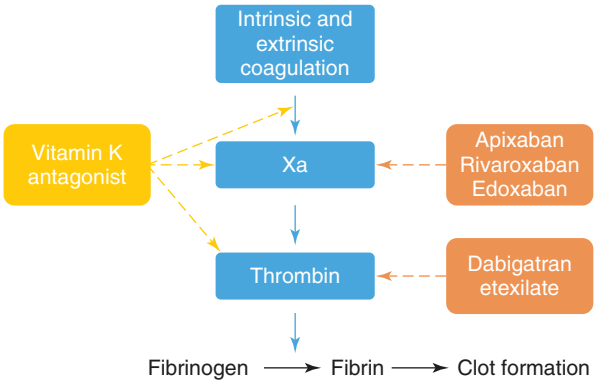

Fig. 7.1 Targets for vitamin K antagonists (VKA) and non-vitamin K oral anticoagulants (NOACs)

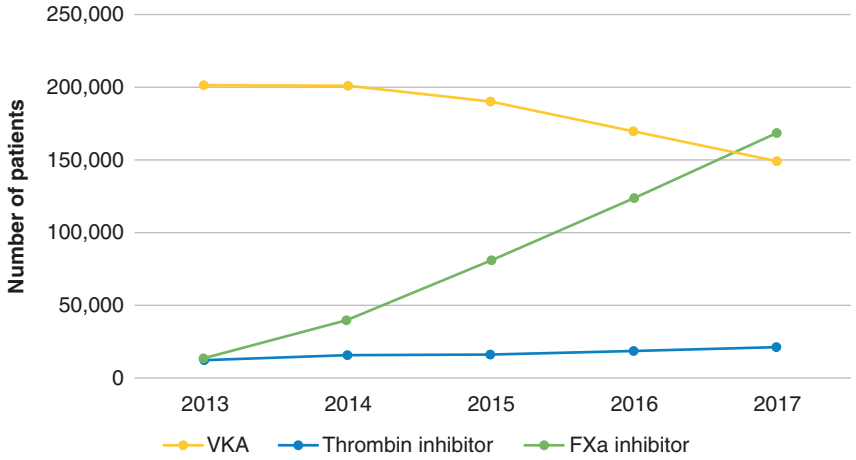

Fig. 7.2 Patients with oral anticoagulants for all indications in Sweden in the period 2012–2017. Adapted from Ref. [4]

Table 7.1 Vitamin K antagonists

	Acenocoumarol	Fluindione	Warfarin	Phenprocoumon
Half-life (h)	10	30–40	35–80	70–100
Steady state (days)	2–3	3–4	3–6	6
Duration of anticoagulant effect (h)	48–96	48–72	96–120	120–150

Adapted from Ref. [8]

Characteristics of the most common VKAs are summarized in Table 7.1. Long-acting VKAs are used more commonly than acenocoumarol.

The effect of VKAs can be assessed by measuring prothrombin time (PT), mostly reported as international normalized ratio (INR). A normal INR is 0.9–1.2, while target levels in patients on OAC depend on the indication. For patients with standard mechanical heart valve prostheses, a median INR of 2.5–3.5 is recommended in guidelines, depending on prosthesis position and concomitant risk factors in the individual patient [2, 7], even though newer prostheses with more beneficial flow profiles are intended to be used with a lower INR range. The anticoagulation of patients on VKA needs to be monitored regularly by measuring INR to ensure both efficacy and safety [9, 10]. A further disadvantage with VKA is the commonly occurring interactions with other pharmaceutical drugs through cytochrome P-enzymes and with fruits and vegetables high in vitamin K.

Compared to NOACs, VKAs need a longer time until steady state is reached and have a substantially longer half-life. Furthermore, the anticoagulant effect is not reversed until sufficiently high levels of the inhibited coagulation factors have been synthesized. This implies that VKAs must be discontinued longer before elective surgery than NOACs. Current guidelines recommend that INR should be $\leq$1.5 in

Table 7.2 Dosing of prothrombin complex concentrate (PCC) to reverse vitamin K antagonists

Patient weight (kg)	Patient INR 1.5–2.0 (IU)	Patient INR 2.0–3.0 (IU)	Patient INR >3.0 (IU)
40–60	500	1.000	1.500
60–90	1.000	1.500	2.000
>90	1.500	2.000	2.500

Adapted from Ref. [15]

VKA patients undergoing major surgery with a high bleeding risk, e.g., cardiac surgery [1, 2, 8, 11]. This usually takes 4–5 days in patients on chronic VKA. For minor surgical interventions with a low bleeding risk, a higher INR is acceptable [12], and discontinuation should be avoided. Bridging with heparin or low-molecular weight heparin in VKA patients is only indicated in highly selected cases with a very high thrombotic risk, e.g., patients with mechanical heart valve prostheses and in patients with a recent thromboembolic episode [1, 2, 8, 11, 13]. Bridging of oral anticoagulants will be discussed in more detail in a separate chapter in this book.

If acute major surgery becomes necessary in patients on VKA, or in the event of large spontaneous or perioperative bleeding, the effect of VKA can be instantly reversed by administration of prothrombin complex concentrate (PCC) [14]. Based on the experience of Swedish anesthetists and coagulation experts it is suggested to use a starting dose of PCC to achieve an INR of 1.5 (Table 7.2) [15]. If the effect is insufficient, further 500–1000 IU may be administered. Concomitant administration of vitamin K (5–10 mg) may also be considered, since the re-synthesis of factor VII and the other dependent factors is enhanced by administration of vitamin K. The PCC dose can also be calculated using the following formula:

$$\textbf{Dose of PCC}: \text{PT ratio}\left(\text{target}\right) - \text{PT ratio}\left(\text{actual}\right) \times \text{bodyweight}\left(\text{kg}\right) \times 0.8$$

Non-Vitamin K Oral Anticoagulants

From a pharmacological aspect, the currently available NOACs can be divided into those targeting factor Xa (rivaroxaban, edoxaban, and apixaban) and the one directly targeting thrombin (dabigatran etexilate) (see also Fig. 7.1 and Table 7.3).

NOACs were developed to overcome the limitations of VKAs, i.e., to achieve sufficient anticoagulation with a wide therapeutic window avoiding monitoring, and to reduce interaction with other pharmacological products. The indications for NOACs are largely the same as for VKAs (atrial fibrillation, systemic venous thromboembolism, and ischemic stroke), and for rivaroxaban; secondary prevention in coronary artery disease patients with peripheral artery disease [3], with the important exception of patients with mechanical heart valve prosthesis and valvular atrial fibrillation (i.e., severe mitral stenosis), in which VKAs are mandatory [2, 7, 8, 11]. In addition, NOACs are also indicated for perioperative thromboprophylaxis.

Table 7.3 Currently registered NOACs (modified after reference [11])

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran Etexilate
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Bioavailability	80%	51–85%	60%	6–8%
T_{max}	2–4 h	3 h	1–3 h	2 h
Half-life	9–13 h	9–14 h	5–11 h	14–17 h
Frequency of administration	Once-daily	Twice-daily	Once-daily	Once/twice-daily
Renal excretion	35%	25%	36–45%	80%
Antidote	Andexanet alfa[a]	Andexanet alfa[a]	Andexanet alfa[a]	Idarucizumab
Discontinuation before elective surgery	48 h	48 h	48 h	48–96 h[b]

[a]Currently registered in the USA only
[b]Depending on renal function

The NOACs have been compared with the VKA warfarin in several large randomized trials. In patients with AF, NOACs compare favorably regarding stroke prevention, intracranial bleeding, and mortality while the incidence of major bleeding is comparable [16, 17], with the exception of gastrointestinal bleeding, where the rate was higher in the NOAC treated groups [18]. These findings are consistent across a wide range of patient subgroups and NOACs are therefore recommended as first-line of therapy in non-valvular atrial fibrillation patients [1]. Furthermore, NOACs have been shown to be effective to prevent recurrent events in patients with pulmonary embolism and venous thromboembolism [16, 17, 19]. All these observations and the avoidance of regular monitoring and interactions favor the use of NOAC instead of VKA in the majority of patients in need of OAC. This is illustrated by the increased use of NOACs at the expense of VKAs in Fig. 7.2.

In patients with ongoing or recently stopped NOAC treatment, plasma concentration of the individual NOAC is the best way to assess the residual activity of the drug and to estimate the perioperative bleeding risk [19, 20]. However, these analyses may not be readily available at all hospitals. The effect of NOACs can also be assessed by measuring diluted thrombin time for dabigatran and anti-factor Xa assays for the factor Xa-inhibitors. More commonly used coagulation assays like PT and aPTT can be normal or only moderately elevated in patients with therapeutic levels of NOACs [19, 20]. Viscoelastic methods have not been proven effective in measuring NOAC activity.

In patients with normal renal function, dabigatran exetilate should be discontinued 48 h before high bleeding risk procedures, like cardiac or other major surgery. In patients with reduced renal function (eGFR <50 mL/min) dabigatran should be stopped 96 h before surgery [17, 19]. Factor Xa-inhibitors should be interrupted 48 h before major surgical procedures independently of renal function. Bridging with heparins is only recommended when there is a recent history of an acute thromboembolic event, such as ischemic stroke or pulmonary embolism.

If a large bleeding occurs, or if acute surgery becomes necessary in a patient on NOAC, there are different reversal options. In patients treated with dabigatran an antidote, idarucizumab, is available [21]. The antidote is a humanized antibody fragment specifically binding dabigatran. Idarucizumab has been approved by EMA and FDA based on the REVERSE-AD trial demonstrating a nearly complete reversal of the anticoagulant effects of dabigatran in bleeding patients within at least 30 min of administration and positive effect on hemostasis [21]. For patients treated with FXa-inhibitors an antidote, andexanet alfa, has been approved for reversal of FXa-inhibitors in the USA, but not yet in Europe. Andexanet alfa is a recombinant human FXa analog that competes for FXa with the FXa-inhibitors. In the ANNEXA-R and ANNEXA-A trials, andexanet alfa reversed the effect of rivaroxaban and apixaban with 92% and 94% efficacy rates, respectively [22]. The effect on bleeding and hemostasis is investigated in the ongoing ANNEXA-4 trials, with positive preliminary results reported [23]. It should be pointed out that both REVERSE-AD and ANNEXA-4 are single arms studies without comparators. If the antidotes are unavailable, off-label use of non-activated or activated PCC may be considered in patients likely to have therapeutic or supra-therapeutic levels of NOACs [17, 19]. Other pro-hemostatic or pro-coagulants such as recombinant factor VIIa are not sufficiently studied regarding reversal of NOAC effect.

Implications for Daily Practice

In conclusion, an increasing share of the population is treated with oral anticoagulants. These patients will develop cardiac diseases requiring acute or subacute surgery. Correct handling of these patients, including discontinuation when possible, bridging in selected patients, and reversal if acute surgery is necessary or if acute severe bleeding occur, is essential for the patients' well-being and prognosis.

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Bridging

8

Pascal Colson

Case Vignette

A 77-year-old female is scheduled for urgent coronary artery bypass graft surgery (CABG) due to an acute coronary syndrome caused by a multi-vessel disease involving all coronary arteries. Apart from this, a recent stroke (3 months before hospitalization) due to a non-valvular atrial fibrillation, a non-insulin dependent diabetes, hyperlipidemia, arterial hypertension, a moderate renal insufficiency with a creatinine between 1.5 and 2 mg/dL (i.e., 133 and 177 μmol/L), and an obesity with a body mass index of 37 kg/m^2 is known.

The patient is on warfarin with an INR of 2.3 on admission to hospital and 500 mg of aspirin was given intravenously before cardiac angiography. Due to the complex anticoagulation and the multi-vessel disease it was decided not to load her with a $P2Y_{12}$-inhibitor. The cardiac anesthesia team is approached on how to manage the warfarin anticoagulation in this patient.

Why Is It Important?

Many patients undergoing cardiac surgery are treated by an oral anticoagulant and/or antiplatelet therapy before surgery. These treatments are aimed at reducing the thromboembolic event risk, mainly stroke, or the ischemic risk, mainly myocardial infarction, in their daily life. However, continuation of these therapies increases the risk for perioperative bleeding. The benefit/risk ratio favors these treatments on daily care, but may be challenged in case of surgery, especially when the bleeding

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risk is high. In this respect, the challenge is to find the equilibrium between the indication of the medical treatment (prevention of the thromboembolic or ischemic risks) and the bleeding risk.

Bridging, which means switching an oral anticoagulant or antiplatelet drug to a more easily manageable drug, usually a parenteral one, is a possible option. If bridging is decided, it should result from an agreement between the cardiac surgeon, the cardiologist, and the anesthesiologist for an individual patient.

In general, the benefit of preventing a thromboembolic or ischemic event is considered to be higher than the risk of bleeding [1–7]. The objective of bridging should be to keep the same benefit, with both risks as low as possible. The main challenge is that surgery is not only associated with an increased risk for bleeding, but may also alter the risk of thromboembolic events due to the surgery-induced inflammatory response and surgical trauma. While the risk for bleeding is maximal during surgery or in the early postoperative period, the risk for thromboembolic or ischemic events peaks in the first days following surgery.

Furthermore, anticoagulant and antiplatelet drugs have a prolonged half-life, which influences the timing of discontinuation. Additionally, not all anticoagulant and antiplatelet drugs have appropriate antagonists. The concept of bridging therapy arose with the assumption that the bridging treatment has a titratable effect, with a predictable and quick reversal possibility. The switch to the bridging treatment needs to be timely managed, and careful attention is required since the effects of the primary drugs can overlap the therapy used for bridging. The purpose of this chapter is to provide insight in bridging options for oral anticoagulants and antiplatelet drugs in patients undergoing cardiac surgery.

Bridging of Oral Anticoagulation

Reduction of the Thromboembolic or Ischemic Risk

Oral anticoagulants are administered to reduce the risk for thromboembolic complications, especially in patients with atrial fibrillation, mechanical heart valves, or venous thromboembolism [8]. Table 8.1 shows the criteria for risk stratification for perioperative thromboembolism.

Even for these few indications the rate of periprocedural thromboembolism for unbridged oral anticoagulant interruptions is estimated at only 0.5% [9]. The perioperative risk of thromboembolism is higher for patients with a mechanical heart valve (1%) than for patients with atrial fibrillation or venous thromboembolism (0.5%) [8, 10]. In patients with left ventricular assist devices, the long-term thromboembolic risk is 1.5% per year. However, the timing of left ventricular assist device implantation is crucial, as the ischemic stroke rate peaks during the first post-implantation years, reaching 5.5% per year, irrespective of the type of implanted device [11, 12]. Despite the high risk for thromboembolic events, the bleeding risk is even higher, estimating 20–25% per year. In these patients, bridging may not be a good strategy [12].

Table 8.1 Risk stratification for perioperative thromboembolism

Indication for anticoagulation			
Risk group	Mechanical heart valve	Atrial fibrillation	VTE
High[a]	• Mitral valve prosthesis • Cage-ball or tilting disc aortic valve prosthesis • CVA/TIA <6 months prior	• CHA_2DS_2-VASc >6 • CVA/TIA <3 months prior • Rheumatic valvular heart disease prior	• VTE <3 months • Severe thrombophilia[b]
Moderate	• Bi-leaflet aortic valve and other risk factors[d]	• CHA_2DS_2-VASc 4–5	• VTE 3–12 months prior • Non-severe thrombophilia[c] • Recurrent VTE • Active cancer
Low	• Bi-leaflet aortic valve without other risk factors	• CHA_2DS_2-VASc 2–3 without prior CVA/TIA	• VTE >12 months prior without other risk factors

Data from the American College of Chest Physicians (ACCP) guidelines [8]
CVA cerebrovascular accident, *TIA* transient ischemic attack, *VTE* venous thromboembolism
CHA_2DS_2-VASc score: congestive heart failure, hypertension, age ≥75 years or 65–74, diabetes mellitus, stroke, vascular disease, female sex
[a]A true high-risk category may be difficult to objectively define in the absence of trials demonstrating benefit of heparin bridging in such patients
[b]Deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities
[c]Heterozygous factor V Leiden or prothrombin gene mutation
[d]CVA risk factors include: atrial fibrillation, prior CVA/TIA, hypertension, diabetes, congestive heart failure, age >75 years

The non-vitamin K oral anticoagulants (NOACs) are increasingly prescribed in the prevention of thromboembolic events in patients with atrial fibrillation or venous thromboembolism. In large trials and registries it was shown that these patients did not experience an increased thromboembolic rate in the perioperative period, irrespective whether they were bridged or unbridged [13, 14]. The rather low incidence of thromboembolic events observed in the literature explains why there is no scientific evidence to support bridging in case of these novel anticoagulants, even in high-risk patients.

Reduction of the Bleeding Risk

Bridging is undoubtedly associated with a higher risk of bleeding [15–17]. A meta-analysis of 34 observational studies of bridging anticoagulation found an odds ratio of 3.6 (95% CI 1.52–8.50) for major bleeding with bridging versus non-bridging, and no significant difference in thromboembolic events or mortality [18]. These results are observed whatever the invasive procedure considered,

and are consistent with the more recent data of the ORBIT-AF study [10]. In this study it was shown that bleeding events in cardiac surgery occurred more frequently after bridging compared to no bridging (7.1% vs. 4.2%) [10]. Similar results were found for NOACS, showing that continuation or short-term interruption of these drugs is safe for most invasive procedures, and bridging should only be considered in patients at cardiovascular risk undergoing major procedures [19].

In summary, there are no solid data supporting bridging of oral anticoagulants, and bridging, therefore, remains based on a case-by-case multidisciplinary decision [6]. However, in specific cases, bridging might be considered in order to prevent further thromboembolic complications, such as patients with a high risk of recurrent VTE, patients with atrial fibrillation and an ischemic event in the last 3 months, or patients with a mechanical heart valve other than a bileaflet valve [20].

Bridging of Antiplatelet Drugs

In analogy with oral anticoagulants, preoperative discontinuation of antiplatelet therapy requires balancing of the embolic and bleeding risks that are associated with cessation or discontinuation. Bridging should only be considered in patients on dual antiplatelet therapy (DAPT), or when high dose aspirin or $P2Y_{12}$-receptor inhibitors are used. Patients requiring coronary artery bypass grafting within the time of dual antiplatelet therapy administration are specifically concerned due to their high risk for ischemic events [21].

Current European Society of Cardiology guidelines state that bridging strategies should only be considered in patients at a very high risk for ischemia (active ischemia, high-risk coronary anatomy, and surgery performed very early after stent implantation) in whom temporary discontinuation of antiplatelet therapy is considered inevitable because of elevated hemorrhagic risk [22]. When patients face a high risk for bleeding, perioperative continuation of dual antiplatelet therapy is inappropriate, whereas the concomitant presence of high ischemic risk mandates the minimization of the total time without antithrombotic protection. In this case, it is recommended to measure the biological effect of antiplatelet therapy on platelet function before surgery. Various platelet function tests are available, and may be used to determine the extent of platelet dysfunction in a point-of-care setting [23]. There are however no data available that support the use of these platelet function tests in the decision to bridge patients. In summary, bridging of antiplatelet therapy is not supported by scientific evidence. Besides low dose aspirin continuation, adding parenteral antiplatelet drugs to maintain antiplatelet activity just before surgery remains discussed. The management of antiplatelet therapy currently consists of maintenance of a low dose aspirin, and to reduce the time, as short as possible, without dual antiplatelet therapy or $P2Y_{12}$-receptor inhibitors.

Implications for Daily Practice

The decision to bridge a patient before surgery is based on the specific condition of the patient, since the therapeutic solutions are rather limited. Postponing surgery would be the first option in some patients. There are various bridging protocols available, which all take the anticoagulant effect duration into account and offer a progressive switch to parenteral anticoagulation [9, 20]. Bridging should only be considered in patients where the risk of thromboembolic events is high. Parenteral anticoagulation includes subcutaneous low molecular weight heparin (LMWH) or unfractionated heparin (UFH). The objective is mainly therapeutic, which means that the LMWH dose is adapted to the weight of the patient or is 1.5–2.5 times the control activated partial thromboplastin time for UFH. Parenteral anticoagulants are started 2 days after the withdrawal of oral anticoagulant, 3 days before surgery, and stopped 12–24 h before surgery. Parenteral anticoagulants are resumed at 6–48 h after surgery according to the bleeding risk [20]. For more detailed information regarding bridging protocols we refer to reference 24.

The perioperative use of LMWH or UFH in patients with coronary stents shows no consistent protective effect against stent thrombosis, while bleeding events increase [4]. European guidelines therefore discourage the use of heparins as bridging treatment for antiplatelet therapy [4]. Indeed, heparin pharmacodynamics are relatively ineffective in the prevention of platelet aggregation, and unfractionated heparin may even activate platelet aggregation [25].

Among parenteral antiplatelet therapy, short acting glycoprotein IIb/IIIa inhibitors (tirofiban or eptifibatide) could be considered as bridging agents [4, 22]. For example, for bridging clopidogrel, tirofiban infusion can be started 5 days before surgery, stopped 4 h before surgery, and resumed at the same schedule at 2 h after the end of surgery, and continued for up to 6 h after the resumption of clopidogrel, unless oral administration could be resumed on the same day of surgery [26].

Cangrelor is a novel non-thienopyridine intravenous antiplatelet agent with a very short plasma half-life (3–5 min), which reversibly blocks the $P2Y_{12}$ receptor. These properties result in a rapid offset of action, within 1 h of cessation of administration, while the onset of action is immediate. The use of cangrelor for bridging $P2Y_{12}$ inhibitor-treated patients to CABG surgery was evaluated against placebo [27]. Cangrelor resulted in a higher rate of maintenance of platelet inhibition and did not increase major bleeding before surgery. Although its characteristics theoretically approach the ideal of an antiplatelet-bridging drug, cangrelor is not yet commercially available everywhere.

After surgery, antiplatelet therapy should be resumed as soon as possible, not only with respect to aspirin to all patients having CABG but also $P2Y_{12}$-receptor inhibitors [22, 23] provided there is no concern of bleeding.

The indication for concomitant oral anticoagulant and antiplatelet therapy makes the perioperative management of patients more complicated. The combination of both thromboembolic and ischemic risks suggests that these patients would probably require a bridging strategy, but there are no scientific data to support clinical

decision-making. A combination of a single antiplatelet agent plus a parenteral anticoagulant (UFH/LMWH) might be considered as a perioperative bridging strategy to protect against both stent thrombosis and embolism [21].

For the 62-year-old lady of the case vignette the decision whether to bridge or not needs an individualized weighing of the risks and benefits. An interdisciplinary consensus recommends for this patient to interrupt warfarin until an INR of <1.5 is reached. Due to the rather high thromboembolic and the moderate bleeding risk with a primary CABG procedure a bridging protocol involving either the intravenous administration of unfractionated heparin (aPTT-guided) or the subcutaneous application of a half (some institutions may prefer full dose) therapeutic dose of low molecular weight heparin (LMWH) is advised for the interruption period until surgery. The half dose LMWH protocol should stop at 12 h (24 h for the full dose protocol) before cardiac surgery to prevent excessive blood loss. Unfractionated heparin may be continued until the start of surgery.

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Part IV

Monitoring of Coagulation and Hemostasis

Platelet Function Monitoring

9

Marcus D. Lancé

Case Vignette

A 63-year-old farmer is admitted to the emergency department with an acute coronary syndrome. He takes aspirin (75 mg/day) and clopidogrel (75 mg/day) after he received a drug eluting stent in the proximal left coronary artery 8 months ago. The coronary angiography showed a near occlusion of this stent. In addition, there are subtotal occlusions in the distal right coronary artery and proximal circumflex artery, so the heart team decides for urgent coronary artery bypass graft surgery. The team questions whether the antiplatelet drugs were effective, and whether platelet function testing could provide sufficient information about the bleeding and thrombotic risk. Moreover, can platelet function analysis be used to estimate the bleeding risk, and valuable for changing therapy?

Why Is It Important?

Antiplatelet therapy is a cornerstone of primary and secondary prevention in cardiology. Particularly, patients with an acute coronary syndrome or a percutaneous intervention frequently receive dual antiplatelet therapy consisting of aspirin and a $P2Y_{12}$-receptor antagonist, like clopidogrel, prasugrel, or ticagrelor, to prevent progression of the disease and stent thrombosis. However, due to a variety of reasons this prophylaxis is not always effective, which renders a risk of a thrombotic event. In addition, treatment with antiplatelet drugs puts patients at risk for bleeding with 4–7 events per 100-person years. In case of an urgent operation this risk must be balanced against the risk of stent-thrombosis [1].

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Looking at cardiac surgery, bleeding still is one of the most important perioperative complications. It increases mortality independently with more than 10%, even if blood products are administered [2]. Some bleeding risk factors are known for a long time, such as the impact of surgical trauma, prolonged use of the extracorporeal circuit, and the use of high dose anticoagulants. Others gained more attention during the last decade, like the deliberate use and combination of antiplatelet and antithrombotic drugs before surgery. It is therefore of importance to understand the individual bleeding mechanism, followed by targeted therapy in order to correct coagulation abnormalities and reduce unnecessary transfusion of blood products. After surgery, most patients restart antiplatelet therapy to protect their grafts, and the timing of discontinuation and resuming of therapy is crucial in the perioperative management in cardiac surgery. The aim of this chapter is to describe the function of human platelets, the approach to test their function, and to translate this knowledge into clinical practice.

Platelet Function

With a diameter of 2–5 μm and counts between 150 and 350 × 10^9/L, platelets are the smallest and second most frequent particular components circulating in blood, with a life-span of about 10 days. Aside their involvement in inflammation, the host defense, angiogenesis, and atherosclerosis, initiation and augmentation of coagulation is the main function of platelets [3]. Platelet contribution to hemostasis was classically described as primary, corpuscular hemostasis separated from the secondary, plasmatic hemostasis. Nowadays it is thought that platelets activate and propagate coagulation in general.

In brief, due to their small size, platelets are pushed to the vessel walls in the blood stream. Here they keep a close contact to the endothelium where they adhere to injured, endothelium-denuded layers (e.g., after a vessel wall lesion) binding to von Willebrand factor (vWF), thrombospondin-1, and under low shear stress directly to collagen. This adhesion initiates the secretion of multiple mediators, like adenosine diphosphate (ADP), thrombin, and fibrinogen, which enhances further platelet activation. The process leads to contraction of the actin–myosin filaments and shape change of the platelets, turning them into an aggregation state. In the activated state, platelets express tissue factor on their membrane, which in concert with a complex of activated coagulation factor VII and tissue factor starts and amplifies the plasmatic coagulation [4]. Yet, the activation of platelets needs different receptors, which have specific agonists (Table 9.1).

The platelet receptor pathways are used as specific therapeutic targets and the assessment of platelet function. Like in other receptor–agonist conditions a high concentration of a weak agonist or a low concentration of a strong agonist is used in these tests to induce and maintain irreversible aggregation [4]. Figure 9.1 shows the different platelet function tests with their respective activators.

What is the Evidence from the Literature?

Continuing aspirin throughout cardiac surgery as a single therapy results in reduced cardiovascular morbidity and mortality, with an acceptable, mildly

Table 9.1 Platelet receptors and their activators

Activator	Receptor	Effect	Characteristics
ADP	P2Y1/P2Y$_{12}$	Enhancing of activation	Secreted from dense bodies Major platelet feedback agonist
Thromboxane A$_2$	Thromboxane receptor	Maintenance of activated state	Weak agonist
Thrombin	PAR 1/PAR 4	Induction of inside-out signaling	Strong agonist Induction of procoagulant surface
Collagen	GPIa/IIa, GPVI	Adhesion to subendothelial layer Secretion	Strong agonist Low shear rate Induction of procoagulant surface
vWF	GPIbalpha (GPIb/V/IX)	Adhesion to subendothelial layer Secretion	High shear rate
Thrombospondin	GPIbalpha	Adhesion to subendothelial layer Secretion	High shear rate
Fibrinogen	GPIIb/IIIa	Cross linking platelets Aggregation and activation (outside-in signaling)	–

ADP adenosine diphosphate, *vWF* von Willebrand Factor

increased bleeding risk [5]. Only in high bleeding risk situations, aspirin could be paused preoperatively. This is different for dual antiplatelet therapy. Although dual antiplatelet therapy reduces the cardiovascular risk, it also increases the burden of bleeding, which is associated with higher morbidity and mortality. For this reason, discontinuation of the P2Y$_{12}$ blocker in a timely manner is advised in most cases. Due to the urgent or emergency character of cardiac surgery, there is frequently no time to discontinue dual antiplatelet therapy on time, which requires intensified hemostatic monitoring. Moreover, some patients are insensitive to platelet inhibitors, and these patients are at an increased risk for postoperative thrombosis, which also justifies hemostatic and platelet function assessment [5].

Platelet Function Tests

Available platelet function tests can be divided into tests directly assessing platelets and assays which detect surrogate parameters of platelet activation. In this section, we focus on the direct tests, which are mainly point-of-care (POC) tests. In general, there are whole blood tests and assays using platelet rich plasma to assess platelet function. Moreover, global evaluations can be separated from (very) specific tests, such as flow cytometry.

PFA-100/200	ADP/EPI/ADP+PGE1
Light Transmission Aggregometry	All possible, ADP/AA/TRAP/Collagen
VerifyNow	ADP/AA/PGE1
PlateletWorks	ADP/AA/Collagen
WBA	ADP/TRAP/Collagen/Ristocetin
TEG-platelet mapping	ADP/AA
ROTEM-MEA	ADP/AA/TRAP

Fig. 9.1 Different platelet function analyzers with their respective activators. *PFA* platelet function analyzer, *WBA* whole blood impedance platelet aggregometry, *TEG* thromboelastography, *ROTEM* rotational thromboelastometry, *MEA* multiple electrode aggregometry, *ADP* adenosine diphosphate, *EPI* epinephrine, *PGE1* prostaglandin E1, *TRAP* thrombin receptor activating peptide, *AA* arachidonic acid

The gold standard for platelet function analysis is light transmission aggregometry (LTA). For this test a sample of citrated whole blood needs to be spun off two times and separated to retain platelet rich plasma and platelet poor plasma. In the next step the material will be mixed with platelet activators, and the change of turbidity is measured by change of light absorption to compare platelet rich and poor plasma. The platelet poor plasma is generally clear and serves as calibrator. An advantage of this method is the freedom to use different activators in various concentrations, and the possibility to detect even mild abnormalities. Unfortunately, this test is work-intensive and time consuming, and not considered as POC. Besides, it seems quite non-physiological, because it excludes all other corpuscular components of the blood. In addition, the test is not properly standardized, which makes it difficult to compare results between different laboratories [4, 6].

VerifyNow™

The VerifyNow is a system based on the light transmission aggregometry principle. The device is more frequently used in cardiology for quantification of antiplatelet drug effects [1]. It works fully automated with cartridges prefilled with fibrin-coated polystyrene beads combined with a platelet activator. According to the pathway to be assessed there are three different cartridges containing arachidonic acid (AA), ADP, or prostaglandin E1 as an activator. After adding a sample of citrated whole blood,

the system measures the change of light transmission over time. The main advantage of the technique is the use of whole blood and the complete automatization.

Whole Blood Impedance Aggregometry

Whole blood impedance aggregometry, like multiple electrode aggregometry, Multiplate™ or ROTEM-platelet™, is a frequently used method to assess platelet function. A blood sample is first anticoagulated, usually with hirudin, and pipetted into small cups. A predefined concentration of an activator, depending on the manufacturer (e.g., ADP, AA, collagen, thrombin activating peptide [11], or ristocetin) is added. For the Multiplate™, the reagents enable the diagnosis of von Willebrand disease with ristocetin, or the effect of antiplatelet drugs by ADP and AA. The ROTEM-platelet™ focuses on detecting an antiplatelet agent effect by ADP, AA, and the thrombin activating peptide (TRAP) test reflecting $P2Y_{12}$ inhibition, aspirin, or GPIIb/IIIa inhibition, respectively.

In the measurement cup, two pairs of electrical wires are built. Between each of them a current is running, while a magnetic stirrer keeps the diluted whole blood mixed. After activation, the platelets will adhere to fibrinogen, which is first condensed to the wires. This causes a change of electrical impedance, which is measured over time. Although initiation of this test needs some expertise, it is easy to perform and does not require much training or time. The results of the impedance change are displayed while the test is running. After 6 min, the test stops automatically and can be read out [4, 12].

