Perioperative Coagulation in Cardiovascular Surgery

14

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14.1 Introduction

The evolution of scientific knowledge in cardiac surgery and cardiopulmonary bypass (CPB) has enabled the reduction of perioperative complications, despite an increase in patient-related risks and in the complexity of surgical procedures. However, the management of hemostasis and coagulation remains a difficult issue, and it is of note that the rates of allogeneic blood transfusion and surgical revision in bleeding patients have not declined in recent years. It is widely recognized that allogeneic blood transfusion carries risks of increased morbidity and mortality (Koch et al. 2006) and that there is a wide difference in transfusion thresholds and practice among hospitals. Transfusion is a controversial issue in cardiac surgery, and there are still gaps in knowledge with respect to indications, efficacy, and even safety.

It is currently recognized that a restrictive transfusion policy, guided by point-of-care (POC) tests, significantly reduces the number of transfused packed red blood cell (RBC) and fresh frozen plasma (FFP) units. Restrictive transfusion strategies do not alter perioperative morbidity (Hajjar et al. 2010) or postoperative quality of life.

A number of risk factors help identify patients at high risk of receiving transfusions, including:

- Chronic renal failure (CRF)
- Chronic heart failure (CHF)

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- Chronic obstructive pulmonary disease (COPD) in elderly patients
- Perioperative anticoagulation or antiaggregation
- Reduced RBC volume (preoperative anemia and/or small body surface)
- Complex surgery (emergency surgery, reoperation, aortic surgery, surgery other than coronary artery bypass grafting (CABG), long-lasting CPB)

Different models for predicting the transfusion risk have been proposed and validated in cardiac surgery (Magovern et al. 1996; Litmathe et al. 2003; Karkouti et al. 2006; Alghamdi et al. 2006; Ranucci et al. 2009b). The guidelines in this chapter are supported by the recommendations of the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) clinical practice guidelines on blood conservation (Society of Thoracic Surgeons Blood Conservation Guideline Task Force et al. 2011). Additional information is provided by clinical practice, expert opinions, and other guidelines and recommendations.

14.2 Preoperative Treatment with Anticoagulants and/or Antiaggregant Agents

Due to the nature of their disease, cardiac surgery patients are usually treated with anticoagulants and/or antiaggregant agents. The optimal timing for surgery on these patients is still debated, and decisions should balance the risk of thrombosis and postoperative bleeding.

A guideline to perioperative antithrombotic treatment management is summarized in Table 14.1.

14.2.1 Unfractionated Heparin (UFH) and Low-Molecular-Weight Heparins (LMWH)

In order to prevent excessive bleeding, LMWH should be stopped 12–24 h prior to surgery, given the fact that LMWH are only partially reversible by protamine (Class IIb, level of evidence C). Heparin can be reversed by protamine, making its use simple, so that intravenous infusion of UFH (in patients with unstable angina or acute coronary syndrome) is not usually stopped before surgery.

14.2.2 Oral Anticoagulants (OAC)

Patients treated with vitamin K antagonists (VKAs) are generally switched to LMWH a few days before surgery. In case of emergency surgery, VKA may be antagonized with a prothrombin complex concentrate (PCC) and vitamin K every 24 h. This treatment has largely proven its superiority over FFP (Class IIa, level of evidence B). Patients with residual VKA effects, as well as patients with poor liver function, have low levels of coagulation factors and a reduced capacity to generate

Table 14.1 Common antithrombotics seen for cardiac surgery patients

Drug	Class	Half-life (h)	Timing to surgery	Reversibility
Heparin	Thrombin and FXa inhibitor	1–1.5	Up to skin incision	Protamine
LMWH	Thrombin and FXa inhibitor	2.5–4	12–24 h	Partial, protamine
Dabigatran	Thrombin inhibitor	8–17	[a]	No
Apixaban	FXa inhibitor	8–15	[a]	No
Rivaroxaban	FXa inhibitor	9–13	24 h	No
Bivalirudin	FXa inhibitor	0.5	2 h before surgery (depending on renal function)	No, but rapidly metabolized and removed by hemofiltration
Warfarin	Vitamin K inhibitor	40	5 days before surgery	Yes, prothrombin complex, FFP
Acenocoumarol	Vitamin K inhibitor	8–11	4 days before surgery	Yes, prothrombin complex, FFP
Phenprocoumon	Vitamin K inhibitor	160	7 days before surgery	Yes, prothrombin complex, FFP
Aspirin	Cyclooxygenase inhibitor	Life of platelet	Usually not discontinued	No
Clopidogrel bisulfate	Thienopyridine ADP receptor antagonist	Life of platelet	5–7 days before surgery, Multiplate AUC >40	No
Ticlopidine hydrochloride	Thienopyridine ADP receptor antagonist	Life of platelet	7 days before surgery	No
Prasugrel hydrochloride	Thienopyridine ADP receptor antagonist	Life of platelet	7 days before surgery	No
Ticagrelor	Thienopyridine ADP receptor reversible antagonist	8–13	5 days before surgery	No
Abciximab	GP IIb/IIIa receptor antagonist	24	24 h before surgery	Fibrinogen (controversial)
Eptifibatide	GP IIb/IIIa receptor antagonist	4–6	6–12 h before surgery	Fibrinogen (controversial)
Tirofiban	GP IIb/IIIa receptor antagonist	4–6	6–12 h before surgery	Fibrinogen (controversial)