Thromboelastography Platelet Mapping

The thromboelastography (TEG) platelet mapping uses citrated whole blood, which is processed by pipetting it into the test-cup. Blood is subsequently spiked with ADP or AA as platelet receptor activator. The results of these two tests are compared to the results of the conventional TEG-traces, which allows conclusions about platelet contribution to clot strength. Particularly, the newer version of the TEG devices, the TEG 6S, is semi-automated and uses cartridges which only need to be filled by pipetting.

PlateletWorks™

The PlateletWorks™ approach uses a standard impedance cell counter and two tubes of blood. The platelet function activator is added to one of these tubes, and the proportional difference in platelet count is given as a surrogate marker for platelet activation. This method correlates well with results from LTA studies [10]. The main advantage is the use of whole blood and of common counter systems, which are widely available. However, the system relies on end-point platelet aggregation, which means that it is sensitive to incomplete aggregation. More importantly, the method is sensitive to all kind of situations, where a cell counting device struggles with (e.g. giant cells,

pseudothrombocytopenia, cell fragments). According to the literature, one EDTA tube is needed for basic counting, while the second tube spiked with an activator should contain citrated blood. This induces a dilution mismatch, resulting in lower platelet counts in the citrated sample even if no platelet activation took place.

Platelet Function Analyzer

The platelet function analyzer (PFA-100/200™) uses citrated whole blood. Blood is aspirated through an activator-coated capillary which mimics shear stress. The time that is required to close the capillary is quantified and correlates with platelet function. The system does not need any preparation of the sample, which eases its use. The application of shear stress allows screening for moderate to severe forms of von Willebrand diseases and Glanzmann's thrombasthenia. There are three cartridges available (collagen/ADP, collagen/epinephrine, and collagen/prostaglandin E1) for the detection of aspirin and $P2Y_{12}$ blocker effects. The main disadvantage is the low sensitivity and specificity of the system [6].

VASP test

Aside to the described tests there are some more which are not very well studied in cardiac surgery. These are mainly the one using surrogate parameters like the Vasodilator-stimulated phosphoprotein phosphorylation assay (VASP), which is more used in cardiology. Principally the VASP test uses PRP in which the phosphorylation state is assessed rather by flow cytometry or by ELISA based assays.

Limits of Platelet Function Tests

Apart from the light transmission aggregometry, all systems have moderate to low sensitivity to mild platelet dysfunction, which could play a role as an ancillary factor when the coagulation system is generally disturbed. This means that a combination of low coagulation factor concentration, low hemoglobin, and mildly decreased platelet dysfunction could result in clinical bleeding, while all laboratory parameters are still at the lower edge of normality.

Moreover, whole blood impedance aggregometry is influenced by temperature, protamine, and tranexamic acid, but not by anesthetic drugs like midazolam, propofol, lidocaine, and magnesium [13]. The literature regarding drug interactions with other platelet function tests is however limited. To a certain degree, all systems are sensitive for changes in hemoglobin, but also for thrombocytopenia. In general, a platelet count below 150×10^9/L will impair platelet function readings, but the critical platelet count threshold depends on the activation pathway. For the Multiplate™ and PFA-100™, a hematocrit below 30% is critical with respect to the reliability of the test results [14]. This could be a major disadvantage in cardiac surgery when

postoperative findings are compared with preoperative data. In particular, the impairment of the $P2Y_{12}$ and collagen receptor due to exposure of blood to the extracorporeal circuit may be detected by these devices [15].

Most systems use whole blood, which is an advantage in terms of user-friendliness and the physiological value of test results. However, discrepancies in the composition of blood impede clear conclusions regarding one corpuscular compartment only, which are the platelets. Except for thromboelastography, which compares the intrinsic activity of fibrinogen, all methods using fibrinogen as an anchor for platelets are sensitive to fibrinogen levels, but specific literature for this phenomenon is lacking. Finally, the human factor still plays a major role, and less automated systems are more subject to measurement errors by the operator than automated systems with cartridges.

Predicting of Perioperative Bleeding

Most evidence regarding the predictive value of platelet function tests for perioperative bleeding is derived from studies using multiple electrode aggregometry. A retrospective study showed that a patient blood management algorithm including preoperative platelet function analysis reduced blood transfusion in general, but the volume of transfused platelets increased [16]. This study underlines the concept of assessing platelet function before surgery, which might contribute to an estimation of remnant platelet function and help in timely ordering of platelet concentrates or the cessation of $P2Y_{12}$ inhibitors [17–19]. Others demonstrated that preoperative multiple electrode aggregometry in a cohort of patients under treatment of $P2Y_{12}$ blockers could identify patients at risk for bleeding [17]. Moreover, they identified preoperative cut-off values for ADP and TRAP tests that were associated with bleeding [17]. In a comparison of multiple electrode aggregometry and the rotational thromboelastometry (ROTEM™) platelet function test it was shown that only multiple electrode aggregometry has a predictive value for bleeding [20]. Both devices showed however a good correlation with perioperative blood loss [21].

Kong and co-workers proposed in 2015 an algorithm to test patients treated under $P2Y_{12}$ inhibition for MEA analysis. They recommend to use the MEA ADP assay and the TRAP assay. Others showed that the ADP test is an indicator for $P2Y_{12}$-related bleeding using multiple electrode aggregometry, while the TRAP test reflects platelet function in general [22]. A comparison of multiple electrode aggregometry and thromboelastography-platelet mapping before and after cardiopulmonary bypass showed that both postoperative tests did not correlate with blood loss during the first 12 h after surgery [23] and is associated with a reduction in blood transfusions [24]. This is in contrast to results from a Scandinavian group, showing that preoperative thromboelastography-platelet mapping was superior in the prediction of bleeding compared to multiple electrode aggregometry [25].

When the VerifyNow™ system was tested in a preoperative and retrospective setting as a predictor for platelet inhibition, it demonstrated a good indication of aspirin-induced platelet inhibition, but without an association with postoperative bleeding [26]. Others however showed that one should be cautious to use the

Table 9.2 Advantages and disadvantages of different platelet function analyzers

Test	Advantages	Disadvantages
PFA-100/200	WB, easy to perform, flow makes it suitable for vWF-disease	Depending on hematocrit and platelet count
LTA	Allows use of multiple activators in different concentrations	Needs preparation of PRP and PPP, poorly standardized
VerifyNow	WB, easy to perform, cartridges	Sensitive to all
PlateletWorks	WB, easy and simple, uses standard devices	Sensitive to all abnormalities interfering with cell count
WBA	WB, easy to perform	Sensitive to low platelet count
TEG-platelet mapping	WB, easy to perform, cartridges	Sensitive to low platelet count
ROTEM-MEA	WB, easy to perform	Sensitive to low platelet count

PFA platelet function analyzer, *LTA* light transmission aggregometry, *WBA* whole blood impedance platelet aggregometry, *TEG* thromboelastography, *ROTEM* rotational thromboelastometry, *MEA* multiple electrode aggregometry, *WB* whole blood, *vWF* von Willebrand, *PRP* platelet rich plasma, *PPP* platelet poor plasma

VerifyNow™ to decide when antiplatelet drugs should be discontinued [27]. In contrast, in a smaller, prospective study the VerifyNow™ had a good association with bleeding when used in the preoperative setting in a cohort of patients treated with dual antiplatelet therapy, including $P2Y_{12}$ inhibitors [28]. Yet, there are several studies deriving from the cardiology field looking at periprocedural events after percutaneous interventions that provide positive evidence for the use of this system in the confirmation of adequate platelet inhibition, which is associated with a decreased risk of stent thrombosis [1].

Implications for Daily Practice

Regarding estimation of thrombosis and bleeding risk around PCI procedures the VerifyNow™ system and the MEA device have been investigated. Additionally, thromboelastography-based platelet mapping and the VASP assay have been tested in this setting, and all systems show added value in the definition of the optimal dose–response relation for antiplatelet drugs, and the reduction of thrombotic and bleeding risks [29]. The evidence for platelet function testing in cardiac surgery is contrasting, and depends on the clinical settings and devices used (see Table 9.2). However, it seems reasonable to plan elective interventions guided by platelet function tests to determine when to stop $P2Y_{12}$ inhibition. The VerifyNow™ and multiple electrode aggregometry are well established in assessing the recovery of platelet function in patients who discontinued antiplatelet drugs. Also, in urgent situations, preoperative platelet function tests demonstrated to help estimating the bleeding risk. Furthermore, platelet function assessment could lead to timely ordering of platelet concentrates.

Intraoperative and postoperative platelet function testing should be interpreted with caution, since the test results are influenced by hemodilution and a reduced

number of corpuscular compartments. Likewise, the use of drugs and cardiopulmonary bypass influences platelet function to an uncertain degree, and it is not reliably to assess platelet function under these circumstances. One should remember that platelet function usually recovers within 12–24 h after surgery. Finally, with the assumption that platelet count and hemoglobin levels are not critical, platelet function testing could be helpful in timing restarting of antiplatelet therapy.

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Coagulation Monitoring

10

Seema Agarwal

Case Vignette

A 35-year-old patient with Marfan's disease presents for an aortic arch replacement which involved hypothermic circulatory arrest and a long bypass time. Prior to separation from cardiopulmonary bypass a TEG is performed as shown in Fig. 10.1. This demonstrates a long R time and low MA on the heparinase TEG (green trace) and a low MA on the fibrinogen TEG (blue trace) [note the test was done while the patient was still on CPB and anticoagulated, hence the straight line on the kaolin (red) trace]. How should this patient be treated?

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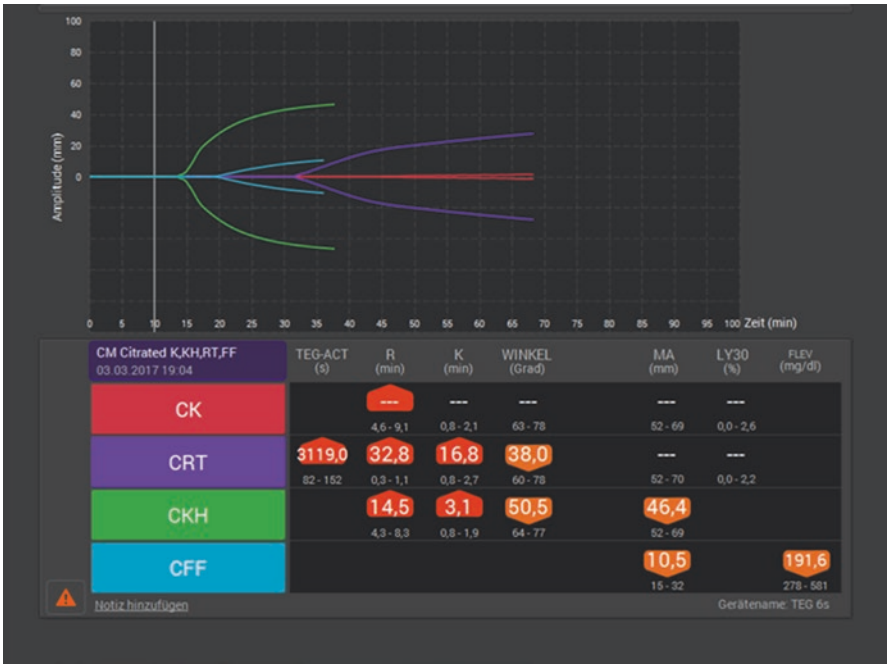

Fig. 10.1 Thromboelastography (TEG) tracing. Author's data (S. Agarwal, Manchester, United Kingdom). Red line = kaolin, purple line = kaolin + tissue factor, blue line = fibrinogen, green line = kaolin with heparinase; R time = time to clot formation, MA = clot strength

Why Is it Important?

Bleeding complications during and after cardiac surgery are common and associated with increased morbidity and mortality. The etiology of bleeding is multifactorial including surgical trauma, heparin rebound, platelet deficits in number and function, factor and fibrinogen deficiency, and fibrinolysis. Left untreated bleeding may lead to further coagulopathy as well as an unfavorable patient outcome. Transfusion of red cells and blood components is crucial; however, this same transfusion may also be associated with an increase in morbidity and mortality, particularly if used inappropriately [1]. While the safety of blood and blood products in terms of viral and pathogen transmission has improved vastly over the past decades, other risks such as transfusion associated acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) remain.

It is therefore important to be able to elucidate the exact coagulation deficit from the array of possibilities and tailor therapy accordingly. Perioperative coagulation testing plays a vital role allowing the detection of any preoperative abnormalities, which may be addressed prior to surgery, intraoperative abnormalities, and can help to elucidate the cause of bleeding postoperatively. Testing may be divided into two

types depending on the location of testing: laboratory based testing and point-of-care testing (POCT). The purpose of this chapter is to give an overview of different coagulation monitoring modalities that can be used in cardiac surgery.

Laboratory Coagulation Monitoring

Principles and Use

Figure 10.2 gives an overview of the standard laboratory tests that are available for coagulation monitoring in cardiac surgery.

Laboratory coagulation tests can be used throughout the patient journey to assess for coagulation abnormalities. The prothrombin time (PT) will be long if warfarin is present, in vitamin K deficiency from malnutrition, biliary obstruction, or malabsorption syndromes, in liver disease, and due to deficiency or presence of an inhibitor to factors VII, X, II/prothrombin, V, or fibrinogen. The activated partial thromboplastin time (aPTT) will be prolonged if heparin is present as well as in the presence of the anti-phospholipid syndrome (with lupus anticoagulant), hemophilia A and B (factor VIII and IX deficiency, respectively), factor XII deficiency, and factor XI deficiency. The PT or aPTT may also be used to assess non-vitamin K oral anticoagulant (NOAC) therapy; however, they are affected to a varying degree depending on the reagents and NOAC used [2]. In general, normal PT or aPTT test results exclude excess levels of dabigatran, rivaroxaban, and edoxaban, but not apixaban. The aPTT correlates better for dabigatran, the PT may be used for factor Xa inhibitors, although one should be aware of the considerable variation in the

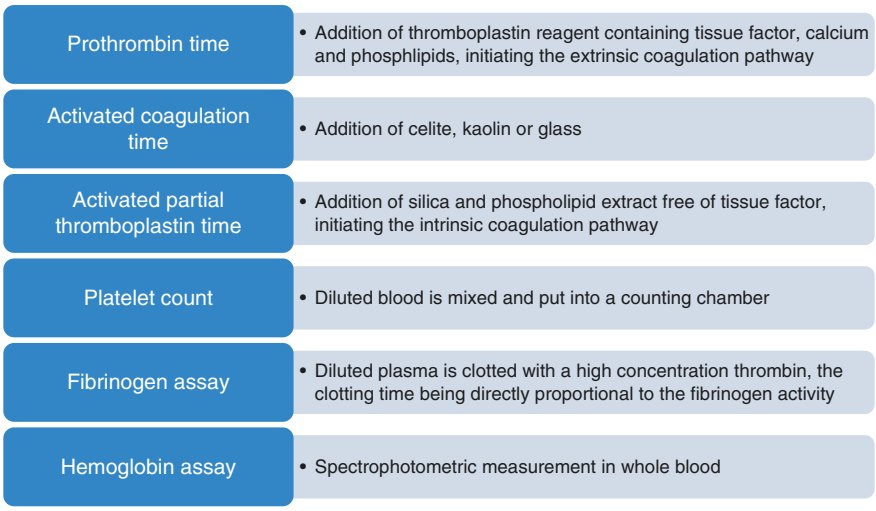

Fig. 10.2 Laboratory tests for coagulation monitoring during cardiac surgery

sensitivity of different PT reagents [3]. Sensitive PT assays, but not the aPTT, can indicate plasma levels of rivaroxaban and edoxaban, but not apixaban. However, the quantification of the concentration of these drugs is not reliable, so this parameter should be used as a screening test only, bearing in mind that low but clinically relevant plasma levels of FXa inhibitors may not be detected. For precise measurement of drug concentrations of all FXa inhibitors, chromogenic anti-FXa-tests are recommended [4]. The activated clotting time (ACT) will be discussed in the next chapter.

The platelet count will tell us the absolute platelet number; however, it will not tell us about platelet function, in particular if residual antiplatelet drug activity is present. Specialist platelet function tests (some of which can provide this information) are generally only available in hematology laboratories, and have turnaround times of hours.

Advantages and Disadvantages of Laboratory Testing

Laboratory testing has the major advantage of having rigorous quality control and is generally performed by highly skilled staff. The tests may be helpful in elucidating the cause of bleeding. However, there are numerous disadvantages. The tests measure one specific part of the coagulation system at one point in time and were not intended for the prediction of bleeding in cardiac surgery. With turnaround time in some laboratories that exceed 30 min, the results are often of little use in the dynamic situation of acute bleeding. Standard laboratory tests are regularly abnormal after cardiac surgery because of dilution and consumption associated low concentrations of procoagulant factors, without any deficit in thrombin generation and without bleeding and the critical values of these tests have not been well defined in cardiac surgery. The tests are performed mainly in plasma rather than whole blood, and at a standard temperature of 37 °C rather than the temperature of the patient. In light of these limitations, clinicians have sought to use point-of-care (POC) testing.

Point-Of-Care Coagulation Monitoring

Viscoelastic Testing

By their nature, point-of-care devices are situated close to the patient and so allow the clinician to see the results quickly, as they develop. They consistently detect changes in coagulation. In cardiac surgery, there are two main viscoelastic principles used: thromboelastography (TEG) and rotational thromboelastometry (ROTEM), while newer techniques (e.g., ultrasound based resonance sonorheometry, SEER) have come to the market recently (see below). Both techniques offer a global view of hemostasis with a visual representation of clot development as shown below. They are performed on citrated whole blood (TEG, ROTEM, and SEER), and the TEG may also be performed on fresh whole blood.

Principles and Use

The mentioned point-of-care devices work in a similar fashion to assess the viscoelastic properties of blood under low shear conditions. The thromboelastography principle is based on a cylindrical cup holding the blood which oscillates for 10 s at a time. A pin is suspended in the blood sample via a torsion wire and is monitored for motion. After fibrin–platelet bonding has occurred, linking the pin and the cup together, the torque of the rotation is transmitted to the pin which is then converted by an electromagnetic signal into an electrical signal, the so-called thromboelastography trace [5]. The strength of the bonds affects the magnitude of the pin motion, so output is directly related to the strength of the formed clot. With clot retraction and lysis, the fibrin–platelet bonds are broken. The same principles apply in rotational thromboelastometry, with the main technical difference being that it is the pin which rotates while the cup remains stationary. The rotational thromboelastometry system also uses a different activator—ellagic acid rather than kaolin, which may make it less sensitive to residual heparin. Both devices suffer from a lack of robust quality control and are operator dependent [6]. The results of two systems are closely related, but they are not completely interchangeable [7].

The SEER method uses ultrasound pulses to measure the stiffness of the clot during the coagulation process that is started by certain activators. Clotting times, clot stiffness, and break down of the clot are measured over time [8].

All POC devices are now available as new generation system to make them easier to use with automated measurement. All have introduced a cartridge-based device with more robust quality control and offer the advantages of a reduction in operator dependent error and technical faults. For thromboelastography, whole blood is inserted into the cartridge and delivered to a microcell that is excited with a multifrequency signal from a piezoelectric actuator. The resulting harmonic motion of the sample is measured optically; as the sample clots and moves from liquid to gel and solid phase the harmonic motion changes, this is represented as the familiar thromboelastography trace. It does not measure the viscoelasticity of the clot directly [9]. The mentioned POC devices are capable of performing four tests simultaneously from one citrated blood sample. Using these devices gives the user the opportunity to perform specific coagulation tests (Table 10.1). The addition of

Table 10.1 Different tests for thromboelastometry (TEG) or rotational thromboelastometry (ROTEM)

TEG™ test	ROTEM™ test	Function
Kaolin	INTEM	Activated test of global hemostasis via the intrinsic pathway—usually performed as a baseline
Functional fibrinogen	FIBTEM	Assessment of fibrinogen
RapidTEG®	EXTEM	Tissue factor activated test of the extrinsic pathway—assessment of clot strength quickly
Heparinase	HEPTEM	Test of global hemostasis via the intrinsic pathway with the effect of heparin removed

Table 10.2 Available point-of-care monitoring devices in 2019

Commercial name	Method
TEG-6S™	Indirect viscoelastometry through an optical method
ROTEM SIGMA™	Viscoelastometry
SonoClot™	Viscoelastometry
Quantra™	Ultrasound detection of resonance
ClotPro™	Viscoelastometry

Table 10.3 The commonly measured variables during thromboelastometry and rotational thromboelastometry

TEG	ROTEM	What does it measure?	Abnormality
R time	CT	Time to first significant clot formation—clot initiation	Increased in factor deficiency or excess heparin
MA	MCF	Maximum strength of clot	Decreased in fibrinogen or platelet deficiency (not in platelet inhibition)
LY30	CL 30	Percent lysis 30 min after maximal clot strength	Increased in fibrinolysis

CT clotting time, *MA* maximal amplitude, *MCF* maximal clot firmness, *LY* lysis, *CL* clot lysis

heparinase to the test reveals the underlying coagulation status when heparin is present.

In addition to thromboelastography and rotational thromboelastometry, a number of other systems exist or are in development. These systems are usually based on indirect or direct measurements of the viscoelastometric properties of the clot, for instance, with ultrasound detection of resonance. Another system uses viscoelastic methods to assess clot kinetics and stability, its novelty lies in the fact that all the reagents will be contained in the pipette tip. However, the newly developed devices do not have a wealth of clinical experience to back up its use nor data from controlled trials or algorithms for its use in clinical practice. Table 10.2 gives an overview of the available commercial devices in 2019 for thromboelastographic or thromboelastometric testing.

The commonly measured variables during thromboelastometry and rotational thromboelastometry are shown in Table 10.3 and Fig. 10.3.

Advantages and Disadvantages of Point-of-Care Testing

Point-of-care coagulation testing enables the assessment of patient hemostasis throughout the surgical procedure. The test results are available in minutes. The tests have limitations and this must be borne in mind. The tests are run at 37° centigrade so cannot reflect the effects of hypothermia. They are not sensitive to the effects of platelet adhesion so cannot detect von Willebrand factor deficiency. Hemodilution and low platelet count as well as the usage of hydroxyethyl starch solutions influence the results of most point-of-care devices. They are dependent on quality control and regular calibration to generate valid results, and the older devices give user-dependent test results.

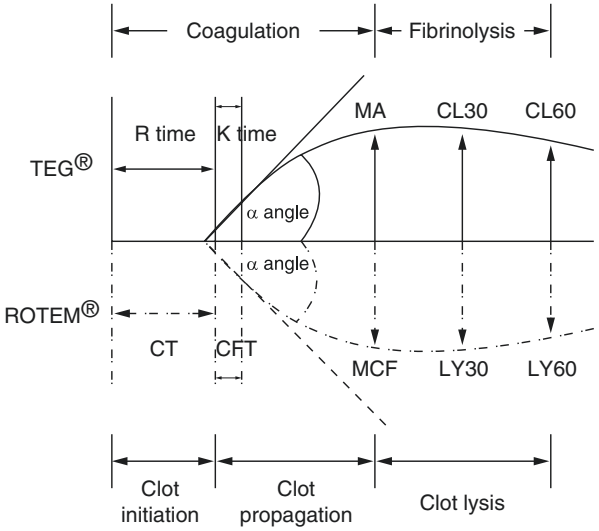

Fig. 10.3 The commonly measured variables obtained with TEG or ROTEM devices. R time/CT time: time from initiation of the test and the point where clotting provides enough resistance to produce a 2 mm amplitude reading on the tracing; K time/CFT (clot formation time): time from 2 min to 20 mm amplitude; alpha angle: slope between R and K for TEG, angle of tangent at 2-mm amplitude for ROTEM; MA: maximal amplitude; MCF: maximal clot firmness; CL and LY, clot lysis: percentage reduction in amplitude 30 min after reaching MA/MCF

Clinical Use of Point-of-Care Coagulation Monitoring

The exact timing of point-of-care testing remains open to debate as the evidence is not clear, with some recommending baseline testing while others prefer to test if a problem is apparent. It is worth noting that there is a poor correlation between baseline tests results and the prediction of subsequent bleeding.

Towards the end of cardiopulmonary bypass, tests may be performed to assess the extent of coagulopathy present. A test for the intrinsic coagulation pathway is usually performed together with an assessment of fibrinogen, both with the addition of heparinase to negate the effect of the systemic heparinization of the patient. These then allow blood products to be requested.

On separation from cardiopulmonary bypass, protamine is administered to reverse residual heparinization and any pre-ordered blood products may be administered specifically aiming at the detected coagulation defects. Further transfusions are then guided by further use of the point-of-care devices. At this point, the four common tests may be performed to assess whether there is any residual heparin, assess fibrinogen levels, obtain a quick assessment of clot strength, and assess whether factor levels are sufficient (Fig. 10.2).

All POC measurements are exquisitely sensitive to heparin. A comparison of a trace with and without heparinase (which neutralises heparin) may show differences. Heparin effect is evident with a prolonged time to clot formation and / or a reduced clot firmness in the trace without heparinase which corrects on the trace with

heparinase. Unfortunately, both thromboelastography and thromboelastometry tests are also sensitive to protamine, i.e., a protamine prolongs the CT of the heparinase assay. So far, it is unclear, whether this occurs with the SEER method as well.

Several algorithms have been published over the past 30 years, starting with relatively simple ones using kaolin and heparinase thromboelastography, to ones incorporating the newer tests such as point-of-care fibrinogen measurements. The use of these algorithms has been shown to reduce transfusion and resternotomy, and a few studies suggest that there is an association with reduced morbidity and mortality [10]. In one of the most recent studies, Karkouti and colleagues again demonstrated a reduction in transfusion and bleeding after cardiac surgery using a point-of-care based algorithm based on ROTEM™ and PlateletWorks™ [11].

In contrast, four recently published systematic reviews looked at the value of viscoelastic testing in cardiac surgery (namely, thromboelastography and thromboelastometry) with respect to treatment and prediction of bleeding, and their conclusions were more ambivalent [12–15]. They concluded that the implementation of thromboelastography or rotational thromboelastometry in a patient blood management program may reduce the need for blood products in patients with bleeding, but the results are mainly based on trials of elective cardiac surgery involving cardiopulmonary bypass, with low-quality evidence [12, 13]. Moreover, thromboelastometry does not predict which patients are at risk for major postoperative bleeding [14]. Finally, the third systematic review could not show an association between viscoelastic testing and a reduction in the proportion of patients receiving any blood product or all-cause mortality. They also concluded that these results are in part caused by the lack of robust randomized controlled trials [15].

All algorithms indicate that POC tests should be performed after protamine administration in the operating room, with continued testing on the intensive care unit if needed. Some also advocate a preoperative test. In a study of 52 patients, Ortmann and colleagues compared thromboelastography and rotational thromboelastometry heparinized tests performed towards the end of bypass to those performed after the administration of protamine, and found that the results were similar, particularly the amplitude of clot strength, confirming the utility of viscoelastic testing at this intraoperative timepoint [16]. Some validated algorithms include platelet function testing. The recommendations here are generally to perform platelet function testing to assess residual antiplatelet drug effects prior to bypass as described in Chap. 9. Viscoelastic testing has been assessed by the British National Institute of Health and Care Excellence (NICE), a government body that aims to improve outcomes for patients producing evidence-based guidance. The review of POC testing concluded that viscoelastic testing (methods assessed were thromboelastography and thromboelastometry) may be effective in reducing transfusion in cardiac surgery, as well as being cost saving [17].

Point-of-care coagulation monitoring should be continued postoperatively in the intensive care unit. Common causes of bleeding at this point include surgical bleeding, postoperative anemia due to hemodilution, acid/base disturbances, hypocalcemia, temperature drop as well as post-bypass platelet dysfunction that may be exacerbated by uremia.

Implications for Daily Practice

Perioperative coagulation testing with point-of-care devices provides a valuable addition to the armamentarium of the anesthesiologist when dealing with bleeding in the perioperative period. Tests should be performed in those patients that are bleeding, followed by repeated tests each time after a clinical intervention has taken place such as administration of blood products or fibrinogen for coagulopathy. This can then guide the indications and timing for surgical re-exploration. Best practice would be to order products based on the results of point-of-care testing and to administer them after protamine has been administered to the patient. The tests should then be repeated to ensure treatment has been successful.

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Part V

Intraoperative Measures to Reduce Bleeding and Maintain Hemostasis

Anticoagulation Management

11

Christa Boer

Case Vignette

A 75-year-old man who requires coronary artery bypass graft surgery with cardiopulmonary bypass is fully anticoagulated with heparin with a target activated clotting time (ACT) of 480 s using celite-mediated activation of the coagulation pathway. The anesthesiologist started with a regular bolus of heparin of 300 IU/kg, which resulted in an ACT of 300 s. More heparin was administered, and after two additional boluses an ACT of 450 s was achieved. The patient is diagnosed with heparin insensitivity. The surgical team decided to start surgery, and heparin was added to the priming solution (5000 IU). During the procedure, several doses of heparin needed to be administered in order to maintain the target ACT. At the end of the procedure, heparin is neutralized by a dose of protamine calculated from the total dose of heparin that is administered during surgery. After protamine administration, the patient shows microvascular bleeding. The anesthesiologist is not in favor of an additional bolus of protamine, since protamine has anticoagulation properties by itself. Rotational thromboelastometry shows a reduced clot firmness in the fibrinogen assay, and after a bolus of fibrinogen concentrate the oozing is stopped.

Why Is It Important?

In order to prevent intraoperative hemostatic activation, patients receive unfractionated heparin (UFH) for full anticoagulation during cardiopulmonary bypass (CBP) or partial anticoagulation during off-pump coronary artery bypass graft surgery. The

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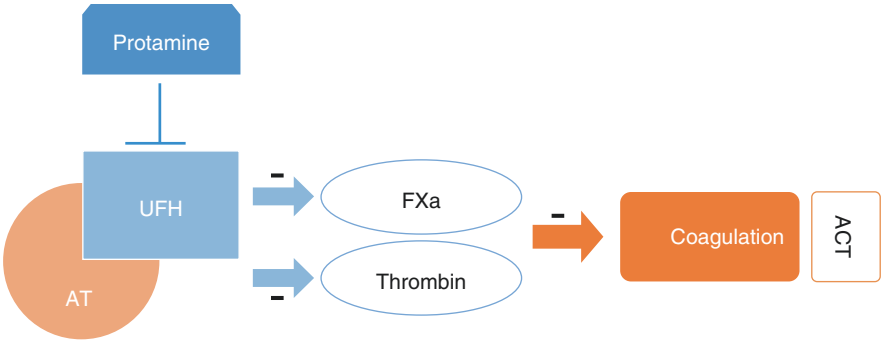

Fig. 11.1 The binding of heparin and antithrombin results in an inhibition of factor Xa and thrombin, leading to a reduction of the coagulation capacity. The effects of heparin on the coagulation are monitored by the activated clotting time. *UFH* unfractionated heparin, *AT* antithrombin, *ACT* activated clotting time

body itself also produces heparinoids to prevent thrombin formation, but these concentrations are insufficient to compensate for intraoperative massive hemostatic activation. Heparin consists of a mix of long and short chained molecules, with a high affinity for thrombin (long chain) or factor X (short chain). It binds to antithrombin, thereby inhibiting the activated clotting factors II, VII, IX, X, and XI. Heparin further binds to the endothelial glycocalyx and plasma proteins affecting its biological availability and half-life. Heparin is neutralized by protamine, which is administered at the end of CPB (Fig. 11.1).

Heparin and protamine are routinely used during cardiac surgery with CPB. Heparin dosing is usually based on the whole-blood activated clotting time (ACT), but some patients have difficulties to achieve a sufficient ACT due to heparin insensitivity. Moreover, the ACT is not sensitive enough to titrate protamine, while excessive protamine itself may exert anticoagulant effects. Correct heparin and protamine dosing therefore requires insight in the characteristics of both drugs and the limitations of available measurement methods. The purpose of this chapter is to discuss anticoagulation strategies during cardiopulmonary bypass, including heparin and protamine management, monitoring tools, and alternatives for heparin.