FXa activated factor X, *ADP* adenosine diphosphate, *GP* glycoprotein
[a]No data available

thrombin. For these reasons they usually require lower doses of UFH to reach and maintain adequate anticoagulation during CPB.

In recent years, VKAs have been partially replaced by novel oral anticoagulants that probably will gain even wider popularity in years to come. The most commonly used are the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban. Patients treated with these drugs cannot easily be treated with PCC, and the timing of surgery should be based on their half-life (Table 14.1).

14.2.3 Antiplatelet Therapy

14.2.3.1 Aspirin

Antiplatelet therapy has the most important role in the prevention of acute coronary syndromes. Aspirin treatment may increase perioperative bleeding and transfusion requirements; however, these side effects seem limited, and discontinuation of the treatment is not recommended. In addition, withdrawing the treatment would unreasonably increase the risk of ischemic events (Class IIa, level of evidence A).

14.2.3.2 $P2Y_{12}$ Receptor Antagonists

The optimal delay between the last dose of clopidogrel and surgery has still to be defined. The 2007 version of the STS/SCA guidelines (Society of Thoracic Surgeons Blood Conservation Guideline Task Force et al. 2007) suggested at least 5–7 days of discontinuation, but the most recent version (Society of Thoracic Surgeons Blood Conservation Guideline Task Force et al. 2011) shortened this period to 3 days. A position statement by the Canadian Cardiovascular Society (Fitchett et al. 2009) suggests at least 5 days of discontinuation, and the European guidelines from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (Task Force on Myocardial Revascularization of the European Society of, C., S. the European Association for Cardio-Thoracic et al. 2010) also confirm 5 days as the minimal discontinuation time for thienopyridine treatment for elective patients undergoing coronary surgery.

Identifying patients resistant to antiplatelet therapy may prevent unnecessarily postponing surgery; conversely, postponing patients who are strongly anti-aggregated may limit the risk of severe postoperative bleeding. A recent study using impedance aggregometry confirmed the interindividual response variability to clopidogrel bisulfate and also showed that its duration of action is not predictable (Ranucci et al. 2011). However, patients who experienced severe postoperative bleeding were identifiable using a preoperative platelet function test (Multiplate®). Therefore, it seems reasonable to test platelet function to establish clear cutoffs for surgical timing (e.g., area under the curve (AUC) <30 on receptor $P2Y_{12}$ measured on Multiplate®).

Prasugrel hydrochloride is a new-generation thienopyridine with a more pronounced effect on platelet function and no, or a very limited number of, resistant patients. It has been associated with a fourfold increase in the risk of bleeding after CABG, compared to patients on clopidogrel (Wiviott et al. 2007). It is therefore recommended to withdraw treatment 5–7 days prior to surgery, when feasible (Class IIb, level of evidence C).

Ticagrelor is a $P2Y_{12}$ receptor antagonist that does not belong to the thienopyridine family. Its action is different from clopidogrel and prasugrel; it reversibly inhibits platelet function and recovery can be expected 5 days after discontinuation (Butler and Teng 2010).

14.2.3.3 Double Antiaggregant Therapy

Double antiaggregation by aspirin and $P2Y_{12}$ inhibitors carries an increased risk of bleeding in patients undergoing CABG (Hongo et al. 2002; Yende and Wunderink 2001; Berger et al. 2008; Pickard et al. 2008; Purkayastha et al. 2006).

Continuing the treatment with aspirin and stopping clopidogrel prior to surgery are currently the best compromise between hemorrhagic and thrombotic risks (Class I, level of evidence B).

14.2.3.4 GP IIb/IIIa Inhibitors

The management of patients under GP IIb/IIIa inhibitors is more controversial; short-acting drugs, such as eptifibatide or tirofiban, can be stopped 4–6 h before surgery, whereas long-acting ones, such as abciximab, need a 24 h interval. In case of emergency surgery, some authors recommend platelet transfusion (Lemmer et al. 2000) (Class IIb, level of evidence C).