Heparin Anticoagulation and Monitoring

The ACT is based on activation of the intrinsic coagulation pathway by celite or kaolin, which both exert different test reference values. The dosing of heparin is commonly based on body weight (300–600 IU/kg), followed by additional doses when the ACT drops below target clotting times. Target clotting times may vary between 300 and 600 s, depending on the type of surgery, the use of a closed or open circuit, biocompatible coating of the circuit, and local protocols. The ACT is relatively inaccurate, as its results are influenced by hemodilution, temperature, and

platelet count. There is no correlation between the plasma heparin concentration and ACT [1].

Alternatively, a heparin dose–response test may be used to determine the sensitivity of a patient for heparin, which may differ due to previously used medication, a variation in antithrombin levels, or the potency of heparin. In particular, lower levels of antithrombin reduce the effect of heparin on thrombin, leading to a relative resistance to heparin. In some patients this might be solved by the administration of additional heparin or fresh frozen plasma. Alternatively, antithrombin is administered to increase heparin sensitivity which is indicated in patients with antithrombin deficiency, aiming for plasmatic levels of antithrombin of 80%. Administration of 50 IU/kg of antithrombin increases the plasmatic concentration to approximately 120% in a heterozygous, antithrombin deficient patient with an initial plasmatic concentration of 50% [2]. It is however not recommended to prophylactically administer antithrombin to reduce bleeding following CPB [3].

There are several publications that aimed to find a reduction in postoperative bleeding and transfusion requirements by individual heparin titration using monitoring devices like the HMS/HepCon™ (Medtronic, Minneapolis, MN, USA), Hemochron RxDx™ (Accriva Diagnostics, San Diego, CA, USA), or anti-Xa measurements in addition to the ACT. When a HepCon™-based heparin and protamine management was compared to a conservative anticoagulation strategy in CABG patients there was no difference in total heparin use between groups, while protamine requirements decreased in the HepCon™ group [4]. There were however no clinically relevant differences in 12-h blood loss and transfusion requirements between groups [4]. Others showed that the use of a HepCon™-based strategy increased heparin dosing and reduced protamine requirements in valve surgery when compared to an ACT-based strategy, with more 24-h blood loss in the control group [5]. A third study showed that heparin and protamine dosing and bleeding rates did not differ between a HepCon™ and ACT-based anticoagulation strategy [6]. All studies were relatively small and lacked clinically relevant primary endpoints, and larger multicenter studies are warranted to determine the added value of individual heparin and protamine titration.

In addition to the ACT and individual heparin dosing, statistical models have been developed to calculate heparin and protamine requirements during surgery. Studies evaluating the effectiveness of these models on clinically relevant endpoints are however lacking [7].

Heparin Rebound

Heparin rebound is re-heparinization after adequate heparin reversal following cardiopulmonary bypass. This re-heparinization is caused by the release of heparin from the endothelium and plasma proteins, and takes place when the patient is admitted to the postsurgical or intensive care ward. Unfortunately, most studies on this topic are relatively old, and focus on residual plasma heparin following cardiac surgery or the occurrence of postoperative bleeding in case of residual plasma

heparin. Only one study showed that continuous postoperative protamine infusion (25 mg/h for 6 h) to neutralize residual heparin resulted in reduced mediastinal blood loss when compared to control subjects who did not receive extended protamine infusion [8]. While protamine infusion resulted in a reduction in 24-h blood loss of approximately 100 mL, this was however not associated with a reduced transfusion rate. Blood heparin levels in the control group were the highest at 3 h following surgery, and normalized within 9 h postoperatively. The study was however limited by the possibility to administer additional protamine to normalize ACT values to pre-heparin values, which occurred more frequently in the control group and might have enhanced postoperative bleeding [8]. The administration of protamine to neutralize heparin may however lead to a contrary effect, since protamine exerts anticoagulation properties by itself. Other studies suggested that the clinical relevance of heparin rebound is limited, showing that heparin levels after surgery are insufficiently low to induce anticoagulation and bleeding [9, 10]. When heparin rebound is suspected, it is important to first measure heparin plasma concentrations rather than the blind administration of protamine.

Protamine

At the end of CPB, protamine is administered to neutralize heparin. Protamines are small basic, arginine-rich, positive charged proteins, and were formerly isolated from salmon sperm. Nowadays, protamine is increasingly produced through recombinant biotechnology. It binds to the anionic heparin in a 1:1 ratio, and has a rapid onset of action. Within seconds, a neutral protamine–heparin salt is formed. The protamine–heparin complex that is formed leads to dissociation of heparin from antithrombin, thereby restoring the procoagulant properties of blood. In parallel, the platelets produce platelet factor 4 (PF4), which also binds to heparin and contributes to the stability of the protamine–heparin complex. It is unclear how the neutral protamine–heparin complex is metabolized, and animal studies suggest a dual route through liver and kidneys.

Protamine has immunological and inflammatory properties, and may induce a response with allergy, hypotension, bradycardia, and pulmonary vasoconstriction as most frequently reported side effects. Patient risk factors for an anaphylactic response include treatment of diabetes mellitus with protamine-containing insulin and allergies for fish proteins [7].

Protamine is regularly dosed based on the initial or total administered dose of heparin throughout the procedure. However, protamine itself exerts anticoagulant effects through interference with pro-hemostatic pathways when excessively dosed [7, 11]. In particular, protamine interacts with platelet function, interferes with coagulation factors, and stimulates clot breakdown [7]. Interventions that may contribute to tailored protamine dosing include the use of heparin measurements, anti-Xa measurements, or computer-based dosing models. Inadequate protamine dosing may influence patient hemostasis and the risk for postoperative bleeding.

Several studies show that individual titration of heparin and protamine results in more heparin and less protamine administration compared to ACT-based strategies.

Protamine dosing based on the initial heparin dose results in a longer clotting time and microvascular bleeding when compared to protamine dosing based on the measured heparin concentration [12]. Others showed that a higher protamine-to-heparin (1.3) dosing ratio is associated with coagulation abnormalities, decreased restoration of post-protamine thrombin levels, and more postoperative blood loss when compared to a lower protamine-to-heparin dosing ratio (0.8) [13]. In contrast, a recent trial in CABG patients showed that a protamine-to-heparin ratio below 0.6 was associated with enhanced blood loss and transfusion requirements compared to patients subjected to a ratio exceeding 0.8, which is suggestive for residual heparin following surgery [6]. In many institutions, the initial ACT is compared to the post-weaning ACT to assess the heparin-neutralizing effect of protamine. Due to the inaccuracy of the ACT, this comparison should be valued with caution. Overall, it can be concluded that liberal protamine administration is unfavorable for the restoration of coagulation, and heparin measurements or calculations might prevent this.

Alternatives for Heparin

Alternatives for heparin or patients with a severe protamine allergy include direct thrombin inhibitors, such as bivalirudin. The only available method to reliably measure therapeutic levels of bivalirudin is the ecarin clotting time, although the ACT can also be used. A baseline ACT value is measured before bivalirudin administration, aiming for a target of an ACT that is 2.5 times the baseline during CPB. Bivalirudin is usually administered in patients with known heparin-induced thrombocytopenia. Bivalirudin has a short elimination half-life (25 min) and its elimination is mainly achieved by proteolytic cleavage and not influenced by impaired hepatic or kidney function [14]. Bivalirudin and heparin are equally safe and effective for systemic anticoagulation during cardiac surgery, without differences in blood loss [15]. However, as stasis should be avoided during bivalirudin, this anticoagulation therapy requires adjustments of perfusion approaches. Its use is, therefore, mainly restricted to patients with heparin-induced thrombocytopenia.

Implications for Daily Practice

Heparin and protamine are among the most frequently used drugs during cardiac surgery, but monitoring of the anticoagulation effect is still limited due to the gross results of the ACT and the influence of exogenous factors on the ACT. Patients with heparin resistance who require subsequent doses of heparin during extracorporeal circulation may therefore benefit from individual heparin titration, for instance, by using a heparin dose–response curve.

While heparin administration may be complicated by the sensitivity of the patient and the quality of heparin, one should also take the side effects of protamine into account. Protamine exerts anticoagulant properties that are mainly present when there is insufficient heparin available to bind. Overdosing of protamine may

therefore lead to disturbed coagulation and prolonged bleeding. In this case, a protamine titration curve might be helpful in determining the adequate protamine dose that will neutralize heparin.

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Fibrinolysis

12

David Faraoni

Case Vignette

A 62-year-old male patient is referred to a cardiac program because of progressive dyspnea. The patient presents with severe aortic valve insufficiency in the context of bicuspid aortic valve and calcified cusps due to an ascending aorta and aortic root aneurysms. The patient was admitted for an elective Bentall operation. After cardiopulmonary bypass, the patient presented severe bleeding requiring the administration of multiple units of allogenic red blood cells, plasma, and platelets. Two hours later, the patient is still bleeding and thromboelastometry shows severe fibrinolytic activation (Fig. 12.1a). Because no antifibrinolytic agents were used, 1 g of tranexamic acid and 50 mg/kg of fibrinogen concentrate were administered. After 10 min, the thromboelastometry tracing is normal (Fig. 12.1b) and the bleeding slowly decreases. The patient is transferred to the cardiac intensive care unit 45 min later.

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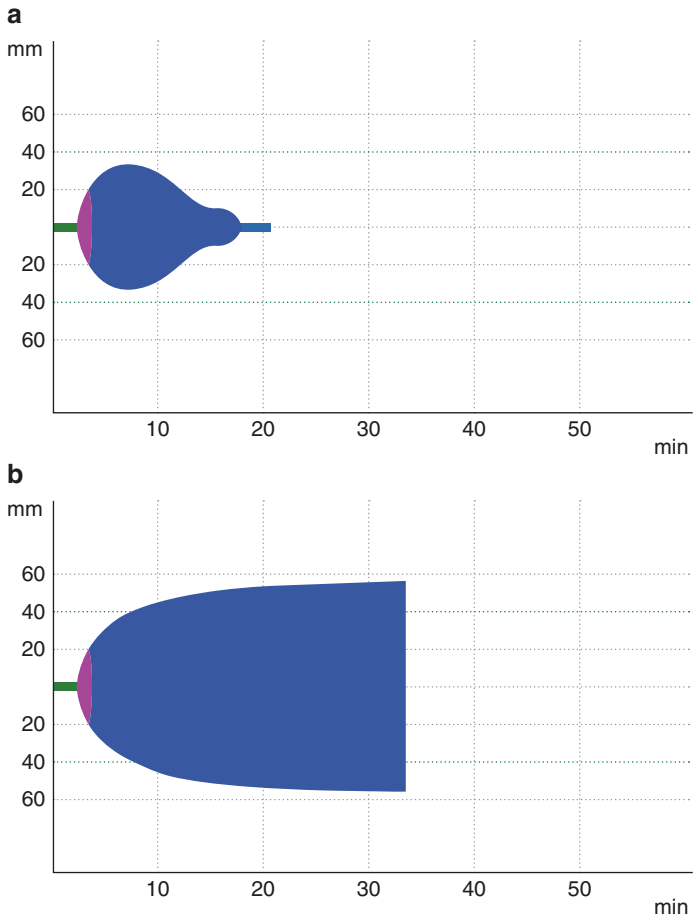

Fig. 12.1 Rotational thromboelastometry (ROTEM™) of a patient with severe fibrinolytic activation (**a**) and restoration of clot formation after administration of antifibrinolytic agents and fibrinogen (**b**)

Why Is It Important?

Perioperative bleeding is one of the most common complications of cardiac surgery. Patients undergoing cardiac surgery are sometimes exposed to large volumes of allogenic blood products and/or concentrates of coagulation factors. Although the requirement for blood transfusion is correlated to the severity of bleeding, both transfusion, bleeding, and even more the association of both have been shown to increase the incidence of postoperative complications and mortality [1]. The pathophysiology of the coagulopathy observed in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) is complex and multifactorial, and can be summarized as follows:

1. Hemodilution coagulopathy due to CPB prime, cardioplegia, and administration of fluids in the perioperative period
2. Contact activation (activation of factor X and thrombin generation) due to tissue injury, tissue factor production, and activation of fibrinolytic pathways, and
3. Consumption coagulopathy due to thrombin, plasmin, and inflammation mediated processes.

All of these factors can generate a vicious circle leading to coagulopathy and systemic inflammatory response [2]. The activation of the fibrinolytic pathway plays an important role in the coagulopathy observed during and after cardiac surgery. The fibrinolytic system begins when plasminogen is cleaved to plasmin and is important because it limits thrombus growth. During cardiac surgery, large amount of thrombin is generated which will lead to the polymerization of fibrinogen. Thrombin also causes a conformational change such that FXIII, (synonymous: plasminogen inhibitor), and tissue-type plasminogen activator (t-PA) become attached to fibrin. Fibrin stimulates t-PA synthesis by endothelial cells and urokinase plasminogen activator (u-PA) synthesis by monocytes, macrophages, and fibroblasts. Both t-PA and u-PA activate plasminogen. Plasminogen can also be activated by FXIIa formed during the contact phase of coagulation. Plasmin is an endopeptidase that cleaves both fibrinogen and fibrin, disrupting them into fibrin degradation products without clotting ability. Plasmin also interacts with the inflammatory system stimulating the complement system and kallikrein. Plasminogen activator inhibitor 1 (PAI-1) is released after t-PA and u-PA as a natural endogenous inhibitor of fibrinolysis (Fig. 12.2).

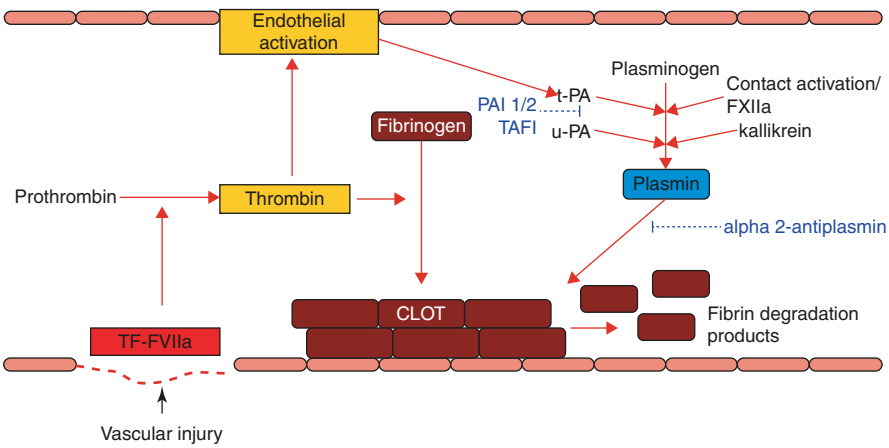

Fig. 12.2 Simplified representation of fibrinolytic activation. *t-PA* tissue plasminogen activator, *u-PA* urokinase-type plasminogen activator, *FXIIa* activated factor XII, *PAI 1/2* plasminogen activator inhibitor type 1 and 2, *TAFI* thrombin activatable fibrinolysis inhibitor

Activation of fibrinolysis at CPB initiation is mainly limited to FXIIa-induced activation related to the contact of the patient's blood with the non-endothelial CPB surface. Fibrinolysis then becomes activated by the release of t-PA from the vascular walls. Overall, cardiopulmonary bypass results in an increase in t-PA, D-dimers, and t-PA–PAI-1 complexes and a decrease in PAI-1 levels, indicating an activation of the fibrinolytic pathway and the consumption of its natural inhibitors. Thrombin and fibrin are known to be important activators of the fibrinolytic pathway. The degree of fibrinolytic activation is significantly correlated to the degree of thrombin generation, suggesting a strong correlation between activation of the coagulation and fibrinolytic pathways. In addition to thrombin, inflammatory markers such as cytokines and endotoxins are also able to promote the activation of plasminogen and its inhibitors. Because both plasmin and t-PA are known to impair platelet function, fibrinolytic activation is also associated with impaired platelet function during and after CPB.

Overall, fibrinolysis can be considered a protective physiologic response that appropriately limits clot formation. However, after major tissue damage and activation of CPB-induced coagulopathy, inhibiting fibrinolysis may potentially limit other responses that contribute to bleeding. Indeed, activation of the coagulation and fibrinolytic systems will lead to a vicious circle promoting bleeding and inhibiting the ability to form stable clot. Even though it would be extremely challenging to study the relationship between the sole activation of the fibrinolytic system and the severity of the bleeding in patients undergoing cardiac surgery, a strong correlation between biomarkers of fibrinolysis and the magnitude of postoperative bleeding has been reported.

The purpose of this chapter is to illustrate the importance of the fibrinolytic system in CPB-induced coagulopathy and bleeding, and to give an overview of agents capable of inhibiting fibrinolysis that can be administered prophylactically to avoid initiation of the fibrinolytic activation [3, 4].

Description of Antifibrinolytic Agents

Antifibrinolytic agents include aprotinin and the lysine analogs (ε-aminocaproic acid [EACA] and tranexamic acid [TXA]). Aprotinin is a broad-spectrum protease inhibitor, isolated from bovine lung and structurally similar to tissue factor pathway inhibitor, that reversibly complexes with the active serine residue in various proteases in plasma (e.g., trypsin, kallikrein, plasmin, and elastase). Aprotinin offers the most complete and potent fibrinolytic inhibition. Apart from these direct effects on the plasmatic coagulation system, aprotinin also inhibits the protease-activated receptor 1 thrombin receptor involved in both coagulation and inflammation. This action has been identified as a possible mechanism for stroke reduction after aprotinin administration in patients undergoing cardiac surgery.

Lysine analogs, TXA and EACA, are the most extensively used antifibrinolytic agents. As discussed above, activation of plasminogen by endogenous plasminogen activators results in plasmin, which causes degradation of fibrin. Binding of

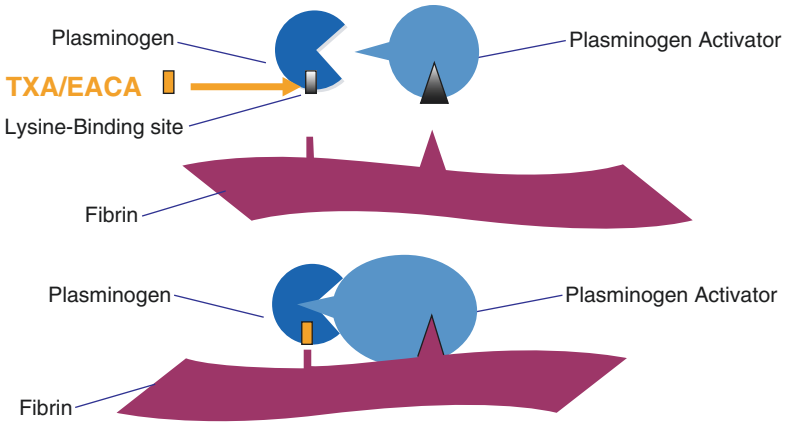

Fig. 12.3 Mode of action of lysine analogs. *TXA* tranexamic acid, *EACA* ε-aminocaproic acid

plasminogen to fibrin makes this process more efficient and occurs through lysine residues in fibrin that bind to lysine-binding sites on plasminogen. In the presence of lysine analogs, these lysine-binding sites are occupied, resulting in an inhibition of fibrin binding to plasminogen and impairment of endogenous fibrinolysis (Fig. 12.3) [5]. Because plasmin generation after tissue injury can induce many other responses, including thrombin generation, complement activation, and activation of monocytes, neutrophils, and platelets, attenuation of these pathophysiologic responses with lysine analogs might provide additional mechanisms to restore hemostatic balance and control of plasmin generation and fibrinolysis [6].

Efficacy of Antifibrinolytic Agents

The efficacy of prophylactic administration of antifibrinolytic agents in patients undergoing cardiac surgery has been extensively studied and discussed. After the publication of the first study in 1987, the efficacy of aprotinin to reduce the requirements for transfusion of red blood cells, platelets, and plasma has been reported in more than 70 studies performed in patients undergoing cardiac surgical procedures of various complexity. Randomized studies of TXA or EACA were much less numerous than trials of aprotinin. Until 2007, aprotinin was the most frequently used agent. In 2007, the efficacy of aprotinin and other lysine analogs was summarized in a Cochrane systematic review and meta-analysis [7]. When compared to a placebo, both aprotinin (77 studies), TXA (29 studies), and EACA (10 studies) significantly reduced the exposure to allogenic blood products (see Table 12.1). The effect of aprotinin and TXA on exposure to allogenic blood product transfusion was only assessed in 10 studies for a total of 1968 patients. Even though a trend in favor of aprotinin was observed, no statistical difference was reported between the two drugs. No difference in terms of adverse events was shown when antifibrinolytic agents were compared to a placebo or to each other. However, it is important to note

Table 12.1 Overview of comparative studies on antifibrinolytic agents in cardiac surgery with blood transfusion as primary endpoint [7]

	Studies	Patients	Risk ratio	95% CI
Aprotinin vs. control	77	8837	0.66	0.61–0.72
TXA vs. control	29	2488	0.69	0.60–0.79
EACA vs. control	10	596	0.65	0.47–0.91
Aprotinin vs. TXA	14	1968	0.85	0.66–1.09

TXA tranexamic acid, *EACA* ε-aminocaproic acid, *CI* confidence interval

that none of the studies published at that time were designed to adequately assess the safety of the drugs.

Safety Concerns of Aprotinin

In 2006, the first study raising safety concerns associated with the administration of aprotinin was published in the New England of Medicine [8]. In this observational analysis of 4374 patients undergoing cardiac surgery and after propensity analysis, the authors found that the use of aprotinin was associated with a significant increase in the risk of renal failure requiring dialysis (5%) when compared to EACA (1%) or TXA (1%). Similarly, the use of aprotinin was associated with an increase in the risk of myocardial infarction or heart failure as well as the risk of stroke or encephalopathy. Neither EACA nor TXA was associated with an increased risk of renal, cardiac, or cerebral events. Around the same time, Karkouti et al. published the results of a propensity analysis comparing aprotinin and TXA in high-transfusion-risk cardiac surgery [9]. Aprotinin and TXA showed similar hemostatic effectiveness in the study population. However, their results also suggested an association between the use of aprotinin and an increased incidence of renal dysfunction. In 2007, the results of the *B*lood conservation using *A*ntifibrinolytics in a *R*andomized *T*rial (BART) study [10], a prospective study performed in high-risk patients undergoing cardiac surgery, reported an increased mortality associated with aprotinin (6% 30-day mortality for aprotinin) compared with lysine analogs (3.9% for TXA and 4% for EACA), which was followed by a Food and Drug Administration (FDA) warning (Fig. 12.4).

In November 2007, following requests of German health authorities and the FDA, Bayer Healthcare (Leverkusen, Germany) announced the withdrawal of aprotinin from the market. In the following years, an intense, sometimes emotional, debate regarding the validity of the reported data and the safety profile of aprotinin ensued. The safety of aprotinin was reevaluated in several retrospective studies with conflicting results, but the overall impression is that the risk of adverse events is essentially observed in a subset of the cardiac population when aprotinin was administered and that the drug remains beneficial when used in patients undergoing procedures with high bleeding risk. In September 2011 Health Canada and in February 2012 the EMA lifted the suspension of aprotinin from the market. Aprotinin should only be given during the primary coronary artery bypass grafting

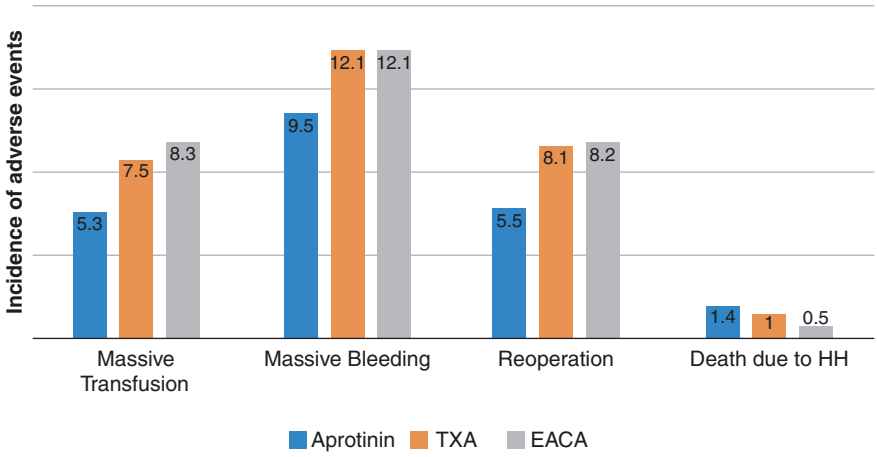

Fig. 12.4 Incidence of adverse events reported in the BART study. *TXA* tranexamic acid, *EACA* ε-aminocaproic acid, *HH* hemorrhage

surgery and should be avoided in patients with pre-operative renal dysfunction due to increased risks of postoperative renal failure and requirement for renal replacement therapy.

Despite this decision, scientific societies have mixed feelings regarding the use of aprotinin in cardiac surgery. As an example, the European Society of Anaesthesiology published the conclusion of a task force created to comment on the use of aprotinin in cardiac surgery [11]. The members argued that the approved indication (isolated CABG) is not really considered high risk and that aprotinin should only be used after careful consideration of the risk-to-benefit ratio, and after alternative treatments (e.g., lysine analogs) have been considered.

Safety Concerns of Tranexamic Acid

The safety of TXA has also been recently assessed in a trial with a 2-by-2 factorial design, where patients undergoing CABG surgery were randomly assigned to receive aspirin or placebo and tranexamic acid or placebo [12]. TXA was associated with a lower risk of bleeding than placebo was, without a higher risk of death or thrombotic complications within 30 days after surgery. However, TXA was associated with a higher risk of postoperative seizures. The risk of clinical seizures associated with the administration of high dose TXA has been highlighted in a few retrospective studies [13]. Although the underlying mechanisms are not fully elucidated, Kratzer et al. suggested that TXA enhances neuronal excitation by antagonizing inhibitory γ-aminobutyric acid (GABA) neurotransmission [14]. In another study it was shown that TXA inhibits neural glycine receptors, whereas inhibition of the inhibiting neurotransmitter glycine is an established cause of seizures [15]. Viewing the similarities in the chemical structures of TXA, GABA, and glycine, it

is conceivable that an interaction of TXA with both GABA and glycine receptors contributes to the increase in clinical seizures. Interestingly, the TXA peak concentration observed in the cerebral spinal fluid was reached approximately 5 hours after the plasma peak concentration. These pharmacokinetic properties might explain the delay reported between TXA administration and the development of clinical seizures after cardiac surgery. Although biochemical mechanisms may well explain the association between TXA and seizures, the special population of cardiac surgical patients and particularly the condition of CPB might also have a large impact on this observation. Understanding pharmacology and pharmacokinetics is crucial.

A recent study measured plasma TXA concentrations in cardiac surgical patients with chronic renal dysfunction for pharmacokinetic modelling and dose adjustment recommendations [16]. This study reported that plasma TXA levels were elevated in proportion to the severity of the renal dysfunction and the reduction in renal clearance. The authors have recommended a simple adjustment strategy to the BART dosing regimen to minimize drug overdosing, accumulation, and potential toxic effects of TXA. The authors also identified that single TXA bolus dosing in stages 1 and 2 chronic renal dysfunction was associated with a rapid decline in plasma levels to sub-therapeutic concentrations, without much risk of toxicity. This is important during prolonged surgeries where repeat doses may be warranted or an infusion is preferable. Bolus dosing among stages 4 and 5 chronic renal dysfunction provided near therapeutic plasma TXA levels with effective fibrinolytic inhibition for several hours. Even though the optimal dose remains to be determined, lower TXA doses should be preferred. The patient's co-morbidities and surgical complexity should be considered.

Implications for Daily Practice

Based on the published evidence, prophylactic administration of antifibrinolytic should be considered in patients undergoing cardiac surgery. If aprotinin can be used in some indications, the benefit-to-risk balance should be carefully evaluated before considering it.

Considering the safety profile of TXA and the non-inferior efficacy, lysine analogs might be preferred over aprotinin. In the absence of strong data regarding the optimal dose, the standard dose scheme should be applied. For tranexamic acid, a 30 mg/kg loading dose can be used followed by a 16 mg/kg/h infusion. In patients with acute or chronic renal dysfunction, the maintenance can be reduced to 5 mg/kg/h. Low doses have also been used in some studies. Sigaut et al. compared the efficacy of a standard dose (30 mg/kg followed by 16 mg/kg/h) to a low-dose scheme (10 mg/kg followed by 1 mg/kg/h) [17]. The incidence of blood products transfused during the first week, the primary outcome, was not different between the two doses, but the authors observed differences favoring the higher dose on blood loss, re-exploration for bleeding, and the incidence and amount of plasma and platelet concentrates transfused postoperatively. The difference might be explained by the low infusion dose used in patients included in the low-dose group. In the

presence of excessive bleeding, additional boluses or higher infusion rates are recommended in order to maintain adequate plasma levels. Further studies are needed to better define the optimal dose and to develop patient-based dosing schemes.

ε-Aminocaproic acid is most extensively used in the USA compared to most countries that use tranexamic acid, but this agent could be considered as an alternative. The dose scheme used in the BART study could be used: 1 g loading dose administered over 10 min followed by an infusion of 2 g/h.

In summary, prophylactic administration of antifibrinolytic drugs helps reduce bleeding and transfusion in patients undergoing cardiac surgery. The administration of antifibrinolytic is highly recommended in the most recent EACTS/EACTA guideline [18].

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Cardiopulmonary Bypass

13

Alexander Wahba

Case Vignette
A 75-year-old lady with a height of 157 cm and a weight of 65 kg is referred to your team for coronary surgery. Her hemoglobin is 11.7 g/dl (7.3 mmol/l). You are concerned about blood transfusion and your team wonders how her risk of transfusion can be minimized during CPB.

Why Is It Important?

The extracorporeal circuit supposedly reinforces the systemic inflammatory response due to contact activation and initiation of the coagulation system. Moreover, the contact of blood with ambient air in the reservoir contributes to blood activation. Blood activation and reduced concentration of coagulation factors due to hemodilution result in an increase of the risk of blood transfusion, particularly in patients with a small body surface area [1]. A number of amendments to the extracorporeal system have been discussed and investigated to ameliorate blood activation and reduce hemodilution. The aim of these improvements is to reduce blood loss by limiting blood activation and hemodilution.

In an effort to optimize cardiopulmonary bypass (CPB), several measures have been combined to reduce the invasiveness of the extracorporeal circuit. These minimized systems are commonly summarized under the acronym of minimally invasive extracorporeal circulation (MiECC) systems, and this system is described in a separate chapter. Relevant measures to improve patient blood management during cardiopulmonary bypass are the use of closed systems, autologous priming, and

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bioactive coating of the tubing. The purpose of this chapter is to provide insight in improvements of the biocompatibility of the extracorporeal circuit during cardiac surgery.

Closed Extracorporeal Circuit

Most closed extracorporeal systems include collapsible bags with integrated screen filters. Despite advantages, closed reservoirs also have the disadvantage of resulting in more complicated perfusion, since the removal of air has to be performed in an active fashion. Moreover, the use of cardiotomy suction requires a separate reservoir and vacuum-assisted venous drainage cannot be applied to the collapsible reservoir bag.

A large number of trials combined several components of a blood conservation strategy during CPB. Therefore, it is difficult to separate the isolated effect of a closed reservoir compared to a standard open reservoir. For instance, some trials combined the elimination of cardiotomy suction with the use of a closed system or investigated the combined effect of surface coating, closed system, and different pumps [2, 3]. It was shown that closed systems reduced thrombin generation and fibrinolysis during coronary artery bypass grafting [2] and reduced levels of a number of markers of blood activation [3] compared to open systems. In a follow-up randomized trial, Nakahira and coworkers isolated the effects of closed systems and found no difference between open and closed systems on markers of coagulation activation, fibrinolysis, and inflammation, including the thrombin–antithrombin complex, D-dimers, and interleukin-6 [4].