14.3 Pathophysiology of Blood Clotting Disorders Induced by CPB

The activation of the coagulation system induced by CPB is multifactorial and involves all pathways. It can lead to microthrombi formation during CPB, excess bleeding after CPB weaning, or a postoperative hypercoagulable state with an increased risk of thrombotic complications.

14.3.1 Primary Hemostasis

During CPB, a significant increase in platelet activation markers, such as granule membrane 140, P-selectin protein, PF4, and β-thrombomodulin, can be observed (De Somer et al. 2002; Vallely et al. 2009; Diago et al. 1997). Platelet dysfunction begins at the same time, with a subsequent decreased platelet response to thrombin. The dysfunction is partially due to mechanical factors (CPB circuit, aspiration, and pump interactions with platelets) and partially due to fibrinogen bound to the CPB circuit. Fibrinogen links to the GP IIb/IIIa platelet receptor and induces the release of procoagulant factors and platelet thrombin production.

Plasmin contributes to the platelet dysfunction by splitting the GP Ib receptor (de Haan and van Oeveren 1998), partially activating the platelet and rendering it less sensitive to agonists such as adenosine diphosphate (ADP) and arachidonic acid (Slaughter et al. 2001; Velik-Salchner et al. 2009). Plasmin can also activate platelets through protease-activated receptor 4 (PAR4), triggering aggregation and degranulation with the release of procoagulant factors (Mao et al. 2009; Quinton et al. 2004).

14.3.2 Secondary Hemostasis

Activation of the extrinsic pathway starts at the operative site, and in spite of the administration of heparin (aiming an ACT >400 s), the initiation of CPB induces a surge in thrombin and fibrin generation (Chandler and Velan 2003; Hunt et al. 1998) even though the level of hemostatic proteins in the plasma is decreased by 30 % at

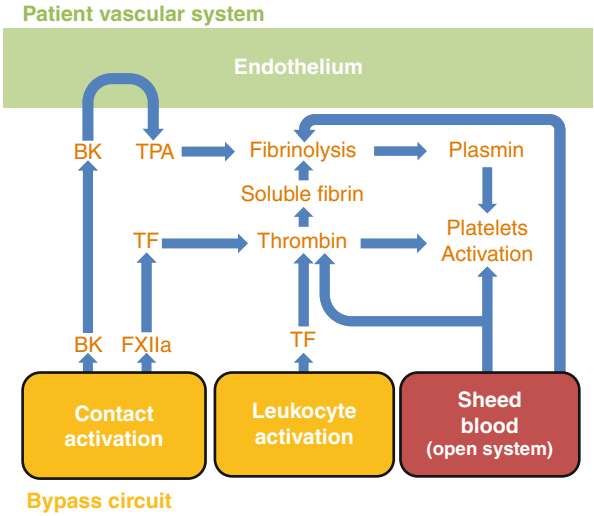

Fig. 14.1 Hemostatic activation mechanisms of cardiopulmonary bypass. *BK* bradykinin, *FXIIa* activated factor XII, *TF* tissue factor, *TPA* tissue plasminogen activator

that time. Hemodilution, blood loss, and volume replacement are responsible for this decrease, whereas the role of consumption is variable and strongly dependent on the duration of the CPB.

During cardiac operations both the extrinsic and the intrinsic coagulation pathways are activated, leading to thrombin generation (Fig. 14.1). However, thrombin generation is largely due to the release of tissue factor (TF) (De Somer et al. 2002) with the consequent activation of the extrinsic pathway. TF is expressed at the site of surgical trauma but is also expressed by platelets due to an interaction with circulating leucocytes (Chung et al. 2007). And, since inflammatory pathways, such as the complement pathway, are intrinsically linked to the hemostatic system, the CPB circuit's surface can increase the release of TF by monocytes and neutrophils. (Tabuchi et al. 2003; el Habbal et al. 1995).

After the onset of CPB, the intrinsic pathway (composed of factors XII and XI, kininogen, and prekallikrein) is activated by interaction with the artificial surfaces (Campbell et al. 2001). Factor XII is activated into factor XIIa, which converts prekallikrein into kallikrein. Kallikrein then cleaves kininogen into kinin, which has two effects: a potent hypotensive effect and a pathway amplifying effect, with a positive feedback on bradykinin production and FXII activation. Factor XII also cleaves inactive plasminogen into its active form plasmin, triggers the complement pathway, and activates FXI into FXIa, initiating the intrinsic pathway.

Prekallikrein and kininogen levels decrease during CPB not only because of hemodilution but also because of consumption and binding to the CPB circuit. On the contrary, bradykinin levels are increased tenfold, through activation of the contact system on the one hand and decreased pulmonary blood flow on the other; the lung and the kidney are responsible for bradykinin metabolism (Campbell et al. 2001).

14.3.3 Fibrinolysis

Increased levels of bradykinin enhance endothelial release of TPA. On average, TPA levels increase tenfold during CPB (Chandler et al. 2000), which in turn increase plasmin by a factor of 10–100. The result is an increase in fibrinolytic activity by a factor of 10–20 (Chandler and Velan 2004). As a consequence, the rates of fibrin generation and fibrinolysis (normally 1 %) are very similar, reflecting predominantly systemic fibrinolysis, not limited to the site of surgery. This hyperfibrinolytic state consumes fibrinogen, decreasing levels available in the postoperative phase. Conversely, during the 24 h after the operation, the patient may experience a hypofibrinolytic state, due to a 15-fold increased level of plasmin activator inhibitor 1 (PAI-1) (Chandler and Velan 2004; Freyburger et al. 1993; Lu et al. 1994). This level can further increase, carrying an associated risk of thrombosis.

14.3.4 Anticoagulation, Antithrombin III, and Protein C

During CPB, 30 % of antithrombin III (AT III) is consumed because its natural anticoagulant activity is markedly increased by UFH. Indeed, UFH increases the catalytic activity of AT III by a factor of 1,000. Inactive thrombin-antithrombin III complexes are formed and then eliminated, allowing for an effective anticoagulation during CPB. If levels of AT III are too low, heparin resistance will be observed. The clinical consequence of this will be the impossibility to reach an ACT >480 s after UFH doses of 300–400 UI/kg. Hence, it is imperative to keep AT III levels high enough to prevent excessive coagulation and inflammation activation, leading to increased bleeding and transfusions (Ranucci et al. 2005a; Paparella et al. 2009). AT III is a circulating plasma protein and can be administered through FFP; alternatively, concentrated recombinant AT III is available and reduces volume load. Although administration of recombinant AT III has proven to lower coagulation and inflammation activation, no study has been able to demonstrate any impact on postoperative bleeding and transfusion rates (Levy et al. 2002; Koster et al. 2003; Avidan et al. 2005).

While thrombin production increases during CPB, protein C activity and endothelial expression of its receptor decrease (Weiler 2010; Danese et al. 2010).

Hemodilution, negative protein C feedback on its own receptor, and negative thrombomodulin feedback on the endothelium all participate in the increase of thrombin formation.

14.3.5 Shed Blood

There also is marked activation of coagulation in shed blood, where large amounts of TF generate thrombin, activating platelets and triggering fibrinolysis (de Haan et al. 1993). Hence, the reinfusion of saved mediastinal blood can potentially

increase hemostasis activation and, as a consequence, the hemorrhagic risk. During both CPB (Class IIb, level of evidence C) and postoperatively (Class IIb, level of evidence B), the processing of mediastinal shed blood using a cell salvage device may decrease lipid emboli, decrease the concentration of inflammatory cytokines, and limit transfusions (De Somer et al. 2002).

14.4 Blood Conservation During CPB

It is currently recognized that measures that aim to reduce hemostasis activation during CPB contribute to both the decrease of preoperative microvascular bleeding and the requirement for blood transfusion (Sniecinski and Chandler 2011). Different strategies may be used to limit the deleterious effects mentioned above.

14.4.1 Avoiding Excessive Hemodilution

The nadir hematocrit in CPB has been associated with postoperative morbidity and mortality (Ranucci et al. 2005b; Karkouti et al. 2005; Fang et al. 1997; DeFoe et al. 2001). Hemodilution during CPB is dependent on the priming volume, cardioplegia volume, and any additional fluid. Any strategy aimed at limiting infused volumes will allow for a higher hematocrit during CPB and its postoperative phase and, consequently, a lower transfusion rate. Many strategies are available in order to diminish the priming volume, such as reducing the length and size of the CPB circuits (Class I, level of evidence A), using vacuum-assisted venous drainage (Class IIb, level of evidence C), and applying retrograde autologous priming (Class IIb, level of evidence B). Reducing priming volume from 1,400 to 800 ml has been proven to significatively reduce transfusion rates. Another technique available for minimizing hemodilution is modified ultrafiltration (MUF): after CPB weaning, blood is ultrafiltrated through a hemofilter connected to the venous and aortic cannulae (Class I, level of evidence A). MUF ensures not only the removal of excess water, minimizing hemodilution, but also the removal of inflammatory cytokines, resulting in a reduction of blood loss and transfusion requirements.