Only a few studies focused on the isolated effect of a closed system. Casalino et al. found significantly reduced transfusion requirements in a small single-center randomized trial [5]. A more recent trial investigated the transmission of microbubbles in different reservoirs and showed that a closed soft-shell reservoir led to less microbubble transmission [6]. However, the effect of this on blood loss or transfusion requirements was not investigated, and most available studies are not powered to show effects on clinical outcomes. In contrast, others found no advantage of closed systems in tests focusing on coagulation activation and inflammation [7, 8]. Adequately sized randomized trials on closed versus open systems are lacking, so that clear recommendations for clinical practice cannot be drawn yet.

Biocompatible Coating

Biocompatible coating aims to improve the hemocompatibility and hydrophilicity of the extracorporeal system by emulating the natural endothelial lining. There are different types of biocompatible coatings available. The first ones used ionic or covalent heparin bonding. However, due to the complexity of manufacturing heparin-based biocompatible coatings, alternative coatings have been introduced, including poly2-methoxy-ethylacrylate (PMEA) and phosphorylcholine.

The isolated impact of biocompatible coating in patient blood management programs may be limited and is still under debate. A systematic review and meta-analysis that was published in 2009 included 36 randomized trials issued between 1992 and 2006, showing that the use of any biocompatible coating reduced the odds for packed red blood cell transfusion when compared to the use of a non-coated circuit [9]. A more recent systematic review of 14 randomized trials confirmed the superiority of second and third generation heparin-coated circuits with respect to perioperative blood loss in about 50% of the included studies and when compared to non-coated circuits only [10]. In a third systematic review it was shown that 6 out of 14 included randomized trials showed better clinical outcome in patients subjected to a biocompatible-coated circuit [11].

In more recent publications it was shown that also the use of phosphorylcholine-coated circuits [12, 13] might contribute to less perioperative blood loss and transfusion requirements when compared to the use of non-coated circuits. However, perioperative hemostasis was not the primary endpoint in any of these studies [12, 13], and the results were biased by comparison of different CPB designs [12]. In a small, randomized trial with perioperative blood loss as study endpoint, the use of a phosphorylcholine-coated circuit was associated with less 6-h blood loss, but without differences in transfusion needs when compared to a non-coated circuit [14].

In addition to placebo-controlled investigations, two smaller studies compared the effect of PMEA, phosphorylcholine, and heparin-coated circuits on postoperative blood loss and transfusion requirements [15, 16]. Only one study showed that PMEA coating was associated with less platelet transfusions when compared to heparin coating [16]. Additionally, biocompatible coatings of oxygenators have been shown to reduce the risk of abnormal pressure gradients and prevent oxygenator failure [17].

Retrograde and Antegrade Autologous Priming

Several methods have been devised to reduce hemodilution in extracorporeal circulation, such as small volume extracorporeal circuits. Antegrade and retrograde autologous priming (RAP) are simple, inexpensive, and efficient ways to address the issue of hemodilution. This is achieved by allowing the blood to displace the fluid in the circuit into an external reservoir in an antegrade or retrograde manner. Antegrade displacement is mediated by the blood pressure of the patient, and retrograde displacement is achieved by pumping the fluid actively into the external reservoir. Retrograde priming is used more commonly, and with this technique usually 200–600 mL of priming fluid can be discarded after retrogradely replacing it with arterial blood before initiation of cardiopulmonary bypass.

The largest meta-analysis on this topic was published by Sun et al. in 2013 [18]. It was concluded that RAP reduced transfusion requirements, but did not influence other clinical parameters such as length of stay [4]. A total of six RCTs that were conducted specifically to investigate RAP are summarized in a meta-analysis including 557 patients [19]. The meta-analysis showed that RAP

significantly reduced the number of patients receiving intraoperative packed red cell transfusions and red cell transfusions during total hospital stay. Furthermore, the number of units of packed red blood cells transfused over the total hospital stay was significantly reduced, whereas the number of transfused packed red cells during surgery was not [19]. These findings were confirmed in a randomized trial on 120 patients with a small body surface area (<1.5 m^2) [1] and a more recent study that included 753 patients [20]. All studies point towards a favorable recommendation regarding the use of retrograde and antegrade autologous priming as part of a blood conservation strategy to reduce transfusion during cardiopulmonary bypass.

Implications for Daily Practice

As part of a blood conservation strategy, the above-discussed measures should be considered. A combination of several measures increases the likelihood of success with respect to a decrease in bleeding and blood product transfusions (Fig. 13.1).

Biocompatible coating, especially coating of oxygenators, is widely implemented in today's systems. However, this comes with an increased cost. The use of closed systems and autologous priming, possibly in combination with blood collection in a cell saver system, needs to be practiced by a perfusion team in order to ensure satisfactory realization. In particular, autologous priming has been shown to be simple and effective to reduce crystalloid load with the priming volume of the CPB circuit. It should be emphasized that blood management during bypass needs to be part of a concerted effort, including the preoperative and postoperative treatment. Liberal fluid therapy on the postoperative unit (for example, intensive care unit) will easily setback intraoperative achievements.

Returning to the case presented at the beginning of this chapter, a combination of measures would be most suitable to reduce the need for transfusion in this patient. As a first step autologous priming is recommended. It is likely that using a closed coated circuit and omission of cardiotomy suction further improves biocompatibility of perfusion.

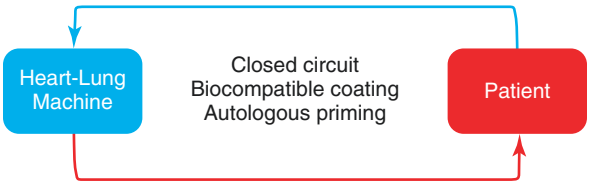

Fig. 13.1 Different technical interventions during cardiopulmonary bypass can be combined as part of a patient blood management program in order to reduce perioperative transfusion requirements

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Blood Conservation Strategies

14

Alexander B. A. Vonk

Case Vignette

After a benchmark with other hospitals, a local cardiosurgical team learned that their bleeding and transfusion rates were relatively high compared to other institutions. In order to expand their knowledge regarding blood conservation strategies they visited other cardiosurgical centers. In one center, the surgeon took some time to perform meticulous surgical hemostasis by cauterizing all bleeding microvessels in the chest wall and during cardiac surgery. While this caused a short prolongation of the total duration of surgery, the team noticed that there was almost no microvascular bleeding at the end of surgery. Although the introduction of this approach in their own center yielded some resistance, they started with meticulous surgical hemostasis in all cardiac cases, with less oozing and blood loss as result. Surgical hemostasis has now become a routine part of blood conservation strategies in their patient blood management program.

Why Is It Important?

The essence of blood conservation in cardiac surgery consists of the principle that no blood of the patient shall leave the theater, unless it is within the patient. Blood conservation techniques must be considered synergistic and should always be applied as part of a comprehensive blood management program. Figure 14.1 shows the different aspects of blood conservation strategies during cardiac surgery. The purpose of this chapter is to describe these different strategies and their contribution to reduced bleeding and transfusion requirements.

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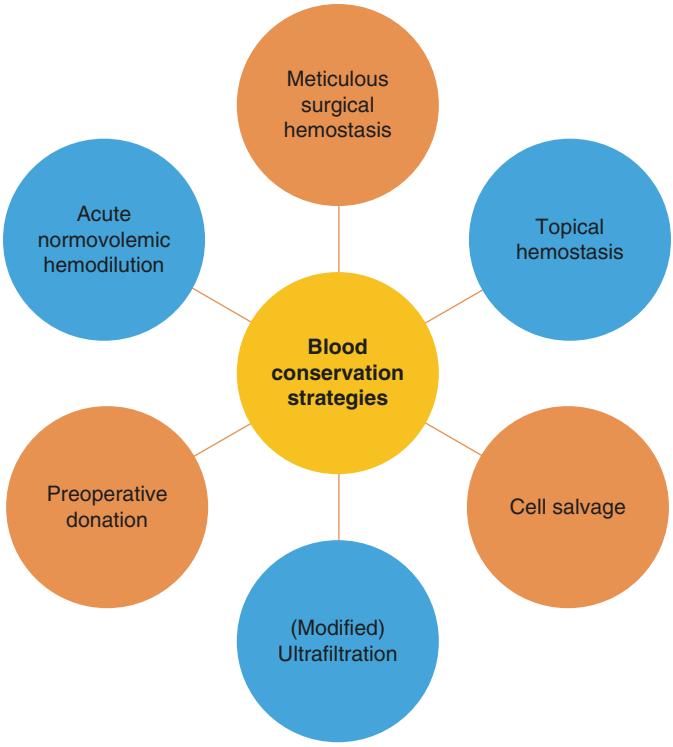

Fig. 14.1 Blood conservation strategies that may contribute to reduced bleeding and transfusion requirements in cardiac surgery

Surgical Prevention of Bleeding

Perhaps because of the obvious nature, high-level evidence on the importance of the application of a meticulous hemostatic surgical technique is scarce. Nevertheless, accurate and conscious hemostasis from incision until wound closure plays a key role in blood conservation without which all other factors are of less importance.

Topical Hemostasis

Prevention of surgical bleeding by topically applied hemostatic agents is not considered effective for routine application, because literature in cardiac surgery is highly contradictory on this matter. As standardization is difficult for topical treatment of bleeding, available literature is mostly based on animal studies. However, i.e., sealants based on polyethylene glycol polymers, a combination of bovine albumin and glutaraldehyde and a combination of gelatin and thrombin, can play an important role in hemostasis in special bleeding situations that would otherwise only be managed with great difficulty [1–3].

Cell Salvage

The use of cell salvage is currently standard practice in many centers due to several factors. Several variants of cell salvage machines are available. The basic principle of cell salvage consists of a vacuum driven suction device that mixes shed blood from the wound with washing fluid, usually heparinized saline. This mixture is suctioned to a bowl which centrifugates the blood and saline solution, thus concentrating the blood cells to a hematocrit of 60% or higher. These washed cells are then collected in a bag and retransfused using a filter to prevent infusion of clots, microaggregates, or other irregularities.

Firstly, cell salvage is considered efficacious in blood conservation and in preventing the need for transfusion [4, 5] in cardiac surgery [6, 7]. As compared to other methods of blood conservation, cell salvage can be used throughout surgery, where other methods aiming for retransfusion or concentration of patient's blood, i.e., cardiotomy suction or ultrafiltration, are limited to the phase of extracorporeal circulation. This also enhances efficacy. Due to the influence of many variables, it is difficult to quantify the advantage of cell salvage in general terms. However, one meta-analysis consisting of 31 randomized trials involving 2282 patients showed that cell salvage significantly reduced the odds ratios for any allogenic blood products and red blood cells only (OR 0.63, 95% CI: 0.43–0.94, $P = 0.02$ and OR 0.60, 95% CI: 0.39–0.92, $P = 0.02$, respectively) without indications for negative side effects [6].

Secondly, shed blood in the wound during surgery expresses an inflammatory response due to contact activation [8] which is present in the plasma. During the cell salvage process, cells are washed and the activated blood plasma is separated from shed blood from the wound. Therefore, cell salvage leads to reduced inflammatory response in comparison to cardiotomy suction [9–11], and can also result in reduced postoperative blood loss [7]. Moderate volumes of cell saved blood with the removal of the accompanying plasma in the cell salvage process do not affect postoperative hemostasis [12] as cell salvaged blood does not contain coagulation factors and platelets. However, discarding larger quantities of plasma will have a deleterious effect on the coagulation system [13]. Oxygen delivery of salvaged cells is preserved, which is not the case in allogenic blood transfusion [14, 15].

Thirdly, standard use of cell salvage is associated with extra cost for the device and the disposables. However, depending on local situations, especially the cost for disposables versus the price of blood products, which may vary per country, these expenses can be outweighed by the benefits due to savings on the cost for allogenic blood transfusions [16].

Ultrafiltration and Modified Ultrafiltration

Using a hemoconcentrator in the extracorporeal circuit, control of the total volume of blood during cardiopulmonary bypass can be achieved by means of ultrafiltration (UF). In modified ultrafiltration (MUF), excess fluid is discarded from the

remaining blood after termination of extracorporeal circulation. Blood from the arterial line and the remaining blood from the venous reservoir is led to a roller pump via a hemoconcentrator. Then, the concentrated blood is retransfused to the patient through the venous cannula in the right atrium. As hemodilution is associated with bleeding, the inverse, concentration of diluted blood, can be part of a blood conservation strategy, especially in anemic patients. Moreover, as with cell salvage, UF and MUF are accompanied by removal of mediators of inflammation and this may also lead to improved hemostasis [17–21]. However, the efficacy of ultrafiltration of residual cardiopulmonary bypass blood is not equivocal [22].

Preoperative Donation

Preoperative donation of blood that is retransfused during or after surgery may reduce the number of allogenic blood transfusions in cardiac surgery. This approach is however limited to patients with relatively high hemoglobin and hematocrit levels, a relatively large body surface area without coagulation abnormalities. It was shown that preoperative donation in elective surgery was associated with a lower occurrence of allogenic blood transfusion, but due to its retrospective nature, the study was biased by multiple confounding factors [23]. In a matched-pair analysis it was shown that retransfusion of preoperative donated blood was associated with a decrease in the overall transfusion of blood products [24]. Large randomized controlled studies on preoperative autologous blood transfusion are currently lacking.

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) is a technique in which a predefined amount of blood is taken from the blood circulation of the patient and replaced with a crystalloid solution. Blood is stored during surgery, and retransfused after the procedure. The effects of ANH on blood consumption are heterogeneous [25, 26] or at best modest [12]. This technique is conflicting with the general strategy in blood management to prevent hemodilution by fluid restriction. One guideline recommends to limit acute normovolemic hemodilution to patients with high preoperative hemoglobin levels, which can be taken into consideration [27].

Implications for Daily Practice

In summary, blood conservation during open heart surgery should primarily consist of a combination of good surgical hemostasis in combination with cell salvage. Meticulous hemostasis during opening of the chest may be somewhat time-consuming, but may reduce the time during chest closure and contribute to a reduction in microvascular bleeding. The evidence for the application of cell salvage during cardiac surgery is conflicting, and seems to be dependent on the timing of cell salvage

(shed and residual blood) and the maximum volume that is retransfused (less than 1 liter). For other techniques, like ultrafiltration, preoperative blood donation, and acute normovolemic hemodilution, the level of evidence is low, and these techniques should only be considered in patients with a clear benefit or high-risk profile.

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Minimal Invasive Extracorporeal Circulation Systems

15

Adrian Bauer, Jan Schaarschmidt, Thomas Eberle, and Harald Hausmann

Case Vignette

A 59-year-old lady with a low body surface area and mild anemia requires coronary artery bypass graft surgery with cardiopulmonary bypass. The patient would benefit from minimal hemodilution and reduced activation of the coagulation system in order to prevent perioperative packed red blood cell transfusions. The clinical perfusionist and cardiac surgeon decide to use minimal invasive extracorporeal circulation in this patient. The system requires a prime volume of 650 mL, and consists of a closed and biocompatible coated circuit with centrifugal pump. Due to the hemocompatibility of the system, no full anticoagulation is required. After an eventless procedure, the patient recovers without complications and transfusion requirements.

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Why Is It Important?

Cardiopulmonary bypass (CPB) is considered to be a contributing factor to perioperative trauma in cardiac surgery. The known side effects of CPB include hemolysis, platelet damage, and cytokine production, which could in turn affect all organs negatively [1]. In particular, CPB is suspected to increase consumption of blood products [2]. From a historical perspective, CPB perfusion systems of the first hour, which are from here referred to as conventional extracorporeal circulation (CECC), used large priming volumes and presented large foreign surfaces to the patient blood. Exposure of blood to the negatively charged artificial surfaces and to air are known to lead to cellular and humoral blood activation. In particular, the activation of the intrinsic coagulation cascade is triggered and may finally lead to disseminated intravascular coagulation and postoperative coagulation disorders. Furthermore, the rough foreign surface of the CECC causes hemolysis of the erythrocytes by a flow-dependent increase of shear stress [3, 4].

Therefore, a mandatory systemic anticoagulation of the patient during CECC with an activated clotting time (ACT) of at least ≥400 s (depending on the ACT method used) should be targeted, which otherwise further enhances the intraoperative bleeding tendency.

Since the pathophysiological mechanisms of CECC were already recognized in the early 1960s, initial attempts of improvements mainly focused on the reduction of the foreign surface contact. As one of the first improvements, the large-area spinning oxygenators were replaced by bubble oxygenators. Although the artificial surface contact decreased, the required priming volume remained high. In addition, safer hypothermia was made possible with the introduction of normovolemic hemodilution perfusion technique, but at the cost of an additional decrease in hematocrit [5].

In summary, it can be postulated that the causes for the need of allogenic blood transfusion in cardiac surgery are multifactorial. Firstly, the components of CECC traumatize blood (contact activation, hemolysis and fibrinolysis), and secondly, the transfusion threshold may already be reached by hemodilution alone (e.g., during induction of CECC). This effect is reinforced by the application of crystalloid cardioplegia and volume deficiency-induced substitution of infusions during CECC. Thirdly, cardiac surgery involves a particularly bleeding-intensive intraoperative situs, and the tendency to bleed is additionally increased by anticoagulation and hypothermia [4]. Fourth, in CECC it was common to directly retransfuse highly activated shed blood (400–900 mL) into the system [6], which causes further triggering and propulsion of bleeding-promoting coagulation cascades. Furthermore, impaired hemostasis and the interacting pathophysiological mechanisms may lead to a systemic inflammatory syndrome or sepsis, the so-called post-perfusion syndrome [7]. The purpose of this chapter is to illustrate how a conventional extracorporeal circuit can be adapted such that it is beneficial with respect to bleeding tendency and transfusion requirements in patients undergoing cardiac surgery.

Improvement of Conventional Extracorporeal Circulation Circuits

All evolutionary stages and technical implementations introduced by clinical perfusionists, engineers, and physicians were triggered by the overall aim to reduce the negative side effects of conventional extracorporeal circulation and its circuit components. For this purpose, new system components such as oxygenators, filters, reservoirs, and tubing systems with smaller artificial surfaces were developed and introduced (see Fig. 15.1). In addition, biocompatible surface coating of the circuit components was developed to mimic the properties of a physiological cell membrane as artificial endothelium. However, all measures provide only a limited effect on the overall improvement of outcome following cardiac surgery with cardiopulmonary bypass.

Ongoing research finally led to a new evolutionary development of the extracorporeal circuit at the end of the 1990s, which combined partial technical improvements and the visions of the past of a novel comprehensive perfusion concept entitled minimal invasive extracorporeal circulation system (MiECC). The enhanced biocompatibility of perfusion aimed at a far-reaching minimization of the side effects of perfusion and consequently the post-perfusion syndrome. Thus, MiECC can be considered an advancement and a summary of manifold improvements in the field of clinical perfusion towards a holistic concept. Improved perioperative biocompatibility also includes the reduced perioperative need for allogenic blood products. In this context MiECC is regularly cited in the scientific literature as one way to save blood transfusions, to reduce derangements of the coagulation system and

Fig. 15.1 Minimal invasive extracorporeal circulation system consisting of the main line. The system is characterized by a closed circuit, minimized dead space, biocompatible coating of the tubing system, and active air bubble removal. *Photographs are made by the authors (Norman Koch, MediClin Heart Center Coswig, Germany)*

Table 15.1 Aspects of minimal invasive extracorporeal circulation systems (MiECC) that are associated with blood conservation

	Mechanisms of action of MiECC for blood conservation	Effect
1	Reduced hemodilution [8, 16]	Lower priming volumes (~600–750 mL) lead to less dilution of the circulating blood volume
2	Blood activation through artificial surface and/or air contact [17, 18]	MiECC systems are considered to be less traumatic in structure by: (a) Use of biocompatible coatings of the artificial surfaces, (b) Large reduction of the artificial surface of the systems, (c) Avoidance of direct blood–air contact, (d) Use of less blood-traumatic blood pumps (centrifugal pumps)
3	Blood management [6, 16]	Suctioned blood is separated and, in most cases, processed by automated autotransfusion devices, which eliminate activated coagulation factors
4	Alternative anticoagulation strategies [19–21]	Potential reduction of the anticoagulation dose due to surface coating of closed circuits

emphasis is put on potential savings and referred to as an argument for the application of this concept [1, 8–15].

Minimal invasive extracorporeal systems work with different mechanisms to achieve this goal, and all different aspects have to be part of the concept of MiECC to achieve the highest gain regarding blood conservation (Table 15.1) [22].

Minimal Invasive Extracorporeal Circulation

The published data which favors the use of MiECC including ten meta-analyses and reviews [8–15, 22–24] is extensive; however, MiECC systems have only partially found their way into clinical routine so far. In fact, most prospective randomized trials and meta-analyses demonstrated less red blood cell transfusions using MiECC compared to conventional systems [1, 8–15].

The largest trial of El-Essawi et al. was performed on 500 patients in a multicenter study in six European hospitals [25]. The study was powered for the reduction of packed red blood cell requirements and showed a clear reduction in the need for red blood cell transfusions in the group with MiECC (MiECC: 333 ± 603 mL) compared to conventional systems (587 ± 1010 mL). Moreover, transfusion rates in the MiECC group were 55.2% compared to 64.7% in conventional systems [25].

In 2007, MiECC received a Class IIb recommendation with a level of evidence B in the Blood Conservation Clinical Practice guideline of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists. In the 2011 update of this guideline it was the only perfusion-associated measure to receive a level I (A) recommendation [26]. In the guidelines for patient blood management of the

European Associations of Cardiothoracic Anaesthesiology and Surgery (EACTA and EACTS) MiECC is a level IIa recommendation with a level of evidence (LoE) of B [27]. Interestingly, however, institutional measures to reduce hemodilution are classified with a level I recommendation (LoE: C), even though reduced priming volume and thus less hemodilution is regarded as one of the major effects of MiECC and hence clearly speaks in favor of using this perfusion technique [1]. For specific recommendations and levels of evidence of particular aspects of MiECC we refer to the aforementioned guidelines.

As a holistic concept MiECC combines various separate aspects. Investigating these features in particular, one finds high levels of recommendations for a reduction in hemodilution and for dealing with shed blood. Many other measures lack evidence or were not sufficient enough to obtain a higher level of recommendation than "II" for a reduction in demand of red blood cell transfusion.

The Society for Minimal Invasive Extracorporeal Technology (MiECTiS) published a definition and several recommendations for the use of MiECC systems [16]. Since this time, the term and application of MiECC is internationally recommended in an interdisciplinary consensus group, which consisted of clinical perfusionists, cardiac surgeons, and anesthesiologists. Many of the MiECC features (Table 15.1) mentioned in the present chapter were recommended in this consensus paper. In order to comply with the definition of the MiECTiS, a MiECC system must provide reduced priming volume, a closed circuit, a coated surface, a centrifugal pump, and a shed-blood management system. To date, MiECC is only assigned with an IIB (LoE; B) recommendation with regard to application of an alternative anticoagulation strategy due to a current lack of a widespread application throughout cardiac centers worldwide and the lack of randomized clinical trials. While reduced need of red blood cell transfusion with MiECC compared to CECC is evident in most of the studies, a reduction in bleeding and the need for rethoracotomies have not been clearly proven [27]. Nevertheless, there may be a link between a MiECC-associated reduced need for anticoagulation and postoperative blood loss. So far, some studies suggest that the combination of MiECC and reduced heparin and protamine dosages may lead to less postoperative bleeding [19, 28]. In this regard, more studies are needed to further evaluate the hypothesis that MiECC contributes to blood conservation by a reduced derangement of the hemostatic system.

Implications for Daily Practice

In conclusion, perfusion related blood-saving measures as an integral part of a patient blood management concept can best be attained by a combination of measures. The MiECC perfusion seems predestined to achieve this goal for it combines many features to significantly reduce the demand for red blood cell transfusion in one concept and thus may lead to considerably less transfusions. The ability to protect blood components and the associated potential reduction of the bleeding tendency should be further investigated in future studies.

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Volume Replacement

16

Matthias Wolff and Michael Sander

Case Vignette

A 75-year-old woman was scheduled for cardiac bypass surgery. After uncomplicated surgery the patient left the operating theater with a fluid balance of +3500 ml, mainly based on the application of normal saline 0.9%. During surgery and at the intensive care unit, the chloride level increased in this patient from a baseline level of 103 mmol/l to a maximum of 118 mmol/l, leading to a hyperchloremic acidosis. Bicarbonate 8.4% had to be administered repeatedly. At the intensive care unit, peripheral edema and an impaired pulmonary gas exchange was noticed, requiring non-invasive ventilation after a moderately delayed extubation. With the application of furosemide, the fluid balance was kept negative over the next 2 days, leading to an improvement in gas exchange and a slight regression of peripheral edema. Vasopressors were stopped at day one after surgery. At day two she left the intensive care unit.

Why Is It Important?

The adequate balance and replacement of all body fluids is a crucial element of perioperative management in patients undergoing surgery. Volume replacement in cardiac surgery covers different needs and indications. For example, the loss

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of body water after fasting before surgery accounts for a volume loss of about 0.2–0.5 ml/kg/h [1]. This can be minimized by enabling patients to drink up to 2 hours before surgery avoiding unnecessary fasting [2]. This should allow to start surgery without a relevant deficit in volume homeostasis. During and after surgery, fluid loss by perspiration has to be considered as well as the compensation of blood loss and the fluid shift in extravascular compartments by injury of the endothelial barrier.

There is a large variety of different kinds of fluids that are available for volume replacement, such as electrolyte free solutions (e.g., glucose 5%), saline solutions, balanced and unbalanced solutions, artificial and human colloidal solutions, and blood products like packed red blood cells, plasma, and platelet concentrates. The rational indication and application of these different kinds of solutions requires sufficient understanding of the physiological background of human volume homeostasis and the composition and indications of the fluids.

In clinical practice, the anesthesiologist has two major approaches for optimizing hemodynamics in patients undergoing cardiac surgery: vasoactive/inotropic drugs and intravascular volume. For hemodynamic optimization it is necessary to identify which patients would benefit from one or the other therapy. Advanced hemodynamic monitoring with different tools and parameters (pressure, volumetric static, volumetric functional and echocardiography) as well as the knowledge of the actual fluid status of the patient allows management of patients undergoing cardiac surgery to be optimized. The purpose of this chapter is to illustrate the essence of fluid therapy and the consequences of volume loading for patient hemostasis.

Physiology of Fluid Distribution and Fluid Therapy

Fluid Compartments

The human body contains about 60% of water (ranging from 50% in elderly people up to 70–75% in infants and newborn). Assumed a total body weight of 70 kg, the total water content of the body can be calculated, and is about 42 l. About two thirds of the water is located in the intracellular space, which is osmotically dominated by potassium ions. One third of the total body water content is located in the extracellular space, which is osmotically dominated by sodium ions. The extracellular space is subdivided into the intravascular space (about 25% or 3.5 l) and the interstitial space (about 75% or 10.5 l) (Fig. 16.1).

Fluids without osmotic or oncotic active ions or molecules (e.g., glucose 5%) will be distributed all over the whole body implicating a minimal intravascular volume effect (theoretically about 8%), but resulting in an increase in intracellular volume (e.g., brain edema). Crystalloids are dominated by sodium ions and will therefore be shifted to the extracellular space. The intravascular effect will be about 25% accompanied by an interstitial fluid accumulation. Artificial and human colloidal solutions as well as blood products will be directly distributed within the intravascular space, and result in a 100% estimated intravascular volume effect.

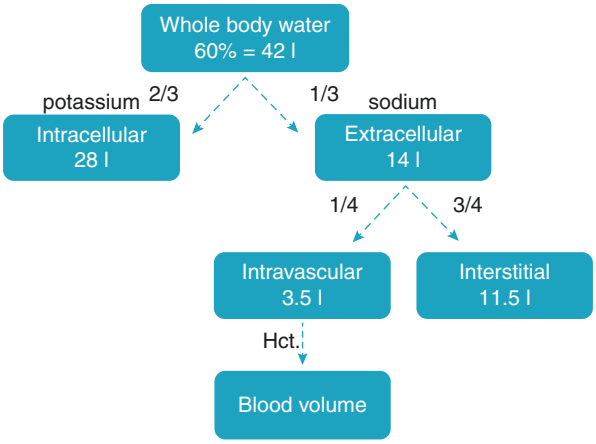

Fig. 16.1 Fluid compartments in the human body. Under physiological conditions the human body consists of 60% of water. The span ranges from 70% to 75% in newborns to 50% in geriatric people. Fluid is principally distributed to the intracellular space (mainly dominated by potassium ions) and to the extracellular space (mainly dominated by sodium ions). The extracellular space is further divided into the intravascular and the interstitial compartment. The intravascular space is about 20–25% of the extracellular space and the interstitial space accounts for 75–80% of the extracellular volume. This distribution is mainly directed by colloid-oncotic pressure, mostly made by albumin. Assumed a hematocrit of about 50% we could calculate a blood volume of about 7l in this model. *Hct* hematocrit

The Starling Principle

The classical Starling concept distinguishes two main forces in capillaries. The first is an outward directed filtration pressure and a small inward directed pressure of the surrounding tissue resulting in a net outward filtration pressure. The second is the intravascular oncotic pressure that exceeds the low oncotic pressure of the surrounding tissue. In the high pressure segment of the capillaries, a net filtration caused by a high filtration pressure is predicted, and at the venular side of the small vessels a net reabsorption caused by a dominant oncotic pressure is predicted. The remaining filtrated volume was drained by the lymphatic vessels. The functional Starling principle requires consequently a protein poor interstitial space, but over the last years questions about the Starling principle are raising:

- There is no protein poor interstitial space
- Intravascular albumin impedes net filtration more than predicted by the colloid-osmotic pressure
- Fluid is not reabsorbed at the venular side but filtered at a variable extent throughout the vasculature

This problem can be solved by augmenting the classical Starling principle by an additional element: the endothelial glycocalyx [3].

The Endothelial Glycocalyx

The glycocalyx is a thin carbohydrate-rich layer that covers the luminal side of the vascular endothelium and plays an important role in maintaining endothelial layer integrity. Over the past years, it has been increasingly appreciated as an important factor in vascular physiology and pathology [3]. The endothelial glycocalyx is an up to 1 μm thick slow-moving plasma layer over the endothelium. Many studies indicate a variety of physiological roles for the endothelial glycocalyx; in addition to modulating capillary red blood cell filling, the glycocalyx may affect the function of the vascular system, whereas under physiological conditions, the endothelial glycocalyx is a key element of the vascular barrier. Damage to this layer—for example, by inflammation, ischemia-reperfusion, or shock—leads to a loss in vascular integrity.

Acid-Base: The Stewart Approach

Composition of intravenous fluids impacts the acid-base status of patients undergoing cardiac surgery. The traditional use of the Henderson–Hasselbalch equation using carbon dioxide/bicarbonate analysis does not account for the important role in the regulation of pH by strong ions, weak acids, and water itself. Peter Stewart developed an approach where the analysis of acid-base disturbances in plasma is based on basic physical and chemical principles. The advantage of this approach is a better understanding of the mechanisms behind acid-base disorders and the effects of different intravenous fluids on acid-base balance.

The use of large volumes of saline 0.9% may lead to an increase in chloride concentration in plasma, due to the relatively high concentration of chloride ions compared to plasma. Therefore, the ratio between sodium and chloride is disturbed as the strong ion difference decreases, which may lead to an extracellular hyperchloremic acidosis. In case of hyperchloremic acidosis, physiological processes like the coagulation system, kidney function, or the tonus of blood vessels may be disturbed [4].

Clinical Studies on Fluid Therapy in Cardiac Surgery

Administration and monitoring of volume replacement require close and repeated assessment of the fluid balance, system hemodynamics, and tissue perfusion. The most important target in volume replacement is to provide adequate oxygen supply to the microcirculation, while keeping negative side effects as low as possible.

In the following part we will discuss important topics concerning the choice of volume in patients undergoing cardiac surgery as well as issues concerning priming solutions of cardiopulmonary bypass, outcome of patients, and kidney dysfunction and failure depending on the kind of the applied solution, the impact on bleeding risk, and the consequences for acid-base balance.

Cardiopulmonary Bypass Priming

For cardiac surgery with cardiopulmonary bypass (CPB), the extracorporeal circuit must be prefilled with a priming solution. For priming of extracorporeal circuits different solutions are available: crystalloids, colloids, or blood products. Randomized clinical trials showed contrasting results regarding a relation to bleeding. Schramko et al. demonstrated no effect on coagulation and rotational thromboelastometry parameters when colloids were added to the priming compared to crystalloids [5]. Others did not find differences in the incidence of coagulation dysfunction after cardiac surgery when a priming solution with gelatin was compared to priming with Ringer's solution [6]. Gurbuz et al. compared a balanced crystalloid priming solution with a 6% hydroxyethyl starch (HES) 130/0.4 as prime solution, but also found no differences in renal or pulmonary function between groups [7]. The intensive care unit stay and postoperative hospital length of stay were shorter in the HES group; however, the study was not powered for this endpoint [7]. Hydroxyethyl starch was not associated with increased postoperative blood loss or transfusion requirements. However, these results need to be confirmed by larger studies to draw any strong conclusions on the choice of the appropriate fluid. Others compared the use of different colloids for priming solutions, but could not show a difference in coagulation function after surgery [8]. A literature review on fluids did also not show a difference in the number of cardiovascular complications, acute kidney injury (AKI) rates, or length of stay between different fluid resuscitation strategies. The authors mentioned the limitations of most trials in this field with small sample sizes based on power calculations using clinically irrelevant endpoints, and therefore are rated as low-quality studies [1].

Kidney Function

Acute kidney injury and failure are relatively common after cardiac surgery. The cause is multifactorial, including renal ischemia, reperfusion, hemolysis, inflammation, oxidative stress, embolic events, and toxins like contrast medium. Patients with renal failure have a fivefold increased risk of death during hospitalization. Preventive approaches are limited but include the preservation of renal perfusion, while avoiding an increased central venous pressure by fluid overload.

Furthermore, the choice of fluids could play an important role for the development of kidney failure. The use of starches and hyperchloremic acidosis was linked in major studies with increased rates of AKI. Skytte Larsson et al. compared a crystalloid with a starch-based fluid bolus in patients undergoing cardiac surgery [9]. Due to hemodilution, both approaches did not improve renal oxygen delivery, and the oxygen extraction fraction was increased in the crystalloid group [9]. Madger et al. could not demonstrate any differences in the incidence of AKI by comparing a resuscitation algorithm with either 0.9% saline or pentastarch [10]. In a retrospective analysis in more than 1500 patients, Momeni et al. demonstrated a reduced

incidence in AKI in patients receiving a cumulative dose of HES below 30 ml/kg compared to those patients receiving more than 30 ml/kg [11].

Regarding fluid balances, Shen et al. demonstrated that a postoperative zero fluid balance was associated with the lowest incidence of AKI in patients who underwent cardiac surgery, and a more negative fluid balance could not further reduce the occurrence of AKI [12]. Recently, in a non-cardiac surgery collective, a more liberal approach led to less AKI compared to the zero-balance restrictive group (RELIEF study) [13]. The volume of fluid intake shows a U-shaped association between postoperative fluid intake and AKI. The effect of a positive fluid balance on AKI was also found by Haase-Filitz et al. [14]. However as also a too restrictive fluid management was shown to increase the risk of postoperative complications, the use of a goal directed fluid management approach might lead to better outcomes [15, 16].

Acid-Base

The application of chloride-rich (unbalanced) solutions for priming or volume therapy is suspected to produce a couple of undesired side effects, like kidney dysfunction or coagulation abnormalities, mostly caused by hyperchloremic acidosis [17]. Few data are available investigating the potential negative side effects caused by unbalanced solutions in patients undergoing cardiac surgery. McIlroy et al. compared the effects of a chloride-rich and chloride-limited infusion strategy [18], but found no difference in the incidence of AKI. Reddy et al. compared the effects of Plasma-Lyte 148™ with 0.9% saline on blood product use and postoperative bleeding in 954 patients admitted to the intensive care unit following cardiac surgery [19]. The main finding of this study was that Plasma-Lyte 148™ was not associated with a reduction in transfusion requirements after cardiac surgery compared to saline, and in the Plasma-Lyte 148™ group patients more frequently received blood products [19]. Recently, in non-cardiac surgery patients, especially in patients with renal dysfunction saline solutions were associated with increased rates of AKI and a trend for increased mortality [20, 21]. Even though there is no proof that saline in a small volume is unfavorable, caution is recommended with the use of larger volumes of saline. Especially in critically ill adults, intravenous administration of balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal replacement therapy, or persistent renal dysfunction.

Bleeding Risk, Coagulation, and Volume Replacement

Volume replacement dilutes circulating coagulation factors and platelets, and may therefore have an impact on blood coagulation. Additionally, specific characteristics of different solutions may impact the coagulation capacity after cardiac surgery. Examples for this include acidosis caused by hyperchloremia, or the effects of HES on platelet function [1]. Some trials investigated the role of colloids (gelatin and

hydroxyethyl starches) and crystalloids on hemostasis and bleeding. The results were however conflicting [1]. Some trials did not show any influence on blood coagulation and blood loss [22], while others demonstrated alterations in hemostasis and transfusion requirements [5, 23, 24].

A recent meta-analysis reported no difference in postoperative bleeding when balanced and unbalanced crystalloids were compared [25]. In a subgroup of three trials, patients with a blood loss of more than 800 ml, lower blood loss volumes were found in patients treated with balanced solutions. Patients treated with balanced crystalloids required a lower amount of red blood cell transfusions. However, these data were obtained in varying populations of patients with different regimens of fluid replacement and cannot be used for cardiac surgical patients without caution [25]. A double-blind RCT investigated the effects on coagulation and blood loss by using 5% albumin, HES 6%, and Ringer's lactate for pump priming and volume replacement. More patients in the albumin and HES group were treated with packed red blood cells compared with the Ringer's lactate group, but without differences in postoperative blood loss among groups [26]. The albumin and HES groups had a weaker clot firmness slower clot development upon arrival to the intensive care unit compared to those patients in the Ringer's group [26].

Recently, an updated black box warning was issued for the use of HES after a previous warning in 2013 by the FDA and EMA. The warning eliminates all starches completely from the ICU and cardiac surgery. One point leading to this warning was the increased risk for AKI and bleeding in critically ill patients. This increased bleeding risk has also been demonstrated for patients undergoing cardiac surgery. In a meta-analysis, Navickis et al. demonstrated that HES was associated with an increase in postoperative blood loss, reoperation for bleeding, and transfusion [27]. Several mechanisms for this class effect are described, including inactivation of factor VIII, impaired von Willebrand factor function, platelet aggregation, and fibrin polymerization [1].

In vivo and in vitro studies demonstrated that gelatins affect some parameters of blood coagulation. However, pump priming with different fluids (20% albumin in Ringer's lactate versus oxypolygelatin) did not affect blood loss after cardiac surgery [28]. The data available for modern gelatin solutions do however not allow recommendations for or against the use of gelatin in cardiac surgery patients yet.

To prevent possible disadvantages of synthetic colloids, albumin is increasingly used as the "natural" colloid in cardiac anesthesia and critical care. It is known that a low preoperative albumin serum concentration is correlated with poorer outcomes after cardiac surgery [29]. In a prospective observational study, Ryhammer et al. compared the effects of a perioperative application of crystalloids, HES, and human albumin [30]. In contrast to other studies, the authors report that the application of albumin was associated with increased rates of new renal replacement therapy compared to starches. Therefore, AKI after cardiac surgery might in part be multifactorial, and cannot be reduced just by using only the "ideal" fluid. Further aspects like timing, patient identification, and goal directed approaches to volume therapy are also known to influence the incidence of AKI and complications in general. This assumption and the conflicting results of some of these studies were supported by

the observation that a global restriction in albumin use in a cardiac surgery intensive care unit did not increase or decrease morbidity and mortality [31].

Theoretically, the therapeutic use of plasma should be an ideal option for volume replacement in patients. However side effects (mortality, infections, etc.) were reported in patients treated with fresh frozen plasma to correct coagulopathy, albeit often insufficient in methodology, dosage, and effect [32]. Trials investigating the effectiveness of plasma for volume replacement are however missing.

Implications for Daily Practice

Maintenance of a quantitative and qualitative balanced intravascular fluid status is crucial in cardiac surgery. Most important physiological principles are the distribution of fluids in different compartments in the body, the understanding of the Starling principle, explaining the filtration and reabsorption in small blood vessels especially supplemented by the function of the endothelial glycocalyx, and the effects of different ions and solutions on acid-base balance.

In contrast to official warnings to prevent starches in clinical practice, artificial colloids seem to be safe in cardiopulmonary bypass priming, but increased bleeding and reoperation was demonstrated for patients undergoing cardiac surgery; however, the trials existing so far have limited quality.

The incidence of acute kidney injury after cardiac surgery has not been shown to be affected by the use of starches or crystalloids. In fact, it seems to be more important to preserve an adequate renal perfusion and to keep a neutral fluid balance. The use of balanced solutions for infusion has not been demonstrated to be superior to a "classical" approach in cardiac surgical patients. However, recent studies point to an increased risk of AKI in a non-cardiac surgery population. The impact of the choice of infusion solution on perioperative blood coagulation and blood loss in cardiac surgery is not clear; some trials demonstrated no differences, while others showed alterations in hemostasis and transfusion requirements. However, while the evidence is often inconclusive on the advantages and disadvantages of infusion solutions in cardiac surgery we have better evidence from clinical fields beyond cardiac surgery. As long as better evidence is provided, clinical decisions concerning the choice of infusion solutions should be based on general recommendations (restrictive of artificial colloids) for clinical use with special respect to basic physiological considerations.

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The Jehovah's Witness

17

Peter M. J. Rosseel

Case Vignette

A 60-year-old man requiring mitral valve surgery and concomitant MAZE procedure is presented at the hospital with a hemoglobin level of 15.5 g/dl (9.6 mmol/l). He is a Jehovah's Witness, and he knowledgeably refuses any allogeneic blood or blood derivatives. He is treated according to the Jehovah's Witness protocol in a local hospital. Preoperative coumadin is stopped without bridging and the preoperative INR is 1.1. The patient did not receive anemia treatment.

After induction, acute hemodilution is performed with 1 l of autologous blood that is replaced by 500 ml gelatin. Intravenous fluid administration is minimalized. Blood loss before heparinization and after protamine is processed through a cell saver system. After a complex procedure, severe residual mitral regurgitation and SAM is noticed and extracorporeal circulation is reinstituted. Additionally, septal myectomy is performed.

Weaning of bypass required a low dose of dobutamine and atrioventricular (AV) pacing with underlying nodal bradycardia. After heparin reversal, 650 ml of cell salvage blood was reinfused followed by retransfusion of 1000 ml of autologous blood. The patient is extubated on the first postoperative day, and shows initial improvement on diuretics. Hemoglobin decreased to 12 g/dl (7.5 mmol/l) on day 1, with a slight rise in creatinine to 1.4 mmol/l. Erythropoietin and intravenous iron were started on day 1, and the course of hemoglobin, platelet count, CRP, and temperature are depicted in Fig. 17.1.

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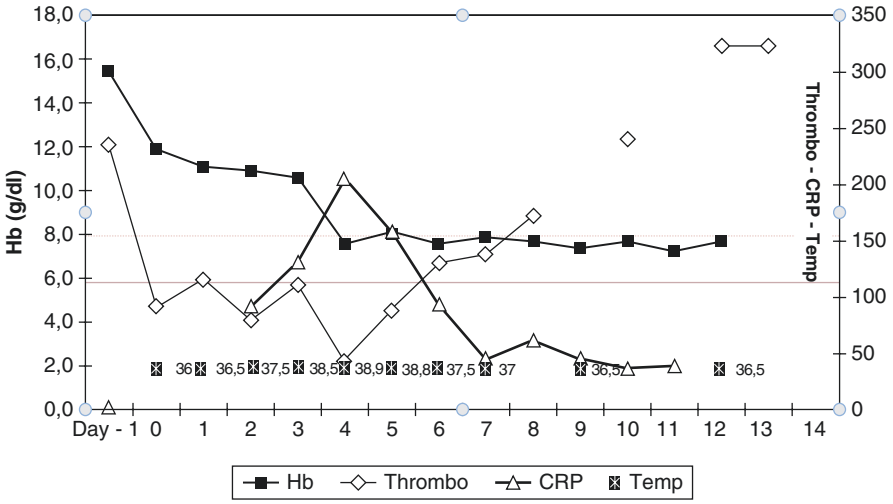

Fig. 17.1 Course of hemoglobin (Hb), platelets (thrombo), C-reactive protein (CRP), and temperature following mitral valve surgery in a Jehovah's Witness

On the third postoperative day, the patient suffered from oliguric renal failure, fever, and respiratory failure. His hemoglobin dropped to 10.4 g/dl (6.5 mmol/l). After reintubation, echocardiography showed severe mitral regurgitation. The risk of reoperation without transfusion is discussed with the patient, but he firmly denies any allogenic blood transfusion. Revisional cardiac surgery follows on the fourth postoperative day with the same precautions as during initial surgery. The native mitral valve was replaced by a mitral valve bioprosthesis. After 11 days the patient was transferred from the intensive care to the general ward while treated with erythropoietin and intravenous iron, and was uneventful discharged on day 17 with a hemoglobin level of 7.7 g/dl (4.5 mmol/l).

Why is it important?

Cardiac surgery accounts for both substantial blood loss and a high consumption of blood products. Transfusion rates during hospitalization for cardiac surgery continue to vary widely among different institutions and practitioners, which reflects a clinical practice that is more based upon idiosyncratic belief than on sound scientific evidence [1]. Evidence is accumulating that both perioperative anemia and packed red blood cell transfusions are associated with adverse outcomes after cardiac surgery [2]. Jehovah's Witnesses who intentionally refuse blood products but require cardiac surgery are a particular challenge for the surgical team [3, 4].

Experience with cardiac surgery in Jehovah's Witness patients has been built up since the 1960s, and it is nowadays quite common to undertake uncomplicated surgery in these patients [5, 6]. In addition, besides a very large number of case reports, large single center studies suggest that Jehovah's Witness patients can safely undergo more complicated procedures like a reoperation, emergency cardiac surgery, and even heart transplantation [6–8].

This chapter will particularly focus on the perioperative management and outcome of Jehovah's Witness patients undergoing cardiac surgery, while implications for patient blood management will be discussed throughout other chapters in this textbook. The chapter particularly focuses on ethical and legal aspects, clinical decision-making, patient blood management (PBM), and management of severe anemia. The experience gained in Jehovah's Witness patients can be transferred to procedures in non-Jehovah's Witness patients.

Bioethical and Legal Issues

The Watch Tower Society (WTS) is the main legal entity used worldwide by Jehovah's Witnesses to direct, administer, and disseminate doctrines for the group. The Jehovah's Witnesses interpretation of three Bible verses requires Jehovah's Witnesses to "abstain from blood" (Acts 15:20). Jehovah's Witness patients believe that allogenic blood transfusion including whole blood, packed red blood cells, white cells, platelets and plasma, and preoperative autologous blood deposit is equivalent to eating blood, which is forbidden. Believers are willing to choose death rather than undergo blood transfusion.

This firm belief and determination in refusing transfusion of blood products poses serious ethical and legal issues to Jehovah's Witness patients themselves, as well as to medical professionals involved, in particular when the risks of denial of blood transfusion may become very real as in cardiac surgery.

Fundamental ethical and legal principles in modern medicine collide with each other and may burden the treating physician of a Jehovah's Witnesses with a burning moral dilemma. On one hand it is a solid general and legally valid principle in most countries that patients have the right to be autonomous and self-determined, even if there is a serious risk that refusal of a particular therapy may pose a direct threat to the survival chances [9, 10].

Doctors treating Jehovah's Witnesses may be liable to legal prosecution if they willingly and knowingly override the refusal to transfuse blood products. However, this poses a serious moral dilemma with the professional obligation to cause no harm as imposed by the Oath of Hippocrates. A doctor may not be forced to refuse a treatment to a patient when he sincerely believes that such refusal may put a life at stake. This, with the right of the patient to be well informed, and the obligation of the doctor to properly inform a patient on the benefits and risks of a particular treatment (or withholding it) implies that prior consent to treatment and its modalities obliges a doctor to respect a decision of a patient. In case of such a moral conflict a doctor most often will be obliged to offer a second opinion or to refer the Jehovah's Witness patient to a doctor that will accept the refusal of blood. In emergency

situations where the refusal of blood products is not clearly ascertainable, the doctor has the right to use his own judgment.

Under the same principle "one should not harm" it is considered unethical to expose Jehovah's Witnesses to risks of surgery without the ability or consent to transfuse, without having a comprehensive program in place that will guarantee a Jehovah's Witness patient the best chances for a successful intervention. This should not only be limited to the medical aspects of treatment, but should include as well the bioethical and legal issues discussed here, while taking into account the governing rules and laws in place as this may differ between countries [9, 10].

The Watch Tower Society is eager to search for and to promote treatment modalities that will allow Jehovah's Witnesses to undergo complicated surgery as safely as possible without giving up the refusal of blood transfusion. They will often actively engage with the medical community in order to convince them of the feasibility of taking Jehovah's Witnesses in charge, advise them on the best therapeutic modalities while accepting not to transfuse even when clearly indicated on sound medical grounds. Although this is very laudable by itself, medical practitioners should be vigilant about serious moral pressure that may be exerted [11, 12]. Even though such practices have officially been forbidden by the Watch Tower Society, local polemics may still subsist. This implies that it should be clearly elucidated that it is the responsibility of the hospital to ensure that Jehovah's Witnesses will be guaranteed continuity of care throughout the entire hospitalization period while respecting the refusal of blood products.

Furthermore, it is very important to realize that the Watch Tower Society will leave the decision to abstain or allow certain blood products or components to the individual Jehovah's Witness patient. Likewise, while in general blood loss sparing treatment modalities, e.g., acute normovolemic hemodilution and the use of a cell saver are allowed, provided that physical continuity with the Jehovah's Witnesses blood is ensured, this is no rule and the individual acceptance of allowable treatment modalities may vary between individual patients. Therefore, the treating physician should clearly elucidate with his patient which blood product or treatment modality may be acceptable to the individual Jehovah's Witnesses and properly record that in the patient file. It is to be strongly recommended to profoundly discuss and clarify—legally as well—all these matters with the local Watch Tower Society subsidiary or responsible Elder, who—in the author's experience—are more than willing to do so, before taking in charge Jehovah's Witnesses.

Outcomes of Jehovah's Witnesses After Cardiac Surgery

Mortality

Numerous publications, mostly case reports or retrospective descriptions of series of Jehovah's Witnesses, show a good or acceptable mortality after cardiac surgery.

Only a few publications describe larger series of Jehovah's Witnesses, often from the Texas Heart Institute [5, 13]. Many of these publications are relatively old, and included a young population with less comorbidities and less complex surgery than modern cases, with a reported mortality rate of 7–10% [13]. In more recent studies, a reported hospital mortality of 5.5% in 91 Jehovah's Witnesses undergoing isolated coronary artery bypass graft or valve surgery [14]. More recently, Vaislic described probably one of the largest series with 500 Jehovah's Witnesses undergoing cardiac surgery between 1991 and 2012 [15], with a mortality rate of 1.5–2.0%. This study results are however limited by a selection bias [15].

Mortality and Morbidity Compared to Non-Jehovah's Witnesses

In the last 15 years, several studies compared mortality and morbidity between Jehovah's Witnesses and non-Jehovah's Witnesses undergoing cardiac surgery [3, 16–21]. All studies mentioned were retrospective studies in prospective clinical registries. All, except one, have accumulating single center experience over a long-time span, ranging from 3 till 28 years. Those studies reporting experience spanning at least 5 Jehovah's Witnesses per year are summarized in Table 17.1.

The comparative studies were very heterogeneous with respect to inclusion and exclusion criteria, differences in the matching technique of the non-Jehovah's Witnesses groups, perioperative management, and outcome parameters. Furthermore, several studies lack comprehensive information regarding preoperative risk factors for transfusion as well as the perioperative management of Jehovah's Witnesses. Some of these comparative studies have been subjected to a meta-analysis reporting on 564 Jehovah's Witnesses versus 903 control patients [22], showing no difference in mortality with pooled rates of 2.6% vs 3.6%, respectively. Only one study reported worse outcomes in Jehovah's Witnesses, but these studies are very small [23].

Morbidity including renal failure, myocardial infarction, and length of stay was similar between Jehovah's Witnesses and non-Jehovah's Witnesses (Table 17.1) [22]. In the latter transfusion rates ranged from 27.4% vs 67.8%, not considering the studies where control patients were transfused per design [3, 4]. There were also no differences in the cost of treatment between both groups [19]. A major caveat with most of these series and comparative studies is that one has to be aware of considerable bias and confounding during acceptance of Jehovah's Witnesses for surgery, finding matching controls and management of the patients. In conclusion, numerous case reports, observational studies, and comparative observational studies suggest that Jehovah's Witnesses can safely undergo low-risk and complex cardiac surgery with similar mortality, morbidity, and length of stay than patients in which transfusion was allowed. However, all available data should be considered with caution due to the high risk of selection bias.

Table 17.1 Observational studies comparing perioperative variables and outcome between Jehovah's Witnesses (JW) and non-Jehovah's Witnesses (NJW)

		Stamou	Reyes	Pattakos	Hogervorst	Marinakis	Reyes Garcia	Bhaskar	Guinn Roberson
Study design	Study era	'90-'04	'98-'06	'83-'11	'97-'13	'91-'12	'88-'13	'02-'05	'05-'12
	JW [n] (average per year)	49 (3.5)	59 (7.3)	322 (11.5)	270 (16.9)	31 (1.5)	172 (6.9)	49 (12.3)	45 (8.4)
	Type of surgery	CABG, valve, CABG+ valve	All	No HTx, VAD or ECMO	Adult, no HTx, VAD, ECMO	All	All	All	CABG, valve, CABG + valve
	Comparison group	NJW	NJW	Transfused NJW	NJW with nadir Hb < 8 g/dl	NJW	NJW	NJW	NJW
Preoperative	Erythropoietin	–	+	?	+	+	+	–	+
	Iron oral or iv	–	+	?	+	+	+	–	+
	Folic acid, Vit B12	–	–	–	–	+	–	–	–
	Preoperative Hb (JW vs NJW)	N.R.	13.6 vs 12.9	Higher in JW	14.5 vs 13.7*	Hct: 43 vs 38%	13.9 vs 13.1*	13.7 vs 12.8*	13.9 vs 12.3*
Intraoperative	ANH	–	–	N.R.	+	–	–	+	+
	RAP	+	–	N.R.	Seldom	+	–	–	+
	Cell salvage	+	+	N.R.	+	+	+	+	+
	Hemofiltration	–	–	N.R.	Seldom	+	–	–	–
	Antifibrinolytics	+	+	N.R.	+	+	+	+	+
	Other	–	–	TEG, DDAVP	–	–	–	–	TEG, DDAVP

Postoperative	Erythropoietin	–	–	N.R.	+	–	–	+	–
	Iron oral or iv	–	–	N.R.	+	–	–	+	–
	Other	–	–	N.R.	Early resternotomy	–	–	FA	Early resternotomy
Outcome JW vs NJW	24 h blood loss (ml)	N.R	446 vs 813*	N.R	N.R	644 vs 582	485 vs 732*	476 vs 843*	N.A.
	Transfusion in NJW %	N.R	N.R	100% per study design	1 PC	27.4%	54.0%	N.R.	67.8%
	Last Hb (g/dl) (mean)	N.R.	11 vs 10	Similar	10.8 vs 10.6	N.S.	10.4 vs 9.7*	10.8 vs 9.9*	11.7 vs 9.8*
	Re-exploration (%)	0 vs 8%	5.1 vs 3.4	3.7 vs 7.1%*	Excluded in selection	6% vs 2%	8.7 vs 6.4%	2 vs 5%	N.A.
	Non-adjusted mortality (%)	6 vs 8% intraop	6.8 vs 8.5%	–	1.6 vs 3.3%	3 vs 2%	–	2 vs 3%	0 vs 0%
	Adjusted mortality JW vs non-JW (% (p) or OR (CI))	0.66 (0.12–3.59)	–	3.1 vs 4.3%	1.6 vs 3.3 0,81 CI (0.05–13.51)	–	1.45 (0.67–3.1)	0.62 (0.12–3.50)	–

CABG coronary artery bypass graft surgery, *HTx* heart transplantation, *VAD* ventricular assist device, *ECMO* extracorporeal membrane oxygenation, *ANH* autologous normovolemic hemodilution, *RAP* retrograde autologous priming, *N.R.* not reported, *N.A.* not applicable, *OR* odds ratio, *CI* confidence interval, *PC* packed cell

*P-value <0.05

Transfusion Compared to Non-Jehovah's Witnesses

Pattakos et al. compared Jehovah's Witnesses with non-Jehovah's Witnesses who were effectively transfused [3]. Hogervorst compared the Jehovah's Witnesses group to a selection of non-Jehovah's Witnesses with an intraoperative nadir hemoglobin below 8 g/dl (5 mmol/l) and/or hemoglobin decrease of more than 50%, and who in addition were transfused with a single unit of packed red blood cells irrespective of platelet and fresh frozen plasma transfusion. Both studies did not show a difference in outcome, suggesting that the absence of transfusion did not adversely influence patient recovery [3, 4]. This observation has been a driving force behind patient blood management programs [24], albeit that most studies do not correct for preoperative predictors of transfusion requirements as possible confounders [25].

Management of Jehovah's Witnesses Undergoing Cardiac Surgery

In older publications it was less clear how Jehovah's Witnesses could be managed in order to maximize their chances without transfusion. Treatment regimens varied between publications and were not always well described. Furthermore, as most series and studies on Jehovah's Witnesses are observational, and mostly cover a very large timespan, one should consider that the gradual improvement of patient blood management programs in cardiac surgery influenced outcome.

The statement that Jehovah's Witnesses can safely undergo cardiac surgery implies that several preventive and therapeutic precautions are taken to overcome the constraint of not being able to transfuse. It is nowadays deemed unethical to perform cardiac surgery in Jehovah's Witnesses without having a state-of-the-art patient blood management program in place. Alternatively, less invasive procedures such as transfemoral aortic valve placement should be considered [26]. Moreover, centers that accept Jehovah's Witnesses for cardiac surgery should have a specific policy regarding medicolegal and ethical issues that is clearly understood and respected by all perioperative team members. Interestingly, Jehovah's Witnesses included in the aforementioned studies had slightly higher preoperative hemoglobin levels, suggesting a selection bias or a better preoperative optimization of this patient population.

The question arises why non-Jehovah's Witnesses are not always treated as Jehovah's Witnesses with regard to blood conservation strategies and preoperative optimization. In Jehovah's Witnesses, anticoagulants are timely stopped, there is more aggressive treatment of preoperative anemia with erythropoietin and/or intravenous iron, and during surgery cell savers are routinely used. Erythropoietin treatment may be administered either empirically or as part of a comprehensive anemia management algorithm including the use of folic acid and vitamin B12. Tanaka et al. reviewed 144 Jehovah's Witnesses undergoing all types of cardiac surgery including a considerable number of complex cardiac surgeries like heart transplantation, ventricular-assist-device implantation, aortic, and congenital cardiac surgery [6]. They reported an overall hospital mortality of 6.6%, but only 2.2% in the subgroup where a preoperative hemoglobin optimization program succeeded in achieving a presurgical hemoglobin that exceeded 12 g/dl (7.5 mmol/l). In contrast,

patients who did not achieve a preoperative hemoglobin of 12 g/dl or more showed mortality rates of 15.9% [6].

During surgery, the mainstay of blood conservation consists of meticulous surgical hemostasis and the use of a cell saver that maintains physical contact with the circulation of the Jehovah's Witness. Regarding the use of cell salvage, it is recommended to limit cell saving to the blood loss fractions before heparin and after heparin reversal in order to prevent excessive loss of coagulation factors and platelets. Most studies report a universal use of antifibrinolytics. Less frequently, acute normovolemic hemodilution and retrograde priming are applied. After surgery, most studies report a swift resternotomy policy in case of excessive bleeding, although most studies show that Jehovah's Witnesses have lower volumes of blood loss as compared to non-Jehovah's Witnesses. Moreover, Jehovah's Witnesses are less likely to undergo re-exploration for bleeding or tamponade, probably due to meticulous hemostasis. Most studies limit blood sampling to further prevent postoperative anemia. In order to enhance hematopoiesis some studies report continuation of erythropoietin and iron therapy after surgery [4, 6, 19, 21]. From the above it may be concluded that cardiac surgery in Jehovah's Witnesses may be considered safe, mainly due to all precautions made by the surgical team before, during, and after surgery (Fig. 17.2).

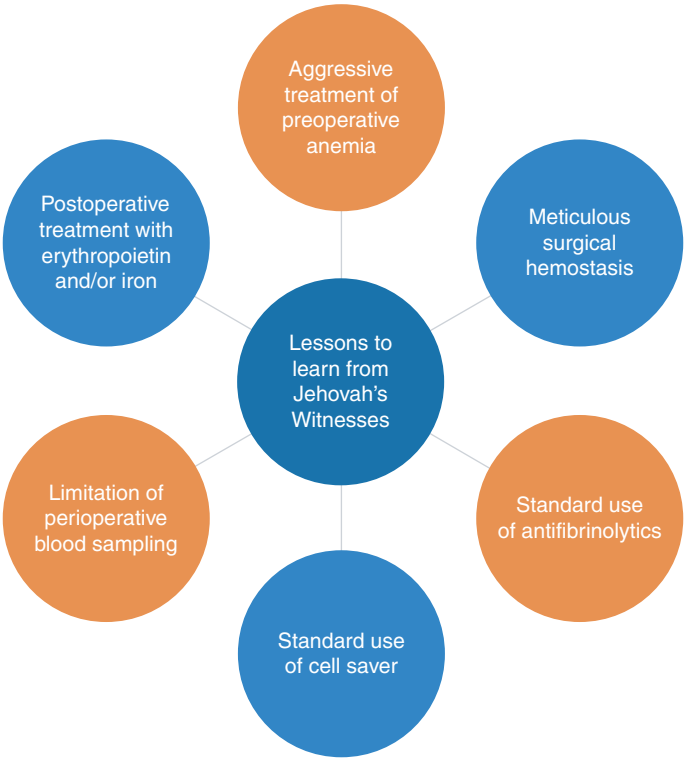

Fig. 17.2 Lessons learned from cardiac surgery in Jehovah's Witnesses that may reduce perioperative bleeding and transfusion requirements in all patients undergoing cardiac surgery

Severe Anemia and/or Bleeding

Notwithstanding the good results in Jehovah's Witnesses undergoing cardiac surgery, a severe drop in hemoglobin levels or severe bleeding is difficult to handle without blood transfusions. This may be the case in emergencies where precautions are difficult or impossible, in perioperative mishaps with sudden or major blood loss or longstanding illness after cardiac surgery. In all these situations, anemia may become life threatening. Carson showed in Jehovah's Witnesses undergoing non-cardiac surgery a proportional increase in mortality and morbidity when hemoglobin levels decreased below 8 g/dl (5 mmol/l). A 1-gram drop in postoperative hemoglobin levels below 8 g/dl had an odds ratio for death of 2.5 [27]. Shander also showed an odds ratio for mortality of 1.8 for each 1 g/dl decrease in hemoglobin adjusted for urgency, ASA score, and age [28]. Composite morbidity and mortality occurred in 30.4% of patients. Both Carson and Shander studied non-cardiac surgery, but Hogervorst reported a similar relationship between a decreasing hemoglobin level below 8 g/dl and mortality and morbidity in Jehovah's Witnesses undergoing cardiac surgery [4]. Viele and Weiskopf identified 50 deaths attributed to anemia in non-transfused Jehovah's Witnesses with hemoglobin concentrations of 8 g/dl or less or a hematocrit of 24% or less [29]. Of the 50 deaths, 23 were thought to be primarily due to anemia. All patients whose deaths were attributed to anemia died with hemoglobin concentrations of 5 g/dl (3.1 mmol/l) or less. In contrast, there were also 25 survivors with a hemoglobin of 5 g/dl (3.1 mmol/l) or less. These observations underpin strong physiological adaptation mechanisms that maintain adequate body and organ functions, even at very low hemoglobin levels. Low hemoglobin levels can be compensated by other determinants, like the partial arterial oxygen pressure (paO_2), cardiac output, oxygen consumption, and the dissolved oxygen fraction. The latter becomes relatively important when hemoglobin is dropping to low levels [30]. Furthermore, tissue oxygenation is the balance between oxygen delivery and tissue oxygen consumption, which in turn depends on, among others, factors like metabolism, nutrition, and temperature. With hypovolemia and very low hemoglobin levels, these adaptive mechanisms have limitations. With further progression of anemia, the fraction of delivered oxygen that is extracted at a tissue level can no longer keep up with the oxygen requirements of tissue, resulting in anaerobic energy metabolism and hypoxia.

Many reports have described successful management of medical, surgical, and obstetric emergencies in patients with severe anemia who have declined transfusions. If there is uncertainty about the wishes of a patient regarding transfusion, it is reasonable to treat according to the accepted standard of care. If there is a clear wish not to receive transfusion, best possible care consists of interventions to maintain hemodynamic stability, reduce blood loss, improve oxygen delivery and red blood cell production. Under life-threatening circumstances, the refusal of transfusion may be re-discussed in a respectful and deliberate way if the patient still can be considered accountable for his/her judgment.

The management of Jehovah's Witnesses with severe and life-threatening anemia consists of aggressive control of the source of active bleeding with surgery or

invasive radiological procedures, pharmacological therapy with fibrinogen and coagulation factor concentrates if prior consent hereto was obtained, minimizing further blood loss, supporting hematopoiesis with erythropoiesis stimulating agents, intravenous iron and vitamin supplements, harnessing the body's defense mechanisms against anemia and decreasing oxygen needs as much as possible. Maintenance of normovolemia, optimization of cardiac function and hemodynamics and providing appropriate respiratory support (including mechanical ventilation) are of paramount importance.

Anecdotal reports have described successful use of procedures that reduce the oxygen demand using sedation and/or mechanical ventilation with pharmacologic paralysis and cooling [31]. Meticulous control of fever is also critical to reduce oxygen demand. All severely anemic patients should receive supplemental oxygen that is titrated to respiratory demand. In addition, administration of hyperbaric oxygen has been described in a number of case reports and summarized in a systematic review [32]. Theoretically, blood substitutes such as hemoglobin-based oxygen carriers and perfluorocarbon emulsion may be considered and have been used in rare instances. Solutions containing human or animal hemoglobin need to be discussed with the individual Jehovah's Witness patient [30]. So far, no blood substitute has been approved for clinical use in Europe or the USA. In some cases, a blood substitute such as a hemoglobin-based oxygen carrier may be administered under a compassionate care regimen.

Implications for Daily Practice

In conclusion, elective cardiac surgery in Jehovah's Witnesses should only be undertaken if legal and ethical issues are clearly unequivocally outlined between the entire medical staff and with the relevant local or national Jehovah's Witnesses community. A clinician who declines to provide care for a patient who refuses blood transfusion should arrange a transfer to another caregiver. Although there is general consensus within the Jehovah's Witnesses community that blood products are not accepted, exceptions may arise. As certain blood fractions and treatment modalities are left by the Jehovah's Witnesses governing body to individual judgment and consent by the Jehovah's Witnesses, these modalities should be thoroughly and timely discussed and documented with the individual patients. The clinician should assure that any refusal of blood transfusion or its components is decided by the individual patient, without overt moral pressure from the Jehovah's Witnesses community. Furthermore, Jehovah's Witnesses should only undergo elective cardiac surgery when an adequate patient blood management program is instituted, aiming at optimizing preoperative red cell mass, stimulating hematopoiesis, minimizing and aggressively treating perioperative blood loss, and recycling blood loss and support of the oxygen supply in case of moderate to severe anemia.

There is sufficient evidence that Jehovah's Witnesses can undergo even complex cardiac surgery, and that clinical outcome is not different in Jehovah's Witnesses compared to non-Jehovah's Witnesses as long as the perioperative nadir

hemoglobin remains above 7–8 g/dl (4.3–5 mmol/l). At lower hemoglobin levels it is reasonable to state that there is a seriously increased risk of morbidity and mortality as compared to patients that could be transfused. Experience with Jehovah's Witnesses shows that complex cardiac surgery is possible and safe without any transfusion at all, a result that is far from being reproduced in conditions where transfusion is "freely" available, even with a strict patient blood management program in place and very restrictive transfusion regimens.

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Part VI

Postoperative Treatment of Coagulopathy and Microvascular Bleeding

Treatment Algorithms for Bleeding

18

Marco Ranucci

Case Vignette

After complicated mitral valve surgery, sternal closure is complicated due to severe microvascular bleeding in an 80-year-old woman, who received antifibrinolytic therapy at the beginning of surgery. Intraoperative blood loss was limited, and the cause of microvascular bleeding is attributed to coagulopathy or disturbed platelet function. The surgical team involved recently introduced a treatment algorithm that includes standard laboratory coagulation testing and point-of-care viscoelastic testing. When they follow the treatment algorithm and can exclude residual heparin, they start with platelet function testing and coagulation monitoring focusing on the clotting time, clot firmness, and fibrinogen component of the clot. Their test results show unacceptably low fibrinogen levels, and a long clotting time. Platelet function was within normal reference values. After the administration of fibrinogen concentrate and prothrombin complex concentrate, the microvascular bleeding stops, followed by sternal closure. The patient left the hospital without further blood product transfusions one week after the procedure.

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Table 18.1 European guidelines on treatment algorithms in the cardiac surgery bleeding patient

Source	Year	Statement	Class	Level
EACTA/ EACTS	2017	Perioperative treatment algorithms for the bleeding patient based on viscoelastic point-of-care tests should be considered to reduce the number of transfusions	IIA	B
ESA	2017	We recommend the use of standardized viscoelastic hemostatic assay-guided hemostatic algorithms with predefined intervention triggers	I	B

EACTA European Association of Cardiothoracic Anaesthesiology, *EACTS* European Association for Cardio-thoracic Surgery, *ESA* European Society of Anaesthesiology

Why Is It Important?

Blood loss due to microvascular bleeding (oozing) is a common issue after cardiac surgery. It may appear immediately after cardiopulmonary bypass (CPB) and heparin reversal with protamine, or in the intensive care unit. For both situations, adequate definitions and grading are available in the literature [1]. Once excessive bleeding is suspected, it is of paramount importance to distinguish between coagulopathic bleeding (to be treated with specific drugs, blood components, and derivatives) and bleeding of surgical cause (requiring further surgical hemostasis and/or surgical re-exploration). Within coagulopathic bleeding, different mechanisms, acting solely or in combination, may be responsible, and their identification is mandatory to correctly guide the therapeutic approach.

Treatment algorithms are therefore required to discriminate between different bleeding mechanisms. These algorithms are based on a combination of point-of-care coagulation tests (viscoelastic tests and platelet function tests) and standard coagulation tests (platelet count, activated partial thromboplastin time, international normalized ratio of the prothrombin time, and fibrinogen concentration).

The pre requisite for the application of treatment algorithms is the evidence of an excessive bleeding. Even if there is a specific surgical setting where a bleeding problem is anticipated, it is reasonable to start a diagnostic procedure based on viscoelastic testing during the late phases of CPB. A routine application of a treatment algorithm is not suggested, because the positive predictive value of viscoelastic testing is low, and this could introduce the risk for an inappropriate correction of the coagulation profile in patients who will not require any intervention. The existing European guidelines suggest the use of treatment algorithm in the cardiac surgery bleeding patient, with different levels of recommendation (Table 18.1) [2, 3]. The purpose of this chapter is to give an overview of the literature that exists on the value of treatment algorithms for microvascular bleeding in cardiac surgery.

Table 18.2 Main randomized trials on treatment algorithms in adult cardiac surgery bleeding management

Study	Year	Main outcome measures and results
Karkouti [4]	2016	Reduction in PRBC and platelet transfusions and major bleeding
Weber [5]	2012	Reduction in PRBC, FFP, and platelet transfusions. Shortening of postoperative mechanical ventilation time, length of intensive care unit stay. Reduction of composite adverse events rate, costs of hemostatic therapy, and 6-month mortality
Girdauskas [6]	2010	Reduction in allogeneic blood products transfusions
Westbrook [7]	2009	Non-significant reduction in blood product usage
Ak [8]	2009	Reduction in allogeneic blood products transfusions
Kultufan Turan [9]	2006	No differences in allogeneic blood product transfusions
Avidan [10]	2004	Reduction in allogeneic blood products transfusions
Nuttal [11]	2001	Reduction in FFP and platelet transfusion. Lower chest drain output. Lower surgical re-exploration rate
Royston [12]	2001	Reduction in FFP and platelet transfusions
Shore-Lesserson [13]	1999	Reduction in FFP and platelet transfusions

PRBC packed red blood cells, *FFP* fresh frozen plasma

Treatment Algorithms in Cardiac Surgery

A number of randomized controlled trials (RCTs) tested the effectiveness of treatment algorithms in the management of bleeding in adult cardiac surgery patients (Table 18.2).

These trials, together with other studies, have been recently incorporated in two meta-analyses. Deppe et al. pooled RCTs and retrospective studies in adult cardiac surgery [14] and reported an overall beneficial effect of the application of treatment algorithms, with a decreased need for allogeneic blood products (odds ratio (OR) 0.63; 95% confidence interval (CI) 0.56–0.71; $P < 0.00001$) and a lower re-exploration rate due to postoperative bleeding (OR 0.56; 95% CI 0.45–0.71; $P < 0.00001$). Furthermore, the incidence of postoperative acute kidney injury (OR 0.77; 95% CI 0.61–0.98; $P = 0.0278$) and thromboembolic events (OR 0.44; 95% CI 0.28–0.70; $P = 0.0006$) was decreased in patients treated according to a viscoelastic testing-based treatment algorithm. Serraino et al. pooled RCT on both adult and congenital patients [15]. They found that the use of viscoelastic testing-based treatment algorithm resulted in reductions in the frequency of PRBC transfusion (OR 0.88; 95% CI 0.79–0.97) and platelet transfusion (OR 0.78; 95% CI (0.66–0.93). Of notice, they calculated that viscoelastic testing-based treatment algorithm did not reduce mortality (OR 0.55 95% CI 0.28–1.10). However, an OR of 0.55 is certainly clinically relevant, and with a larger sample size would have resulted in a statistically significant difference.

Overall, it is well evidenced that the use of treatment algorithms results in a reduction of allogenic blood product transfusions. Less evidenced is their role in containing other bleeding-related complications (surgical re-exploration), while their impact on other clinical outcomes (length of intensive care unit stay, acute kidney injury, and mortality) remains elusive. However, transfusion algorithms are designed to control bleeding and bleeding-related complications, and it is probably inappropriate to ask them to (directly) reduce other adverse outcomes.

Treatment Algorithms: How to Do It

The pre requisite for the application of treatment algorithms is the presence or strong suspect of microvascular bleeding exceeding the usual acceptable level and requiring specific interventions. To this respect, a standardized definition of the bleeding degree may be useful. Recently, a Universal Definition of Perioperative Bleeding (UPB) in cardiac surgery was proposed [1]. This grading scale considers intraoperative parameters (delayed sternal closure) and chest drain output after sternal closure. Given the fact that in the majority of the cases treatment algorithms start inside the operating room, at open chest, their application is often based on clinical judgement ("wet surgical field"). However, more objective measures of blood loss due to microvascular bleeding have been proposed. Among these, different authors have applied a definition of excessive microvascular bleeding based on a direct measure of blood loss contained in swabs placed into the surgical field for a 5-min period [4, 16].

The existing guidelines do not recommend one specific treatment algorithm among the various published ones. The reason for this is quite simple: there are no RCTs or even non-randomized studies comparing different treatment algorithms. So, the possibility to adhere to this recommendation is based on the development of a local treatment algorithm, or on the application of an already published algorithm. To this respect, there are certainly huge differences among the different published treatment algorithms, as well as important lacks in knowledge that need to be addressed before reaching a "universal" treatment algorithm for the cardiac surgery bleeding patient.

A first general difference is between "horizontal" and "vertical" algorithms. A horizontal algorithm (Fig. 18.1a) is based on point-of-care and standard coagulation tests whose results are interpreted simultaneously without a priority in interventions. A vertical algorithm (Fig. 18.1b) proposes a step-by-step analysis and interventions based on priorities. In turn, these priorities consider on one side the likelihood that a certain mechanism is responsible for bleeding (i.e., hyperfibrinolysis is one of the last mechanisms to be considered) and on the other the clinical weight of the intervention (residual heparin triggering protamine administration in first position, surgical re-exploration in the last). Additionally, vertical algorithms consider that the sequence of interventions should be respectful for the pathophysiology of

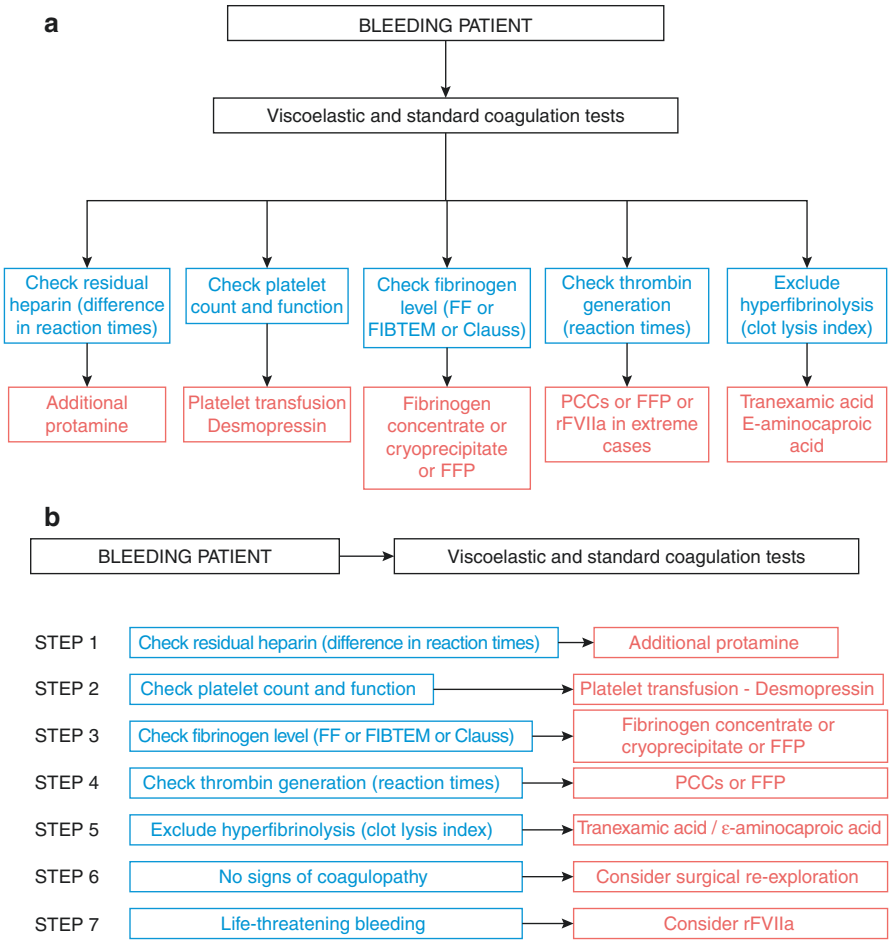

Fig. 18.1 An example of a horizontal (**a**) and vertical (**b**) treatment algorithm. *FF* fibrinogen fraction, *FIBTEM* fibrinogen test in rotational thromboelastometry, *PCC* Prothrombin complex concentrate, *FFP* fresh frozen plasma

bleeding: before enhancing thrombin generation (with prothrombin complex concentrates or even rFVIIa) the substrate generating the clot (fibrinogen and platelets) should be available in sufficient amounts. Therefore, vertical algorithms seem more adequate in clinical terms [17–19].

As already stated, the positive predictive value of viscoelastic testing is poor. Conversely, their negative predictive value is high. Therefore, a correct application of a step-by-step treatment algorithm should be based on "ruling out," one-by-one, each specific mechanism. Clear cut-off values (triggering specific interventions) are not universally accepted; conversely, the adequate test(s) to rule out the different bleeding mechanisms are more consistent in the literature.

Step-by-Step Approach in Treating Algorithms

Treatment algorithms for microvascular bleeding during and after cardiac surgery consist of specific steps that may be enrolled in a horizontal or vertical algorithm.

Ruling Out Residual Effects of Heparin

Despite it is a common practice to use the difference between the post-protamine and baseline activated clotting time (ACT) as marker of residual heparin effects, this approach is certainly misleading. After CPB, all the coagulation tests are moderately altered due to the consumption of coagulation factors, fibrinogen, and platelets. A prolonged ACT may simply express this combination of factors, and is not specific for residual heparin. The right way is looking at the time until first fibrin formation is initiated (R-time in thromboelastography and clotting time (CT) in rotational thromboelastometry) difference in tests run with or without heparinase. A prolonged R-time or CT that normalizes in the heparinase-tests might be specific for residual heparin effects, albeit this specific test is prolonged by protamine which impairs specificity to detect residual heparin and requires caution with the interpretation of the results.

Despite its limitations, a prolonged ACT (with respect to the post-protamine value) in the first postoperative hours may suggest a heparin rebound that should however be confirmed by viscoelastic testing before prompting a protamine supplementation. In conclusion, heparin rebound is a rare problem, and prolonged clotting times may rather be a result of other coagulation disturbances (see Chap. 11).

Ruling Out a Platelet-Dependent Bleeding

Despite the fact that bleeding due to poor platelet count/function is one of the most common mechanisms after cardiac surgery, unfortunately, at present, little evidence exists with respect to the diagnosis of this bleeding mechanism and to the cut-off values suggesting platelet transfusions and/or desmopressin. The existing guidelines [2, 3] propose an arbitrary value for platelet count <50,000/μl, and simply mention "acquired platelet dysfunction" without addressing the type of platelet function test to be applied, nor the cut-off values. The existing published algorithms sometimes include platelet function testing based on the multiple electrode aggregometry ADP and TRAP test. However, the suggested cut-off values are mainly based on clinical practice with poor scientific evidence only.

An ADP test <30 U or a TRAP test <50 U have been suggested [5, 17], but they appear probably too liberal. A recent study on about 500 consecutive adult cardiac surgery patients [20] highlighted that the ADP test is more predictive of severe bleeding than the TRAP test, and found a positive predictive value of 42% for an ADP test <8 U and a negative predictive value of 94% for an ADP test >18 U [20].

Another common approach to assess the platelet contribution to clot strength is looking at the difference between the clot firmness in standard thromboelastography

or the EXTEM assay of rotational thromboelastometry, and the fibrin-dependent clot firmness (functional fibrinogen or maximum clot firmness (MCF) as measured using the FIBTEM assay). The assumption is that if the fibrin component is normal, and the general clot firmness is poor, then the platelet contribution is poor. Different algorithms include this concept [4, 5, 17], suggesting similar cut-off values. Karkouti et al. [4] propose an EXTEM MCF at 10 min (A10) <35 mm with a concomitant FIBTEM A10 >8 mm (A10 difference <27 mm) as a trigger for platelet transfusion. Other studies propose differences in A10 of 30 mm [5] and 24 mm [17]. However, these values are not supported by any sound evidence. Additionally, this approach was recently challenged in a review article [21], where the authors highlighted that the difference in amplitude between standard thromboelastography or EXTEM and functional fibrinogen or FIBTEM is an arbitrary measure, because clot elasticity is not linearly correlated with the amplitude (that is artificially ceiled at high levels).

Ruling Out Low Fibrinogen Levels

Low fibrinogen levels are associated with postoperative bleeding, and early fibrinogen supplementation was suggested by different studies [22–24]. The existing treatment algorithms suggest fibrinogen supplementation (with fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate) based on fibrinogen contribution to clot strength at the viscoelastic test. Different trigger values have been proposed. Algorithms based on FIBTEM propose cut-off values <8–10 mm [4, 5, 17]. Agarwal et al. proposed a functional fibrinogen level <1 g/l at thromboelastography [25]. This last approach is certainly more arbitrary, because it is based on a conversion equation between maximum amplitude and fibrinogen levels that is included in the thromboelastography software. However, there is a poor correlation between fibrinogen levels derived from this equation and Clauss fibrinogen levels, as recently demonstrated by the same authors [26]. A recent study on about 3000 adult cardiac surgery patients found a positive predictive value for severe bleeding of 50% for a Clauss fibrinogen level <115 mg/dl (about 4 mm at FIBTEM) [27]. Overall, the recent EACTA/EACTS guideline proposed to consider fibrinogen supplementation for Clauss fibrinogen levels <1.5 g/l, which roughly corresponds to a FIBTEM value <6 mm [3].

Ruling Out Poor Thrombin Generation

Poor thrombin generation should be treated with fresh frozen plasma or prothrombin complex concentrates. Only in life-threatening bleeding, and after correction of the substrate (fibrinogen and platelets), rFVIIa may be considered. Viscoelastic testing-based treatment algorithms consider the diagnosis of poor thrombin generation based on the absolute value of reaction times at heparinase-based or extrinsic pathway activation tests. Again, there is no homogeneity with respect to the cut-off value triggering specific interventions. A thromboelastography reaction time >20 mm [13] or 14 mm [25] was proposed. Other rotational thromboelastometry-based studies propose a CT value >80–90 s in the ExTEM assay to trigger interventions [4, 5, 17].

Ruling Out Hyperfibrinolysis

This condition is usually placed at the end of a vertical treatment algorithm, or not mentioned at all, because it is rare in cardiac surgery, due to the routine use of antifibrinolytics [3]. It is usually diagnosed based on the clot lysis index provided by viscoelastic testing that however seems to be sensitive only to high-degree hyperfibrinolysis. In general, the cut-off value is placed at a lysis index >15% [7]. In the presence of hyperfibrinolysis, tranexamic acid or ε-aminocaproic acid is suggested, and after being unavailable for a long period of time, aprotinin is back on the market in different European countries. Given the break-down of fibrinogen, a fibrinogen supplementation could make sense in severe cases.

Implications for Daily Practice

In general, it can be concluded that treatment algorithms play a very important role in a patient blood management program in cardiac surgery. In particular, a standardized evaluation of coagulation abnormalities may be supportive in the development of local treatment protocols. However, a number of "black boxes" and lack of evidence is still present, especially with respect to bleeding related to poor platelet function. Further comparative studies are required to confirm the existing cut-off values.

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Treatment with Procoagulants

19

Daniel Bolliger and Alexander J. Spanjersberg

Case Vignette

A 60-year-old man underwent replacement of the ascending aorta and the aortic arch under hypothermic circulatory arrest. Preoperative hemoglobin was 15 g/dl (9.3 mmol/l), and conventional coagulation laboratory results were normal. After induction of general anesthesia and cannulation according to the institutional standards, tranexamic acid was started with a bolus of 30 mg/kg, followed by an infusion of 10 mg/kg/h during surgery. Surgery and weaning from cardiopulmonary bypass were uncomplicated and protamine was administered to neutralize heparin. However, the surgeon complained about persisted microvascular bleeding. In the thromboelastometric testing 10 min after heparin reversal, there was evidence of low fibrinogen levels (maximal clot firmness in the rotational thromboelastometry fibrinogen test (FIBTEM) of 6 mm) and coagulation factor deficiency (clotting time in the thromboelastometry test for extrinsic coagulation (EXTEM prolonged). According to the institutional coagulation algorithm based on viscoelastic testing 4 g of fibrinogen concentrates and 500 U of a four-factor prothrombin complex concentrate (PCC) were infused. The surgeon noticed less oozing, allowing him to close chest aperture. The hemodynamically stable patient was transported to intensive care unit. The patient did not require any blood transfusion, and the further course was without complications.

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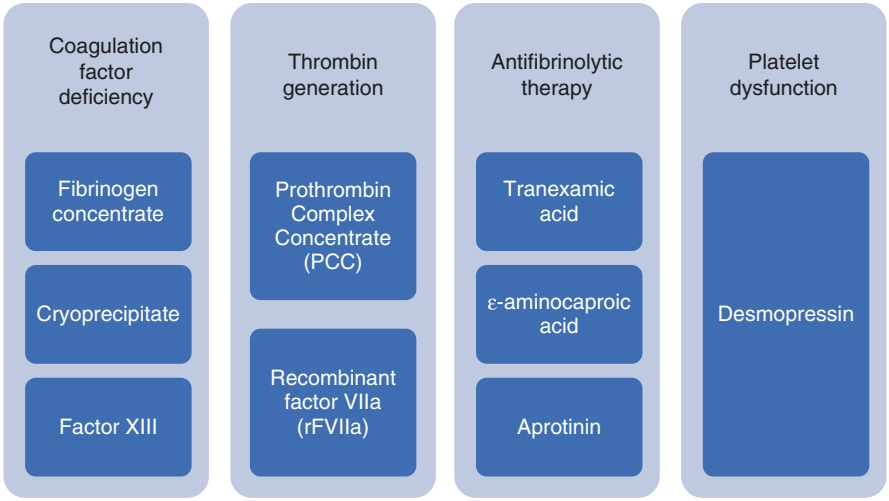

Fig. 19.1 Procoagulant therapies described in this chapter

Why Is It Important?

Perioperative hemostasis management is a precondition when applying patient blood management (PBM) to patients undergoing cardiac surgery. When managing perioperative bleeding, factor concentrates can be more effective than indiscriminate liberal transfusion of allogeneic plasma, but inappropriate use can be costly and associated with worsening hemorrhage or thromboembolic complications. Bleeding after cardiac surgery is often multifactorial. After establishing basic conditions for hemostasis (e.g., temperature, calcium, pH), exclusion of hyperfibrinolysis, and reversal of anticoagulants, a point-of-care (POC) coagulation-based diagnostic and therapeutic algorithm should be used in the coagulopathic patient. This chapter reviews the procoagulant interventions in the management of the bleeding patient after cardiac surgery and the roles of coagulation factor concentrates in perioperative hemostatic therapy in cardiac surgery (Fig. 19.1) [1].

Fibrinogen Supplementation

Background

Fibrinogen plays an essential role in coagulation process, as it is the substrate of thrombin in hemostatic clot formation. It is recognized to be one of the first factors to be depleted during massive bleeding and hemodilution [2]. Low preoperative fibrinogen concentration [3] and hypofibrinogenemia after cardiac surgery (<2 g/l) [4] have been associated with increased postoperative bleeding. Fibrinogen

supplementation has, therefore, been recognized as one of the primary hemostatic targets in perioperative coagulopathy after cardiac surgery aiming to limit postoperative bleeding and transfusion requirements.

Perioperative Monitoring of Fibrinogen Concentrations

Given the importance of fibrinogen in perioperative hemostasis, the perioperative monitoring seems useful. However, the optimal pre- or postoperative thresholds of fibrinogen concentration remain unclear. The fibrinogen concentration can be easily determined by either using the Clauss method or using POC-based assays (e.g., FIBTEM test in rotational thromboelastometry or functional fibrinogen test in thromboelastography). There is a good agreement between the determination of the fibrinogen concentration by the Clauss method and the maximal clot firmness in the FIBTEM [5, 6]. However, the level of agreement decreases after fibrinogen supplementation [6]. Alternatively, immunological assays using antifibrinogen antibodies are available.

Perioperative Fibrinogen Substitution

For fibrinogen substitution, either fibrinogen concentrate or cryoprecipitate is suggested. Fibrinogen concentrations in plasma products are generally <2 g/l, and are therefore not suggested for fibrinogen substitution. Fibrinogen concentrate and cryoprecipitate might be similar effective when used with similar doses [7]. However, the approval of fibrinogen or cryoprecipitates for acquired hypofibrinogenemia might differ between countries. Randomized controlled studies have only been performed with fibrinogen concentrate.

In a randomized controlled double-blinded study including 48 patients, the prophylactic substitution with 2 g of fibrinogen concentrate before cardiac surgery slightly increased intra- and postoperative fibrinogen concentration, but did not reduce postoperative bleeding in CABG patients [8]. The therapeutic fibrinogen administration after protamine reversal was tested in four randomized double-blinded placebo-controlled trials, with contrasting results. Two studies including 167 patients undergoing complex cardiac surgery showed reduced requirements for allogenic blood products in the fibrinogen group [9, 10]. In both studies, fibrinogen concentrate was administered aiming for maximal clot firmness in FIBTEM of 22 mm. These findings agree with a Cochrane review published in 2013, showing a reduced relative risk of blood transfusion after fibrinogen supplementation (relative risk (RR) 0.47; 95% confidence interval (CI) 0.31–0.72) [11]. However, two more recent trials in 272 bleeding patients after complex cardiac surgery could not confirm the previous findings [12, 13]. In one of these studies, the administration of fibrinogen concentrates was even associated with a higher rate of administration of allogeneic blood products [13]. A posthoc analysis from a randomized controlled trial showed that substitution with fibrinogen concentrate to more than 2.87 g/l (or maximal clot firmness of 14 mm in the FIBTEM) could not further reduce bleeding volume [6].

Safety

Data from a Cochrane review including 124 patients from three randomized controlled trials [11] and a propensity-score analysis in 380 patients undergoing cardiac surgery [14] suggest no increased risk of thromboembolic events or death after fibrinogen substitution aiming for normal values.

Conclusion

Prophylactic fibrinogen substitution is not recommended for reducing postoperative bleeding and transfusion risks. Current evidence seems insufficient to generally support or refuse routine administration of fibrinogen concentrate in patients undergoing cardiac surgery [15]. However, in patients with low fibrinogen concentrations and signs of persistent microvascular bleeding, fibrinogen substitution to achieve high normal levels (e.g., between 2 and 3 g/l) may be considered to improve hemostasis and reduce transfusion requirements.

Factor XIII Supplementation

Background

Factor XIII (FXIII) is the terminal enzyme in the coagulation cascade, and is necessary for cross-linking of fibrin monomers to form a stable and strong fibrin clot. Low FXIII levels have been reported after cardiac surgery, and an association between low FXIII levels and increased bleeding has been reported in cardiac surgery [16, 17], especially in patients with postoperative FXIII level of <70% [16]. FXIII is available as recombinant and plasma-derived concentrate.

Perioperative Monitoring of FXIII Concentrations

Specific immunological assays are needed for determination of functional FXIII activity. Detection of FXIII deficiency by a point-of-care device has been described but such tests never received widespread acceptance in perioperative hemostasis management.

Postoperative FXIII Substitution

Three randomized controlled studies with low to moderate quality evaluated the effect of FXIII administration after protamine administration [16, 18, 19]. These three studies included a total of 527 patients undergoing cardiac surgery with minor to moderate risk of bleeding and transfusion. Substitution dosages ranged from 10 to 50 IU/kg. The most common dosages were 17.5 IU/kg and 35 IU/kg. There was no difference in postoperative bleeding volumes and transfusion rates in any study

with any FXIII dosage used. However, bleeding volume was higher in patients with FXIII levels <70% as compared to patients with FXIII levels of >70% [16], but FXIII activity <70% was rarely achieved in the above-mentioned randomized trials. FXIII is, therefore, not suggested to be used prophylactically or in patients with normal FXIII levels (70–120%). However, the postoperative administration of FXIII concentrates might potentially reduce postoperative bleeding and transfusion of blood products in patients with reduced FXIII levels. Finally, there was no difference in adverse events including thromboembolic events and death between the intervention and the control groups.

Conclusion

There is no evidence that prophylactic FXIII administration without evidence for FXIII deficiency might be beneficial regarding the reduction of postoperative bleeding volumes and transfusion rates.

Prothrombin Complex Concentrate

Background

Prothrombin complex concentrates (PCCs) contain lyophilized, human plasma-derived vitamin K-dependent coagulation factors that originally emerged from the search for factor IX replacement for hemophilia B patients. In Europe, only 4-factor concentrates are available containing the coagulation factors II, VII, IX, and X. Whereas the concentration of factor IX is standardized, the amounts of the other factors might vary between the different available products. For example, PCCs with very low activity of factor VII are used in the USA under the labelling "3-factor concentrates." PCCs might contain various amounts of antithrombin, protein C, S, and Z, as well as heparin [1].

Perioperative Monitoring of PCCs

For monitoring of vitamin K-dependent coagulation factors, typically the prothrombin time or the international normalized ratio (INR) is used. Rotational thromboelastometry parameters correlate only weakly with prothrombin time or INR, but INR POC devices are available.

PCC for Acute Reversal of Vitamin K-Dependent Oral Anticoagulants

In patients with very high INR (>4–5) due to intake of vitamin K-dependent oral anticoagulants and urgent or semi-emergent surgery, the use of PCCs adjusted to the INR value might be advantageous compared to fresh frozen plasma (FFP) due to

more rapid normalization of INR. In a randomized study including 40 patients with INR >2.1, the perioperative administration of PCC reversed anticoagulation safely, and reversal was faster and postoperative bleeding volume was lower as compared to the administration of FFP [20].

PCC for Treatment of Massive Postoperative Bleeding

PCCs are sometimes used for factor supplementation in excessive bleeding after CPB in an "off-label" indication. Three retrospective cohort studies in 402 patients published between 2012 and 2016 showed that the use of PCC as compared to the administration of FFP might be associated with less re-exploration due to bleeding, lower blood loss, and less transfusion of RBCs [21–23]. Recently, a propensity score-matched analysis in 117 patients per group found lower rates in RBC transfusion, massive transfusion, and refractory bleeding [24]. However, evidence remains scarce. Recommendations for dosing are not well established, and administration might be tailored to the individual patient based on laboratory and clinical variables.

Safety

Safety data are scarce but the use of PCCs in the bleeding patients after CPB might be associated with an increased risk of thromboembolic events and acute kidney injury [22]. If PCCs are used in the postoperative setting, using a rather low dose might be prudent due to increased thrombin generation in a status of low antithrombin level [2].

Conclusion

PCCs are potentially useful in patients undergoing urgent surgery with preoperative elevated INR values due to intake of oral vitamin K antagonists. They might also be used cautiously as an alternative to FFP in the bleeding postoperative patients. However, the evidence for efficacy and data on safety in the latter setting are limited.

Recombinant Factor VIIa

Background

Activated clotting factor VII (FVIIa) is available as a recombinant preparation (rFVIIa), which was originally developed for the treatment of bleeding hemophilia patients with inhibitors. The hemostatic properties come from the supraphysiologic

increase in available factor VIIa, which in combination with tissue factor (TF) and clotting factors Va and Xa generates a massive thrombin burst and is, therefore, considered rather a "pharmacological" than a factor replacement therapy.

Use in Cardiac Surgery

In the last two decades, rFVIIa has increasingly been used in cardiac surgical patients with refractory bleeding in an off-label indication. The use of rFVIIa has been found to reduce both bleeding and rate of re-operations [25]. However, its use has also been associated with increased mortality, stroke, and renal failure [26]. A 2012 Cochrane review analyzed 29 RCTs with respect to the prophylactic (1361 patients) and therapeutic use (2929 patients) of rFVIIa in patients with or without hemophilia. Prophylactic rFVIIa use just failed to reach significance to reduce transfusion rates (RR 0.85; 95% CI 0.72–1.01) compared with placebo, but this result was associated with an increased risk of thromboembolic adverse events (RR 1.35; 95% CI 0.82–2.25).

Safety

Recombinant FVIIa has the potential to initiate hemostasis wherever there is TF expression. This may lead to diffuse arterial and venous thrombosis. Hence, the conclusion of the 2012 Cochrane review was that the use of rFVIIa outside its current licensed indications should be restricted to clinical trials [27].

The thromboembolic risk associated with the use of rFVIIa might be especially high when rFVIIa is used in "hemophilic" doses (i.e., 90 mcg/kg). In a recent study, the addition of rFVIIa at low dose (<20 mcg/kg) after early and specific restoration of hemostatic capacity was effective in restoring hemostasis in 97.8% of bleeding patients without increased mortality or risk of other major complications [28].

Conclusion

Current data do not support the routine use of rFVIIa in cardiac surgery patients. Therefore, rFVIIa should be limited to rescue therapy, and in treatment algorithms it is usually the last available step in case of uncontrollable bleeding. However, low dose rFVIIa might be beneficial without increasing adverse side effects.

Perioperative Use of Other Factor Concentrates

Coagulation factor concentrates such as factor IX, factor VIII, or factor VII might be used in patients with specific coagulation factor deficiencies. However, the evidence of such factor concentrates is limited to in vitro studies, case reports, and

small case series. Generally, a factor activity of at least 50–60% of normal should be achieved before cardiac surgery and the first day(s) after surgery [3]. A treatment plan specifying time points and administration intervals should be defined after consultation of an experienced hematologist. No general recommendations can be made for such specific patients.

Antifibrinolytic Therapy

Hemostasis is a constant balance between clot formation and clot degradation. Therefore, improvement of hemostasis can be achieved by inhibiting fibrinolysis, which is commonly associated with the use of CPB, major surgery, and dilutional coagulopathy. Of the three approved and used antifibrinolytics, tranexamic acid (TXA) and Ɛ-aminocaproic acid (EACA) are lysine analogues, whereas aprotinin is a serine protease inhibitor.

Tranexamic Acid

Tranexamic acid (TXA) modifies the fibrinolytic pathway by competition to the lysine-binding site on plasminogen. It has a strong affinity for the lysin binding sites on tissue plasminogen activator (t-PA) and plasminogen molecules, reversibly blocking them to form the t-PA-plasminogen-fibrinogen complex, thereby inhibiting fibrinolysis [29].

A plasma level of 100 mg/l is needed to inhibit the t-PA activity by a 100% [30]. A loading dose of 30 mg/kg and a continuing infusion of 16 mg/kg usually result in intra-operative plasma levels between 100 and 150 mg/l. TXA has minimal plasma binding (mainly plasminogen) and is metabolized to a small extent [31]. TXA crosses the blood–brain barrier, rendering cerebrospinal fluid concentrations of 10% of plasma concentrations. Elimination of the drug is mainly unchanged by the kidneys, following first order kinetics. Dosing regimens should, therefore, be adjusted to renal function [32].

TXA has become the most widespread used antifibrinolytic, especially after the BART trial suggested TXA to be safer than aprotinin [33]. However, the BART trial has been recently questioned for some limitations in data analysis and interpretation. A meta-analysis in the Cochrane collaboration in 2011 (including 34 trials) showed that TXA was effective in the reduction of the need for blood transfusion in cardiac surgery in 3006 patients, of whom 1578 were randomized to TXA and 1428 were randomized to a control group who did not receive TXA [34]. There was a significant 32% relative reduction in the rate of exposure to allogeneic blood transfusion in those patients treated with TXA (RR 0.68 95% CI 0.57–0.81). Total blood loss was also reduced by about 300 ml per patient. There was no significant effect on re-operation for bleeding (RR 0.80; 95% CI 0.55–1.17) or mortality (RR 0.60; 95% CI 0.33–1.10).

In a recent prospective trial in 4631 patients, undergoing various types of cardiac surgery (OPCAB, CABG, combination of CABG and valve surgery), the primary

endpoint was a combined adverse effect of TXA administration (composite of death and thrombotic event) [35]. The effect of TXA on the primary outcome was negative; however, secondary outcomes were interesting. Transfusion rate of any blood product was lower in the TXA group (37.9% vs 54.7%, $p < 0.01$) and re-operation for bleeding was reduced (RR 0.36; 95% CI 0.21–0.62). The median number of units of any blood product transfused during hospitalization was 3 (IQR 2–6) in the TXA group and 4 (IQR 2–8) in the placebo group ($p < 0.001$).

In off-pump surgery, TXA has been demonstrated to have a beneficial effect on perioperative bleeding, with a reduction in transfusion requirements [36–38]. These were small studies and not sufficiently powered to detect a difference in rare events such as thromboembolic complications [39, 40].

The most important complications are thromboembolic events that may have devastating consequences, like graft thrombosis, stroke, myocardial infarction, or pulmonary embolism. Most retrospective analyses have shown that TXA is relatively safe. Although several case reports were published suggesting an increased risk of thromboembolic events including cerebrovascular accident, pulmonary embolism, intracardiac thrombosis, and DVT [29, 41–43], the ATACAS trial did not show an increased risk of death and thromboembolic events with the use of TXA. However, patients with prior thromboembolic events, those with inherited and acquired hypercoagulable states, or patients receiving other prothrombotic medications should be cautiously treated with TXA.

A special attention has to be paid to seizures associated with the use of TXA. Although the mechanism is not completely understood, receptor-binding studies have suggested that this may be caused by TXA binding to GABA-A receptors, thereby inducing hyperexcitability by blocking GABA-mediated inhibition in the central nervous system. These laboratory findings corroborate with clinical data. Patients undergoing cardiac surgery seem to be at an increased risk for suffering from seizures, potentially due to disruption of the blood–brain barrier by microemboli. A large meta-analysis from 2016 in 26,079 patients in the TXA exposure group and 7395 patients in the non-TXA exposure group who underwent cardiac surgery or pulmonary endarterectomy reported an overall seizure incidence of 2.7% (95% CI 2.0–3.3) [44]. The authors found that the odds ratio (OR) of seizures in the TXA exposure group versus the non-TXA exposure group was 3.91 (95% CI 2.22–3.91). In the ATACAS trial including mainly coronary artery bypass graft surgery, seizures occurred in 0.7% of patients treated with TXA and in 0.1% of patients in the control group ($p = 0.002$). In this trial, higher doses of TXA were associated with increased risk of seizures.

Ɛ-Aminocaproic Acid

Ɛ-aminocaproic acid (EACA) is a highly water-soluble synthetic crystal with a similar mechanism of action as TXA. EACA inhibits fibrinolysis in vitro at a concentration of 130 mg/l. EACA may be administered intravenously before or after heparinization, but before initiation of CPB [45]. A loading dose of 70 mg/kg after

heparin administration followed by a continuous infusion of 30 mg/kg/h results in blood concentrations of about 260 mg/l [46]. The drug is eliminated by renal excretion, with a clearance approximating creatinine clearance. The terminal elimination half-life is approximately 2 h.

In a Cochrane review of 649 patients (338 EACA vs 311 controls), EACA reduced the risk for the need of allogeneic transfusion by about 30% (RR 0.70; 95% CI 0.52–0.93), but did not decrease the risk of re-exploration for bleeding (RR 0.35; 95% CI 0.11–1.17) [34]. Mortality appeared to be unaffected by treatment with any of the antifibrinolytic drugs and the lysine analogues were free of serious adverse effects. Therefore, EACA might be a safe antifibrinolytic agent, with comparable efficacy as TXA; however, extensive clinical evidence is lacking.

EACA has a low risk profile for side effects. In common with other antifibrinolytic drugs, it might induce hypercoagulability. The intravenous solution of EACA contains benzyl alcohol, and there may be hypersensitivity to this substance.

Aprotinin

Aprotinin is a non-specific serine protease inhibitor. Its main antifibrinolytic activity is based on direct, non-competitive inhibition of free plasmin [29]. Besides, also trypsin, chymotrypsin, kallikrein-factor XII, and platelet protease-activated receptor-1 (PAR 1) are blocked. The kallikrein inhibition is responsible for the anti-inflammatory properties of aprotinin. The inhibition of the PAR 1-receptor may contribute to a platelet sparing effect during cardiopulmonary bypass [47]. Despite this inhibition, platelets are still responding to epinephrine, thrombin, ADP, or collagen stimuli.

Aprotinin is metabolized by lysosomal enzymes and is excreted renally. Plasma half-life is prolonged in renal failure, and dose adjustment might be required. During hemofiltration, aprotinin will be freely filtered and removed from the circulation, because the commercial filters have a molecular cut-off of about 14,000 Dalton and aprotinin has a molecular weight of 6500 Dalton. This will not affect the plasma concentration unless the filtered volume is replaced during this period. There are several dosing regimens available, but supporting evidence for the right dose in modern cardiac surgery is currently missing.

The effectiveness of aprotinin has been well established in several high-quality studies in mixed cardiac surgery. Aprotinin reduced blood transfusion (OR for any transfusion: 0.33 (95% CI 0.26–0.42)) with a clear dose–response relationship (higher doses were more effective) [48]. Compared to TXA, aprotinin had a better blood sparing effect. In CABG only surgery, aprotinin significantly reduced the number of patients receiving any transfusion (OR 0.61 (95% CI 0.58–0.66)) [49]. The limitation of the available literature is that most data are relatively old, and it is unclear whether the beneficial effects of aprotinin on transfusion requirements can also be proved in the current surgical setting. After the withdrawal of aprotinin, and the routine use of TXA, there have been several reports on the increased use of blood products, suggesting aprotinin has stronger blood conserving properties [50, 51].

Aprotinin was taken off the market in November 2007 due to safety concerns expressed in four studies in the New England Journal of Medicine [33, 52–54]. One of these studies, the BART trial, was designed to compare the safety of aprotinin to TXA and EACA [33]. The study was terminated early, because of excess mortality in the aprotinin group. However, there have been raised several issues against the BART methodology, like off-label use of aprotinin, bias due to financial support from drug companies, unexplained exclusion of large sets of patients, which would have changed outcome data (137 excluded patients from the intention-to-treat analysis), disparities in the use of heparin, inappropriate monitoring of anticoagulant use, and improper design to examine mortality relative to the lysine analogues. This has led to the conclusion that a complete suspension may have been premature, and since 2011 aprotinin is available in Canada and some countries in Europe for use with isolated CABG procedures with a high risk of major blood loss only and under strict monitoring in the Nordic Aprotinin Patient Registry (NAPaR) [50, 55–57].

The only absolute contra-indication is the presence of IgG antibodies against aprotinin. Whereas it is not clear which patients should be tested, it is generally advised that at least first doses are small (10,000 KIU) and that there should be a high level of awareness for possible anaphylactoid reactions. Especially patients with repeated exposure within 12 months are at increased risk. Aprotinin may influence in vitro clotting times, like aPTT and ACT. Therefore, during cardiopulmonary bypass higher ACTs are advised, for example, celite ACT >750 s and kaolin ACT >480 s. Safety concerns will remain an issue with aprotinin, and hopefully in the future the NAPaR will give more directive data.

Conclusion

Antifibrinolytics are widely used in cardiac surgery, as they are a mainstay of hemostatic treatment. At the moment, data support the prophylactic use of lysin analogues, of which tranexamic acid has the largest body of evidence. The current guideline on perioperative hemostasis classifies antifibrinolytic therapy with lysin analogues as class Ia recommendation [58]. Aprotinin has certain advantages; however, safety concerns and regulatory issues limit its use.

Desmopressin

Background

Desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin) enhances primary hemostasis by releasing von Willebrand factor (vWF) and coagulation factor VIII from the Weibel–Palade bodies in the vascular endothelium. By the action of vWF, platelets become more reactive and have better adhesion under flow conditions [59].

Use in Cardiac Surgery

Desmopressin has been used in surgery for the treatment of congenital bleeding disorders for almost four decades. In cardiac surgery, DDAVP is typically administered IV after heparin reversal at a dose of 0.3 mcg/kg. However, routine use in cardiac surgery is not advocated. A Cochrane review including 957 patients showed only a minimal reduction in number of transfused allogeneic blood products (−0.52; 95%CI −0.96–0.08) as compared to placebo [60]. When compared to tranexamic acid, desmopressin is less effective (mean increase for DDAVP 0.6 units; 95% CI 0.09–1.11). However, in patients with platelet dysfunction, the number of red cells transfused was lower and the amount of blood loss reduced. Further, the addition of desmopressin to routine tranexamic acid was not effective in reducing blood loss in 135 bleeding patients [61]. However, it remains uncertain whether desmopressin is effective in reversing platelet dysfunction in a clinical setting [62].

Safety

The administration of desmopressin can be accompanied by clinically significant hypotension, requiring volume therapy or vasoconstrictive agents (OR 9.78; 95% CI 2.48–38.58), water retention, and hyponatremia even associated with states of unconsciousness after prolonged use [63, 64]. In addition, it triggers the release of t-PA [65]. This side effect might be neglected when antifibrinolytics are routinely used.

Finally, an increased risk for myocardial infarction (OR 2.39; 95% CI 1.02–5.60) was reported in a meta-analysis from 1999 [48]. However, these data were not significant in the last Cochrane review (OR 2.72; 95% CI 0.60–12.37) [60]. The findings of these meta-analyses must interpreted with caution, as the numbers of included studies were low, and no large trials on the safety of desmopressin were performed in cardiac surgery.

Conclusion

DDAVP might enhance primary hemostasis. However, its clinical value remains uncertain, especially in reversing platelet dysfunction.

Implications for Daily Practice

In contrast to hereditary conditions, where a single factor concentrate or procoagulant is indicated, the perioperative coagulopathy often requires multiple hemostatic interventions. Clinical data, mainly reported from European centers in the last years, demonstrated that a perioperative therapy with coagulation factor concentrates is feasible and safe, and might be helpful to reduce the transfusion of allogenic blood

products during cardiac surgery [1]. A strategy based on the use of coagulation factor concentrates might be especially efficient and safe when using transfusion algorithms based on viscoelastic point-of-care coagulation tests [1]. However, additional efficacy and safety data are needed to establish proper indications in the perioperative setting, target levels for specific factor replacement, and cost implications.

Hyperfibrinolysis is a common problem in cardiac surgery. Therefore, routine use of antifibrinolytic drugs has the highest recommendation. Lysin analogues, especially tranexamic acid, have both a safe profile and a widespread use, and therefore are the first-choice antifibrinolytic therapy. Coagulation factor concentrations such as fibrinogen or PCC are rather well esthablished and commonly used for PBM in cardiac surgery. Other agents like rFVIIa, aprotinin, and desmopressin have promising properties, but may be reserved for specific indications. Further clincial studies are mandatory to clarify optimal transfusion algorithms and strategies to re-establish the balance of hemostasis in the bleeding patient after cardiac surgery.

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Transfusion Thresholds for Packed Red Blood Cells

20

Andreas Koster

Case Vignette

A 76-year-old male patient with an acute myocardial infarction is scheduled for urgent coronary artery bypass graft surgery. Due to severely impaired left ventricular function and instable hemodynamics, an intra-aortic balloon pump is implanted prior induction of anesthesia. Surgery is performed with cardiopulmonary bypass (CPB). Weaning from CPB is possible with epinephrine 0.2 µg/kg/min. However, the cardiac index is 1.8 l/m^2, the arterial vascular resistance (Rart) 2200 dyn/s/cm^{-5}, the mean arterial pressure (MAP) 80 mmHg, the pulmonary artery wedge pressure (PCW) 15 mmHg, and the mixed venous oxygen saturation ($SmvO_2$) 50%. At this time, the hemoglobin level is 12.5 g/dl (7.8 mmol/l). A continuous infusion of the inodilator levosimendan is started and shortly before chest closure the cardiac index is 2.2 l/m^2, the Rart 1600 dyn/s/cm^{-5}, the MAP 70 mmHg, the PCW 12 mmHg, and the $SmvO_2$ 58%. At this time, after infusion of 2 liters of crystalloid and colloid volume, the hemoglobin value is 10.5 g/dl (6.5 mmol/l). The surgeon complaints about diffuse microvascular bleeding, although viscoelastic tests showing a normal coagulation profile. However, preoperatively assessed platelet aggregation testing revealed a significant response to preoperative dual antiplatelet therapy. The anesthesiologist orders two units of apheresis platelet concentrates and two units of RBC. Is this good clinical practice?

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Why Is It Important?

Oxygen delivery (DO_2) to the tissues is determined by the cardiac output and oxygen content of the blood:

$$\text{Hemoglobin} \times \text{oxygen saturation} \times 1.39 + \text{arterial oxygen pressure} \times 0.0031 \quad (20.1)$$

A compensation of anemia via an increase of cardiac output may be limited, particularly in patients with critical cardiac disease and patients undergoing major cardiac surgery [1]. However, besides the menace of severe immune reactions, the transfusion of packed red blood cells (PRBC) still carries the risk of transmitting viral and bacterial infections [2]. Additionally, transfusion of PRBC has been associated with an increase in serious healthcare associated infections [3]. Besides, PRBCs are a scarce resource and expensive [4]. The transfusion threshold has to balance potential benefits and risks of both, anemia, and PRBC transfusion. The purpose of this chapter is to discuss the transfusion threshold for PRBC in the setting of cardiac surgery.

Transfusion Modalities and Outcome

A large number of large prospective, controlled, randomized trials in different clinical settings assessed the effect of a so-called restrictive transfusion trigger (hemoglobin (Hb) <7–8 g/dl (<4.3–5 mmol/l)) versus a so-called liberal transfusion trigger (Hb <9–10 g/dl (5.6–6.2 mmol/l)) [4]. The terms restrictive and liberal will be used throughout this chapter to denote a lower or higher transfusion threshold. The difference between a restrictive and a liberal transfusion strategy accounts for 1–2 (additional) units of PRBCs that need to be transfused or not. In this regard, one should ask if the (additional) transfusion of such small numbers of PRBC units is associated with a significantly increased risk for complications.

The Brazilian single center Transfusion Requirements After Cardiac Surgery (TRACS) trial from 2009 to 2010 was the first large prospective, randomized non-inferiority trial that compared a liberal transfusion trigger (hematocrit (Hct) ≥30%) with a restrictive transfusion trigger (Hct ≥24%) in 502 patients after cardiac surgery [5]. The per-protocol analysis showed that 78% of patients in the liberal and 48% in the restrictive group ($p < 0.001$) were transfused postoperatively. No difference was noted in the composite endpoint of 30-day mortality or severe morbidity. However, in the multivariate Cox regression analysis the number of transfused PRBCs was independently associated with an increased risk of death (hazard ratio (HR) 1.2; 95% confidence interval (CI) 1.1–1.4; $p = 0.002$). In the multiple logistic regression analysis, each unit of PRBC transfused was associated with an increased risk for severe complications, such as renal injury, respiratory problems, and infections. Even though this result seems impressive, one should consider that in this trial only non-leukocyte depleted (LD) PRBCs have been transfused. Leukoreduction of PRBCs plays a pivotal role in transfusion-related immune modulation. Particularly

in cardiac surgery, this quality of blood appears to have an impact on patient outcome [6]. In this regard, it remains questionable if the results of this trial can be translated to Europe where PRBCs are routinely LD. The PRBC transfused in the TRACS trial had a median storage time of 3 days. Large retrospective single center investigations showed a dramatic increase in mortality when older (>14 days storage time) RBC were transfused in cardiac surgery patients [7]. This finding could however not be confirmed in randomized prospective multicenter trials, which, exclusively used LD PRBCs [8]. In conclusion, transfusion of leukocyte-depleted or non-depleted PRBCs appears to impact outcomes of patients undergoing cardiac surgery. However, when using LD PRBCs, outcomes are not affected by the storage time of the transfused blood.

In a large retrospective registry study from the state of Michigan (USA), the impact of the transfusion of 1–2 PRBCs on the outcome of >22,000 patients undergoing isolated coronary surgery was assessed [9]. A battery of sophisticated and complex statistical methods was used to adjust for risk between groups. Transfusion was associated with a significantly increased risk for 30-day and in-hospital mortality and severe morbidity. However, when analyzing the reason for death of patients from the same database, the authors had to conclude that this event may be secondarily associated with other patient related factors [10]. Even when large observational trials reveal a significant statistical association between a transfusion and an adverse outcome, this is not an irrefutable proof of a causative relationship. The risk of reverse causation bias is the most important limitation of such observational studies [7].

Comparison of Transfusion Thresholds

Two recent large randomized, prospective multicenter trials and one randomized two-center trial compared outcomes of a restrictive to liberal transfusion strategy in cardiac surgical patients. Given the fact all three trials represent contemporary standards in cardiac surgery (and presumably quality of PRBCs) and the quality of blood banking, the results of these trials will be discussed in particular in the following.

The Transfusion Indication Threshold Reduction (TITRe2) trial from 2009 to 2013 was performed in the United Kingdom and compared a postoperative restrictive transfusion threshold (Hb <7.5 g/dl (4.7 mmol/l) with a liberal transfusion threshold (Hb <9 g/dl (5.6 mmol/l) [11]. Although not expressively outlined, it can be assumed that according to national standards, only LD PRBCs were used. A total of 2003 patients undergoing non-emergency coronary and/or valve or aortic surgery were included. The median European System for Cardiac Operative Risk Evaluation (EuroSCORE) was five in both groups, indicating an intermediate risk for perioperative death. Patients were enrolled when the postoperative Hb was <9 g/dl (5.6 mmol/l). A total of 63.7% (median 1 PRBC) patients in the restrictive and 94.9% (median 2 RBC) in the liberal group (RR 0.58, $p < 0.001$) were transfused. Of note, in both groups approximately 25% of patients had received transfusions before postoperative enrollment. The intention to treat analysis showed no

difference regarding the combined primary outcome of serious infection and ischemic events, including acute kidney injury, within 3 months after randomization between the restrictive and the liberal group (31.5% vs. 33%, OR = 1.11, $p = 0.30$). Moreover, most secondary outcomes such as duration of the stay in the intensive care unit (ICU), severe pulmonary complications (esp. prolonged mechanical ventilation), and 30-day mortality were comparable between groups. However, the 90-day mortality was increased in the restrictive group (4.2% vs.2.6%, OR 1.64; 95% CI 1.0–2.67, $p = 0.045$). Of note, severe non-adherence to the protocol was noted in 6.2% in the liberal and 9.7% in the restrictive group of patients.

The Transfusion Requirements in Cardiac Surgery (TRICS) III trial was an international trial performed from 2013 to 2017 which included 5243 patients undergoing cardiac surgery with a moderate to high predicted risk of death (EUROScore 1 > 6) [12]. The restrictive transfusion threshold was a perioperative Hb of <7.5 g/dl (4.7 mmol/l), while the liberal transfusion threshold was a Hb of >9.5 g/dl (5.9 mmol/l) intra- and postoperatively on the ICU, or < 8.5 g/dl (5.3 mmol/l) in the non-ICU ward. Unfortunately, no information with regard to LD of transfused PRBC is provided. The primary outcome was a composite of death from any course, myocardial infarction, stroke, and new onset of renal failure needing dialysis during the first 28 days or period of hospitalization. Secondary outcomes included, e.g., the duration of mechanical ventilation and stay on the ICU, acute kidney injury, prolonged low cardiac output state after surgery, and infections. A total of 52.3% patients were transfused in the restrictive group and 72.6% in the liberal group (OR 0.41; 95% CI 0.37–0.47) with a median of 2 PRBC in the restrictive group and 3 PRBC in the liberal group (OR 0.85; 95% CI 0.82–0.88). No difference was noted regarding the primary outcome [11.4% in the restrictive group versus 12.5% in the liberal group (OR 0.90; 95% CI 0.76–1.07, $p < 0.001$ for non-inferiority)] and secondary outcomes between groups. Protocol suspension was noted in 11.1% and 14.3% of patients. The most recent published analysis of data at 6 months after surgery also showed no difference in the primary composite outcome between groups [13].

In the TRICS III trial, a subanalysis for patients >75 years was performed. In this subgroup the risk for the primary endpoint was lower (OR 0.7; 95% CI 0.54–0.89) in the restrictive group. This observation remained after using logistic regression adjusting for baseline conditions and type of surgery. In the aforementioned TRACS trial, a subanalysis of patients ≥60 years ($n = 260$) showed that the restrictive TT was associated with a numerical increase in the incidence of cardiogenic shock ($n = 16$, 12.8% vs. $n = 7$, 5.2%, $p = 0.031$) while the composite endpoint showed no differences between groups [14]. Of note, these results must be considered with caution, as subgroups were not randomized for age and no risk adjusted regression analysis was performed.

A double center randomized trial (India and the USA) in cardiac surgery patients undergoing coronary or valve procedures compared a restrictive transfusion threshold with a hematocrit of 24% to a liberal threshold of 28% [15]. Between 2007 and 2014, 722 patients had been enrolled with 717 patients being analyzed. No information regarding LD of PRBCs is provided. The combined primary endpoint was a composite of postoperative morbidities, like prolonged ventilation [>24 h], renal

failure, stroke, severe infection, and in-hospital mortality. Secondary endpoints included duration of ICU- and hospital stay and the number of PRBC transfused. The trial was prematurely terminated after the second planned interim analysis when the predefined futility boundary was crossed. There was no detectable treatment effect of the liberal transfusion threshold (OR 0.86; 95% CI 0.29–2.54, $p = 0.71$), while the restrictive group received lesser transfusions compared to the liberal group (54% vs. 75%, $p < 0.001$).

How to Interpret Current Evidence?

The results of the contemporary randomized, prospective trials in patients undergoing cardiac surgery suggesting restrictive transfusion thresholds can be safely applied for a large number of patients undergoing different procedures. Such a strategy leads to approximately 50% of patients receiving no PRBC transfusions during the entire period of hospitalization. In contrast, the results of the TITRe2 trial might indicate that a liberal threshold may be favored, and largely affected conclusions of a meta-analysis in cardiac surgical/high-risk patients performed after its publication [16]. However, it has to be taken into consideration that in the TITRe2 trial, the primary outcome—a composite of a serious infection or an ischemic event within 3 months after randomization—did not differ between groups, that the increased 90-day mortality was only a secondary outcome, that the statistical significance was borderline (HR 1.64 (1.00–2.67)), and that non-adherence to the protocol was approximately 8% in the overall group. Even though, adding the results of the large TRICS III trial in the most recent meta-analysis let the pendulum swing more towards a restrictive transfusion threshold [17]. In this regard, conclusions are in line with results observed in other patient groups [4]. However, this rather swift paradigm shift also highlights the volatility of evidence in this complex clinical scenario and critical patient population.

Viewing the complexity of the key question, it appears worth to discuss, whether 30-day mortality or even composite endpoints are the ideal endpoints for such a complex scenario as patient blood management in cardiac surgery. However, the non-inferiority result of a restrictive threshold also translated to important secondary clinical outcomes, such as the duration of mechanical ventilation and ICU stay, which largely reflect a routine clinical course.

The transfusion threshold has to balance the risk between anemia and potential clinically relevant side effects of the (additional) transfusion of 1–2 PRBCs. Therefore, trials also have to be analyzed in this regard. One meta-analysis of randomized controlled trials from a variety of clinical settings showed an increase of serious health care associated infections when a liberal threshold was used instead of a restrictive threshold [3]. This finding remained consistent when restricting to trials in which LD PRBCs have been used exclusively. One large multicenter prospective observational study in cardiac surgery patients from the USA showed a dose-dependent increase in infections (29% per unit of transfused PRBC) in patients being transfused [18].

Of note, in this study exclusively LD PRBCs had been used. However, in this study no uniform transfusion threshold was predefined thus increasing the risk of reversed causation. Results of the three contemporary prospective randomized trials in cardiac surgery, which defined the transfusion threshold, do not confirm this observation, as no association between more liberal transfusion of PRBCs and postoperative infections was noted.

Therefore, viewing the very low risk for viral and bacterial infections transmitted by a PRBC transfusion in developed countries, particularly when using LD blood, the underlying risk of an additional transfusion of 1–2 PRBCs appears to be rather low [2]. These findings clearly contrast with results of large retrospective and prospective observational studies and have to be considered when balancing the risk of a moderate (1–2 PRBC) number of transfusions and anemia [9, 10, 16].

The border zone of the three trials between a restrictive and a liberal threshold is grey. Thresholds defining a liberal or restrictive transfusion regimen overlap between trials. In so far, a general sharp definition of a restrictive or liberal threshold has not been established by now. Additionally, the evaluation of a defined transfusion threshold in critical heart disease patients is not limited to the group of patients undergoing cardiac surgery. Two recent meta-analyses addressed the subject. Carson et al. concluded that in patients undergoing cardiovascular surgery, a restrictive transfusion threshold with a Hb value of 7–8 g/dl (4.3–5 mmol/l) is safe and decreased PRBC use by 24%. However, results of two smaller trials in patients with acute myocardial infarction revealed an increased mortality (OR 3.88; 95% CI 0.83–18.13) of a restrictive regimen [17]. The meta-analysis performed by Cortés-Puch et al. in patients with critical heart disease concluded that a restrictive threshold in patients after corrective cardiac surgery is safe, while it appears that in critical heart disease patients undergoing non-cardiac procedures it is associated with an increase in major adverse coronary events and mortality [19].

These findings might highlight that the restrictive threshold of a Hb of 7–8 mg/dl (4.3–5 mmol/l), in certain risk conditions, might be considered to be a critical "flex point." Therefore, as outlined in most current guidelines, additional patient-related physiological transfusion triggers are considered to be helpful in guiding the decision to transfuse or not [7, 20]. The $SmvO_2$, regional tissue oxygenation, oxygen delivery, and blood gas analysis have been discussed as valuable parameters in this regard [7]. Unfortunately, this more physiological approach, which has no thresholds for interventions, is currently not supported by any evidence from larger prospective trials.

Implications for Daily Practice

Viewing the current data, it is evident that in a large number of patients undergoing cardiac surgery, including those with an intermediate to high operative risk, a restrictive transfusion threshold can be safely employed. Nevertheless, a clear general recommendation whether to transfuse or not in a non-bleeding, normovolemic cardiac surgical patient who has a Hb value of approximately 7.5–8.5 g/dl (4.7–5.3 mmol/l) cannot be made currently. The underlying risks associated with the (additional)

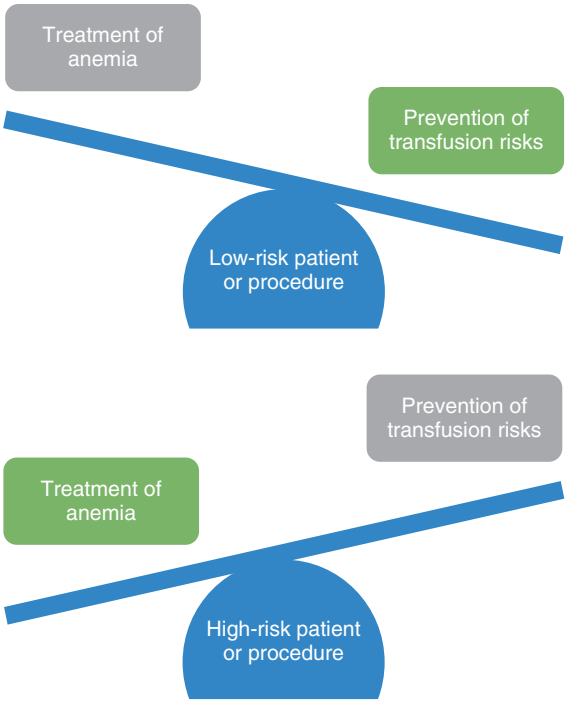

Fig. 20.1 The decision to transfuse depends on the condition of the patient and invasiveness of the procedure. In relatively healthy patients and/or low-risk procedures, the balance turns to restrictive transfusion thresholds (upper panel), while in case of high-risk patients and/or procedures anemia is treated at the risk of transfusion-related complications (lower panel)

transfusion of 1–2 PRBCs appear to be low. Physiology and data of the most recent meta-analyses might suggest that in patients with critically impaired cardiac function or acute myocardial infarction, a more liberal threshold might be favored [1, 16]. Viewing the complexity of the clinical scenario and heterogeneity of patients, the hemoglobin value as sole transfusion trigger has obvious limitations. In patients with a complicated perioperative course and prolonged cardiac and or pulmonary dysfunction additional parameters for guiding PRBC transfusions are needed. Further studies have to focus on the evaluation of physiological triggers related to tissue oxygen metabolism, and the potential benefits and risks of a more restrictive or more liberal transfusion threshold in these very critical patients (Fig. 20.1).

The management of the case can be supported by current evidence. Although the patient has undergone corrective cardiac surgery, the consequences of myocardial infarction and acute revascularization with ischemia/reperfusion injury and myocardial stunning will take days to recover. Additionally, although the patient was on temporary mechanical support, hemodynamics remained borderline. In this regard the cardiac surgery can be evaluated as being not immediately corrective. Furthermore, hemoglobin values are dynamic. Although the patient did not experience massive active bleeding, transfusion of the platelet concentrates diluted further. Moreover, with the decrease of the arterial resistance and opening of the arterial system, more volume demand to maintain normovolemia can be expected. In this regard, the transfusion of two units of PRBC maintained a hemoglobin value of approximately 9 g/dl (5.6 mmol/l), which can be deemed to be adequate in this situation.

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Bleeding Management in the Intensive Care Unit

21

Michael Sander, Marit Habicher, and Matthias Wolff

Case Vignette

A 63-year-old male patient with coronary artery disease and aortic stenosis developed acute delirium after hospital admission and computed tomography showed subacute ischemia of the arteria cerebri. Furthermore, he developed acute heart failure and echocardiography showed severely impaired left ventricular function. The surgeon performed emergency revascularization and valve replacement. The initial cardiopulmonary bypass time (CPB) was 200 min and the first weaning attempt from CPB was not successful. The patient developed acute right ventricular failure that resolved after hemodynamic optimization and prolonged reperfusion. After a total bypass time of 345 min, the patient could be successfully weaned. After separating from bypass the bleeding situation was difficult to control. The patient was anemic, rotational thromboelastometry showed a prolonged CT in the INTEM and a reduced A10 in the FIBTEM as well as a thrombocytopenia with 42/µl was measured. Therefore, the patient received 8 units of packed red blood cells (PRBC), 6 units of fresh frozen plasma (FFP), 2 units of platelets and fibrinogen (2 g). After initial stabilization of the bleeding situation and chest closure on arrival in the intensive care unit (ICU) again increased bleeding was noticed.

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The patient was sedated, intubated, and hemodynamically stable with vasopressor/inotropic therapy. The results from the laboratory showed an activated partial thromboplastin time (aPTT) of 57 s, INR of 1.8, activated clotting time (ACT) of 114 s, platelet count of 93/µl, fibrinogen level of 1.42 g/l, and a hemoglobin level of 8.1 g/dl. Blood loss via chest tubes was 200–300 ml/h during the next 4 h, and there was also significant blood loss via the thoracic bandage.

Over the next hours the patient received another 2 units of RBC, 1 unit of platelets, and 2 g of fibrinogen. As further treatment with FFP was judged to put this patient at risk for decompensated right heart failure due to fluid overload, 2000 IU of prothrombin complex was administered. Due to anticipated platelet dysfunction, 30 µg desmopressin was given. During the next 4 h, his condition became more stable, vasopressor/inotropic administration could be reduced and then stopped, and overall blood loss was decreasing. In the following hours blood loss from the chest tube decreased significantly to 100–150 ml/h and stopped on the next morning.

Why Is It Important?

Bleeding and transfusion are relatively common complications after cardiac surgery. According to recent reports, cardiac surgery is responsible for about 20% of all allogeneic blood products transfused worldwide. Moreover, a majority of packed red blood cell (PRBC) transfusions occur in the cardiac surgery setting, with a percentage of the total amount of PRBC transfused ranging from 7% in the United Kingdom and up to 25% in the USA [1, 2].

Some minor blood loss will occur in each patient undergoing heart surgery procedures due to bleeding from surgical incisions, cardiopulmonary bypass, hemodilution, and iatrogenic blood loss from blood drawing for laboratory testing. In some patients, massive bleeding up to a life-threatening extent can occur due to surgical bleedings. However, as cardiac surgery patients often receive drugs interacting with the hemostatic system due to their underlying cardiac disease, also in some patients massive bleeding occurs due to non-surgical conditions (dual antiplatelet therapy, anticoagulants, coagulation disorders) or cardiopulmonary bypass related mechanisms. These mechanisms will be discussed later in this chapter.

The extent of bleeding that leads to a severe compromise of cardiovascular function and oxygen delivery depends obviously on the preoperative baseline hemoglobin levels, volume status prior to the bleeding event, rate of bleeding, and preoperative coagulation parameters of the individual patient. Bleeding after cardiac surgery has an important impact on surgical outcome, and is associated with increased in-hospital mortality and complication rates in cardiac surgery patients. Due to the nature of this condition in bleeding patients, procoagulant drugs and blood products are used. Therefore, further complications associated with major bleeding may be also

thromboembolic. Ranucci et al. showed in a single center retrospective study, using a database from 2000 to 2012 with over 16,000 patients, an association between bleeding and mortality after cardiac surgery [3]. The results showed that postoperative bleeding was significantly associated with postoperative mortality in the univariate and multivariate analysis (odds ratio (OR) 3.45; 95% confidence interval (CI) 2.78–4.28) [3]. Similar results were shown in a prospective observational study with over 9000 cardiac surgery patients pinpointing that massive blood loss, defined as the need of at least 5 units of PRBCs within 1 day, was associated with eightfold increase in in-hospital mortality [4]. At the same time, thromboembolic complications as mesenteric ischemia and infarction, pulmonary thromboembolism, perioperative myocardial infarction, and importantly postoperative cerebral ischemia occurred after cardiac surgery.

Bleeding Management in the ICU

Blood loss to a certain extent after cardiac surgery occurs in almost all patients undergoing cardiac surgery as stated above and has to be considered normal. Accordingly, minor bleeding has no impact on surgical outcome and mortality. However, major bleeding is a serious complication, and has to be identified early and treated aggressively as it has an important impact on patient outcome. A multitude of studies have linked major bleeding to unfavorable outcome and increased costs as shown in Fig. 21.1 [5–10].

One problem of many studies is that bleeding complications between different studies are hard to compare as different definitions are used. Therefore, experts proposed a universal definition of perioperative bleeding in adult cardiac surgery (Universal

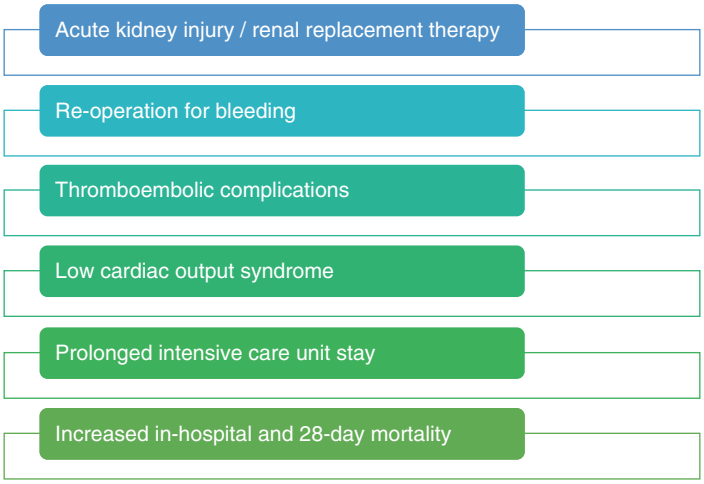

Fig. 21.1 Management of antiplatelet therapy in patients having coronary artery bypass grafting surgery, unmodified from Bartoszko et al. [10]. This article is available under the terms of the Creative Commons Attribution License (CC BY)

Definition of Perioperative Bleeding (UDPB) [7]. It is depending on nine special events, which can occur during surgery or within the first postoperative day and defines five perioperative bleeding classes, which characterize the severity of bleeding, regardless of the cause [7]. The nine events that are used in this definition are depicted in Fig. 21.2.

The contribution of each of these events to the UDPB is presented in Table 21.1.

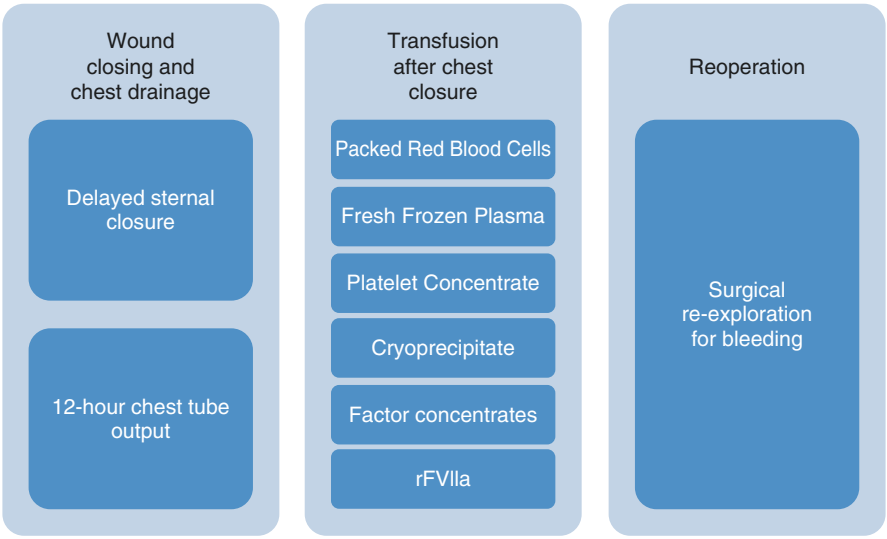

Fig. 21.2 The UDPB in cardiac surgery [7] depends on nine events that may occur in the perioperative and postoperative period. *rFVIIa* recombinant factor VIIa

Table 21.1 Universal definition of perioperative bleeding in adult cardiac surgery, unmodified from Christensen et al. [5]

Bleeding definition	Sternal closure delayed	12-h chest tube blood loss (ml)	PRBC (units)	FFP (units)	PLT (units)	Cryo	PCC	rFVIIa	Reoperation
Class 0	No	<600	0	0	0	No	No	No	No
Class 1	No	601–800	1	0	0	No	No	No	No
Class 2	No	801–1000	2–4	2–4	Yes	Yes	Yes	No	No
Class 3	Yes	1001–2000	5–10	5–10	N/A	N/A	N/A	No	Yes
Class 4	N/A	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A

Class 0 insignificant, *Class 1* mild, *Class 2* moderate, *Class 3* severe, *Class 4* massive, *PRBC* packed red blood cells, *FFP* fresh frozen plasma, *PLT* platelet concentrate, *Cryo* cryoprecipitate, *rFVIIa* recombinant factor VIIa, *N/A* not applicable

In some studies risk factors for increased postoperative bleeding were elucidated. However, also a shortcoming of these studies is that different definitions of bleeding were used, and in most studies no external validation is available. Nevertheless, some risk factors were published to be associated with an increased risk of reoperation, bleeding, and transfusion [11] (see Chap. 2 on risk factors).

Implications for Daily Practice

Preoperative Risk Evaluation

Preoperative patient preparation has to be optimal with a detailed bleeding history, screening for risk factors and acquired or hereditary bleeding disorders. Even when there is little evidence that standard laboratory testing can predict postoperative bleeding, these tests should be performed and evaluated. According to the recently published EACTA/EACTS guidelines, preoperative fibrinogen levels may be considered to identify patients at high risk of bleeding, and platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors or who have ongoing dual antiplatelet therapy [12]. Furthermore, it is not recommended to use routine viscoelastic and platelet function testing as a routine monitoring tool to predict bleeding in patients without antithrombotic treatment [12]. During and after surgery the following factors have to be evaluated as they have major impact on bleeding and coagulation: hypothermia, hemodilution, and coagulopathy due to dilution, acidosis, anemia, hyperfibrinolysis, hypocalcemia, mechanical injury of thrombocytes, especially after long bypass time, and hereditary coagulopathy (rare). Furthermore, a detailed history of anticoagulants has to be taken and the patients managed accordingly. The drugs should be stopped sufficiently early to prevent increased or fatal bleeding events (see Chaps. 7 and 8 on antiplatelet and anticoagulant drugs).

Bleeding Management Algorithm in the ICU

Management of severe bleeding in the cardiothoracic ICU should be performed according to an algorithm that has to be adapted to local standards and needs. This algorithm needs to include risk factors related to the patient, the surgery, and the treatment. These risk factors should be addressed accordingly. Prior to managing individual coagulation factors as a general measure, the physiological conditions of hemostasis and covariates of the patient should be optimized. Table 21.2 shows different clinical parameters that have to be kept in their respective limits.

In bleeding patients in the ICU, the first step—as surgical site bleeding accounts for 2/3 of all major bleedings—should be the exclusion of surgical bleeding that can only be managed by reoperation [13]. The surgeon should therefore assure meticulous hemostasis during index surgery and evaluate further surgical options. Furthermore, the optimal strategy for management of the severely bleeding patient

Table 21.2 Overview of clinical parameters important for the management of bleeding and their respective limits

Clinical parameter	Reference
No surgical bleeding	
Body temperature	>36 °C
Prevention of acidosis	pH >7.2
Fibrinogen	>1.5 g/l
Platelet count	>50/µl
Calcium concentration	>1.0 mmol/l
Hemoglobin	>8 g/dl (5 mmol/l)

should be discussed by members of a multidisciplinary team. Another early step should be exclusion of a residual heparin effect. If residual heparin is suspected, this should be excluded by more specific tests, including heparin monitoring systems, or viscoelastic testing [14].

In bleeding patients, hyperfibrinolysis should be excluded and treated. In difficult cases, viscoelastic testing-guided management is indicated. In most countries, tranexamic acid is used first line to treat or prevent hyperfibrinolysis. Nevertheless, two other drugs were studied for this indication in cardiac surgery: aprotinin and EACA. All three drugs were successful to reduce blood product transfusion [12]. Of note is that high doses of tranexamic acid might be associated with an increased risk of seizures [15, 16].

In bleeding patients with low fibrinogen levels, fibrinogen concentrate or cryoprecipitate administration are indicated as preoperative fibrinogen levels <1.5 g/l were linked with increased bleeding after cardiac surgery. The indication for treatment with fibrinogen can also be assessed with viscoelastic testing. Therefore, bleeding patients with low fibrinogen levels and/or pathological viscoelastic test results may be managed with fibrinogen concentrate or cryoprecipitate whatever is available. Prophylactic treatment with fibrinogen concentrates and/or fresh frozen plasma (FFP) is not indicated on a general basis. In bleeding patients an initial dose of 20–50 mg/kg can be recommended. A certain fibrinogen level to be targeted is still controversial [12, 17].

In bleeding patients with low coagulation factor levels, treatment with FFP and/or prothrombin complex concentrate (PCC) should be considered to reduce bleeding rates. To achieve adequate levels of coagulation factors by treatment with FFP, a minimum dose of 20–30 ml/kg body weight is required. The risk of iatrogenic fluid overload and transfusion-related acute lung injury (TRALI) syndrome (low incidence in Europe and in all countries outside Europe where women of childbearing age have been excluded from plasma donor programs) [18] has to be considered. Commercially available products of PCCs contain in Europe coagulation factor II, VII, IX, and X. PCCs were shown to reduce bleeding due to coagulation factor deficiency, e.g., pretreatment with vitamin K antagonists or in patients with increased transfusion requirements after cardiac surgery [19]. However, major studies looking at safety endpoints that were adequately powered are still missing. So far, no safety issue compared to a FFP-based strategy was published. Of note, some

standard PCCs contain heparin and are therefore contraindicated in heparin-induced thrombocytopenia (HIT) type II patients. In bleeding patients with coagulation factor deficiency PCCs can be dosed at 20–30 IU/kg. As a rule of thumb 1 IU/kg PCC increases the prothrombin ratio by 1%.

In bleeding patients with acquired or hereditary platelet dysfunction, DDAVP (desmopressin) can be used to reduce bleeding. DDAVP stimulates the release of von Willebrand factor and factor VIII from endothelial cells and is primarily indicated for patients with von Willebrand disease as some studies have shown some beneficial effect of DDAVP in patients undergoing cardiac surgery with impaired platelet function [12]. However, the effect is small and due to the low level of evidence, the clinical benefit of this treatment is uncertain [20]. In patients with low platelet levels (<50/µl) treatment with platelet concentrates is indicated [12]. A typical dose of DDAVP is 0.3 µg/kg. As DDAVP may activate fibrinolysis, antifibrinolytic medication should be given concomitantly.

In bleeding patients with ongoing bleeding after treatment, factor XIII can be measured and in patients with a factor XIII concentration <70% treatment with factor XIII concentrate may be considered [12, 21].

As a salvage procedure in life-threatening bleeding if the physiological conditions of the coagulation systems are optimized (no surgical bleeding, body temperature >36 °C, pH >7.2, fibrinogen >1.5 g/l, platelet count >50/µl, calcium concentration >1.0 mmol/l, hemoglobin >8 g/dl (5 mmol/l)), the application of rFVIIa can be tried to reduce the rate of bleeding. Apart from several small studies and case reports one prospective randomized trial showed that this approach reduces blood loss, transfusion requirements, and rate of reoperation, however, with increased risk of thromboembolic complications [22]. Due to unproven efficacy and safety concerns prophylactic treatment is not indicated [12]. In rare cases when salvage therapy with rFVIIa is decided a typical dose would be 90 µg/kg. Treatment with rFVIIa is considered as live-saving therapy when other therapeutic options are not effective.

In conclusion, the treatment of bleeding in the ICU patient resembles the treatment modalities that are available during surgery. Basic physiological principles and conditions should be considered and maintained, including normothermia, normal pH, and regular levels of coagulation factors. It is recommended to use specific treatment algorithms (see Chap. 18 on treatment algorithms) and to standardize the diagnostic and therapeutic approach. Finally, patient blood management requires the involvement of the surgical team as a whole, including the intensive care physician, and multidisciplinary protocols are warranted.

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Venous Thromboembolism Prophylaxis

22

Marcus D. Lancé

Case Vignette

A 46-year-old teacher is scheduled for an elective biological aortic valve replacement because of a stenotic bicuspid valve. Her cardiac function is well preserved, but the left ventricle shows hypertrophy. Except a well-regulated arterial hypertension, the patient has a varicose vein on her left calf, without current symptoms or history of thrombosis. She takes a beta-blocker and an ACE inhibitor daily. The surgical team questions whether this lady has an increased risk for perioperative venous thromboembolism, and how this could be prevented.

Why Is It Important?

Venous thromboembolism (VTE) describes the third most frequent cardiovascular, preventable, life-threatening event based on clotting in the venous system [1]. As an umbrella the term VTE covers deep vein thrombosis (DVT) and pulmonary embolism (PE). While the first mainly affects calf, femoral, and pelvic veins, the latter describes a clot mobilizing and moving through the right ventricle and obstructing the pulmonary circulation [2].

Without adequate prophylaxis, medical patients develop a DVT in 10–40% of surgical cases. Untreated DVT increases the mortality risk due to pulmonary

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embolism by tenfold [2]. The incidence among surgical patients runs up to 60% in orthopedic patients. General risk factors for VTE are older age, obesity, malignancy, prolonged immobility, pregnancy, varicose veins, and history of DVT [3]. A recent report showed a VTE incidence in patients after elective coronary artery bypass graft (CABG) surgery of 25% [4]. Pharmacological thromboprophylaxis reduces this risk dramatically; however, timing and choice of prophylaxis depends on the settings (i.e., risk factors for DVT and bleeding, kind of operation, pre-existing disease).

Regarding cardiac surgery, we must consider some special conditions in this very inhomogeneous population. There are patients who are for other reasons already using therapeutic anticoagulation (mainly due to atrial fibrillation, artificial valves). On the other hand, CABG surgery is frequently supported by cardiopulmonary bypass (CPB), which is associated with massive fluid shifts and changes in the coagulation system. Finally, the trend to minimal invasive interventions results in less tissue trauma and fluid shift, which allows patients to recover and mobilize much faster, taking away immobilization as one of the major risk factors.

The aim of this chapter is to describe the benefits and risks of VTE prophylaxis in patients after cardiac surgery. Moreover, current preventive strategies and recommendations will be reviewed.

Prevention of Venous Thromboembolism

In general, the evidence for VTE prophylaxis in cardiac surgery is weak. In a recent Cochrane review the authors could not provide clear recommendations, because of the low quality of the studies [5]. Likewise, a systematic review from Ho and coworkers did not identify high quality investigations [3]. In cardiac surgery, some patients will need anticoagulation for other reasons than VTE prophylaxis due to valve replacement or atrial fibrillation [6]. This leaves patients undergoing CABG procedures as the main group of interest for VTE prophylaxis [7]. Ideally, the risk for perioperative thromboembolic complications should be estimated by reliable scoring systems like the Wells score, which has been extended for usage in surgical patients [8]. Alternatively, the Padua prediction or the Caprini score is endorsed and validated for medically ill patients and non-cardiac surgery patients, respectively [1, 9]. The heterogeneity in cardiac surgery population hampers easy stratification by general risk factors only. Yet, two recent publications describe specific risk factors for perioperative VTE risk estimation in cardiac surgery [3, 10].

Apart from commonly accepted risk factors for VTE like age, history of VTE, and obesity other, more specific risk factors are important in cardiac surgery. Among them impaired left ventricular function, prolonged presence of a central venous line, and perioperative blood transfusion might be more relevant in cardiac surgery [3]. Table 22.1 shows particular risk factors for DVT.

In contrast to other populations, in cardiac surgery the bleeding risk is higher due to periprocedural coagulation manipulation and the invasiveness of the procedure. This was pinpointed in a database investigation on more than 90,000 patients after CABG surgery [11]. Here the authors reported the use of VTE prophylaxis in the first 48 h after the operation in about 40% of the patients. While the incidence of

Table 22.1 Risk factors and predictors for venous thromboembolism in cardiac surgery (modified from [3, 10])

Period	Risk factor/Predictor
Preoperative	Heart catheterization Bed rest Left ventricular failure Heart transplantation
Perioperative	Blood product transfusion
Postoperative	Left ventricular failure Bed rest >3 days Mechanical ventilation >3 days Failed extubation/re-intubation Central venous line >7 days

VTE was 0.7%, the incidence of bleeding was 1.4%. Interestingly, hemorrhage was nearly independent of the use of VTE prophylaxis. However, the authors concluded that VTE prophylaxis should be avoided, as the benefit is lower than the risk. Still, it is not clear whether these patients received platelet inhibitors in addition to standard pharmacological prevention. Also, there is no indication about the severity of bleeding, as the authors defined bleeding indirectly based on the number of transfused blood products after surgery. Another point of criticism is the identification of VTE, which seems to be done by clinical signs only and could underestimate the incidence of VTE [11]. On the other hand, a recent survey in the USA including 68 institutions and all types of cardiac surgery showed that about 89% of the patients start with mechanical prophylaxis and 64% with pharmacological prophylaxis within the first 2 postoperative days [12]. The by far most common reason (80%) not to start pharmacological prophylaxis was fear of bleeding [12].

Yet, in the Cochrane review, bleeding was more frequently detected in patients receiving vitamin K antagonist for therapeutic anticoagulation, while Ho et al. described an increased risk when aspirin was used together with other pharmacological prophylaxis [3, 5]. Although prophylaxis could theoretically increase the bleeding risk, administration of low molecular weight heparins (LMWH) was not associated with higher risk of pericardial effusion or cardiac tamponade [3]. The bleeding risk did not increase, even in case of systemic anticoagulation for the treatment of confirmed VTE. In contrast, the usage of oral, therapeutic anticoagulation was associated with an increased hemorrhage risk.

Looking at the best method to prevent VTE, mechanical prophylaxis seems to carry the lowest risk of bleeding with an established benefit for the patient. Preferentially, intermittent pneumatic compression stockings (IPC) should be used above elastic stockings [10, 13]. In contrast, there is no consensus regarding pharmacological prophylaxis. While it is doubtful whether the risk of bleeding exceeds the benefit of reducing the VTE risk, it is still matter of debate which drug to choose. The traditional use of unfractionated heparin (UFH) combines the advantage of a short half-lifetime and the possibility to reverse the effect with protamine. Yet, UFH puts the patients at risk for developing heparin-induced-thrombocytopenia type II (HIT II), which carries a pro-thrombotic risk itself. In this light, LMWH might reduce the risk for HIT II. However, most of these compounds are eliminated by the

kidneys, which could lead to accumulation in case of renal dysfunction (renal creatinine clearance below 30 ml/min).

Another issue in LMWH usage may be drug monitoring. Although measurement of anti-Xa levels allows monitoring of adequate LMWH prophylaxis, these assays need calibration for each LMWH and are not always available. However, the LMWH agents are no homogenous group with the main difference in affinity to FII and FX and clearance route. Some small studies investigated patients admitted for heart valve surgery and showed superior effect of dalteparin above UFH in terms of lower VTE incidence and bleeding complications. In a recent study, 78 patients were randomized to fondaparinux VTE prophylaxis or placebo after CABG with monitoring of asymptomatic DVT by ultrasound scanning of the legs [14]. Hence the authors were not able to show superiority of prophylaxis versus placebo and concluded there is no need for early VTE prophylaxis in CABG surgery. Important is the small sample size and the short time frame of this study (11 days), so that the conclusion of the authors should be interpreted with caution [14].

In 2010, Schwann and co-workers published a retrospective study in a larger cohort of roughly 1000 patients. The authors included all patients without restrictions regarding type of cardiac surgery or DVT prophylaxis [10]. All patients received mechanical prophylaxis with IPC and antiplatelet drugs, enoxaparin or warfarin in case of therapeutic anticoagulation. Unfortunately, the authors did not stratify according to their patient's treatment in their analysis. However, the results indicate a high incidence of asymptomatic DVTs despite prophylaxis, but a low number of bleeding events. One conclusion from this study could be a more aggressive approach to pharmacological prophylaxis [10].

Interestingly, antiplatelet drugs like aspirin, which are used early in the perioperative period for prevention of graft occlusion in CABG surgery, could also be advantageous for VTE prophylaxis. From orthopedic surgery it is known that the use of low dose of aspirin may reduce the incidence of VTE. Therefore, the ESA guidelines on perioperative venous thromboembolism prophylaxis recommended aspirin in this context [15].

In 2013, a study on 100 patients undergoing off-pump CABG surgery investigated whether the combination of ASA with UFH compared to UFH alone reduced the incidence of VTE. The combination of the two drugs reduced the VTE-risk without increasing bleeding complications [16]. Regrettably, there are no other studies to support this approach.

Implications for Daily Practice

The risk for VTE in the patient in the case vignette seems moderate, because she only has a history of varicosis without DVT and no current thrombosis. Her cardiac function is well preserved and she does not suffer from pre-existing arrhythmias. The main risk factors are specific ones, like the use of the extracorporeal circulation with huge fluid shifts, central catheterization, and immobilization. Assuming there is not much blood loss during the operation there is no additional risk due to extensive hemostatic therapy. The patient has no contraindication for mechanical

prevention by intermittent pneumatic compression stockings like acute thrombosis, infection, or severe peripheral vascular disease. Ideally, intermittent pneumatic compression stockings should be used during the whole postoperative period.

Table 22.2 gives an overview of measures that can be taken to prevent perioperative thromboembolism. Low dose aspirin therapy could be started shortly after the

Table 22.2 Strategies for venous thromboembolism prophylaxis

Choice	Pro/Con	Recommendation
Mechanical		
Elastic stockings	No bleeding risk Local irritation Local constriction Painful at vein harvesting side	Not advised
IPC	No bleeding risk Local irritation Painful at vein harvesting side	Preferred used
Pharmacological		
Aspirin	Accepted in vascular surgery Accepted in orthopedic surgery Standard use after CABG surgery Mildly increased bleeding risk No reversal Limited monitoring	75–1000 mg/day
UFH	Traditionally known Easy to monitor (aPTT) Easy to reverse Risk of HIT Risk of bleeding	Start from first day after surgery possible Intravenous dosing according to aPTT Subcutaneous dose 5000 IU bi-daily
LMWH	Safe Well known Monitoring by anti-Xa Incomplete reverse Low risk of HIT Possible accumulation Risk of bleeding	Start from first day after surgery possible Subcutaneous enoxaparin 20–40 mg daily Dalteparin 5000 IU daily
Fondaparinux	Safe Well known Monitoring by anti-Xa No reversal Very low risk of HIT Possible accumulation Risk of bleeding	Start from first day after surgery possible Subcutaneous 2.5 mg daily
Vitamin K antagonist	Well known Oral availability Monitoring by INR Multiple drug interactions Reversible Difficult titration	Not recommended for DVT prophylaxis

IPC intermittent pneumatic compression stockings, *CABG* coronary artery bypass grafting, *UFH* unfractionated heparin, *aPTT* activated partial thromboplastin time, *HIT* heparin-induced thrombocytopenia, *LMWH* low molecular weight heparin

operation (within 2–4 h, if there are no signs of bleeding). Depending on the need for short-term therapeutic anticoagulation due to the biological aortic valve, one could rely on starting low molecular weight heparin injection on the morning after the surgery. If a twice daily approach is used, the second dose (to reach therapeutic levels) might be administered 12 h after the first dose. This gives enough time to check for bleeding problems, which would of course delay the second dose, keeping heparin in prophylactic ranges only. Vitamin K antagonists should be avoided in the early postoperative period (first 3–5 days).

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