14.4.2 Shed Blood Management

The recuperation of pericardial or pleural shed blood can potentially contribute to saving blood units, since it returns blood and coagulation factors to the patient. Nevertheless, hemostasis, inflammation, and fibrinolysis are very active in this blood volume and if reinfused could worsen fibrinolysis and platelet dysfunction. The treatment of salvaged shed blood using a cell salvage device, which includes washing and centrifugation, reduces the activation of hemostasis and inflammation and is associated with a decrease in blood loss and transfusion rates (Wang et al. 2009) (Class IIb, level of evidence B).

14.4.3 Pumps and Circuits

Biocompatible circuits and oxygenators, by definition, decrease inflammatory responses, limit hemostasis activation, and preserve platelet function. Closed circuits are designed to reduce the foreign material contact surface and to minimize blood-air contact by suppressing the cardiotomy reservoir. When used in combination with closed systems, heparin-coated circuits allow for a reduction in the heparin dose, with loading doses of less than 300 UI/kg still achieving an ACT of at least 300 s. Two meta-analyses have confirmed the role of biocompatible circuits in reducing allogeneic transfusion (Mangoush et al. 2007; Ranucci et al. 2009a). The type of pump used in the CPB circuit may play a limited role in sparing blood. Roller pumps are occlusive pumps that sequentially compress a segment of the CPB circuit, propelling blood through the tubing. Centrifugal pumps are nonocclusive, generating blood flow by centrifugal force. This latter type of pump preserves platelet count and functions better than the former (Wheeldon et al. 1990) (Class IIb, level of evidence B). Hence, it is thought that the use of centrifugal pumps can reduce postoperative blood loss and the associated transfusion rate.

14.4.4 Anticoagulation

It is common to achieve anticoagulation for CPB by using a loading dose of 300–400 UI/kg of heparin to obtain an ACT >400 s. Yet this strategy is based more on tradition than on actual evidence. The response to an intravenous loading dose of UFH is highly variable across patients (Young et al. 1978). Individual sensitivity to heparin is influenced by nonspecific binding to plasma proteins and endothelial cells and by AT III availability (Finley and Greenberg 2013). During CPB, measurement of the plasma heparin level decay is problematic because its metabolism is altered by hemodilution and hypothermia.

ACT monitoring during CPB is essential to accurately titrate the doses of heparin and protamine. When compared with ACT-based anticoagulation management, individualized heparin and protamine management during cardiac surgery with CPB is associated with greater heparin doses, a lower protamine to heparin ratio, and reduced platelet and plasma transfusions (Despotis et al. 1995). For individualized management, heparin-ACT dose-response curves can be manually constructed by measuring the ACT at baseline and after the administration of the loading dose of heparin (Szalados 1994). The heparin concentration at the end of CPB and the protamine dose needed can then be extrapolated from the curve. Today automated devices are available that construct the patient-specific dose-response curves and calculate the appropriate doses of heparin and protamine.

One prospective randomized study has demonstrated that the target ACT can be achieved using a loading dose of 200 UI/kg and that patients having received smaller amounts of heparin suffer less postoperative blood loss (Shuhaibar et al. 2004).

Few issues are more controversial than the adequate heparin dose during cardiac surgery, with some authors supporting high-dose regimens and others suggesting heparin dose reduction through the use of closed and biocompatible circuits.

14.4.5 Fibrinolysis

The hyperfibrinolytic state induced by CPB can be attenuated by the administration of antifibrinolytic agents such as lysin inhibitors (tranexamic acid and aminocaproic acid) or nonspecific serine protease inhibitors (aprotinin). Tranexamic acid is more potent than aminocaproic acid, has a longer elimination half-life, and is the better studied agent in cardiac surgery (Ozier and Bellamy 2010). The prophylactic administration of lysin inhibitors is associated with an overall reduction in blood loss, as well as a reduction in the number of patients transfused (Class I, level of evidence A).

14.4.6 Mini Circuits

Although all of the abovementioned strategies can be applied to a conventional CPB circuit, using mini circuits can prove even more beneficial (Class I, level of evidence A). These circuits are small closed loop CPB systems with or without a flexible reservoir and driven by a centrifugal pump, minimizing hemolysis. The priming volume is less than 1,000 ml, and the surfaces are biocompatible, providing protection for blood components. Blood aspirated from the pericardial area is treated separately in a cell salvage device. The total dose of heparin needed is significantly reduced with these circuits. All these strategies, combined in a mini extracorporeal circuit, result in a 60 % decrease in the transfusion rate (Ranucci and Castelvecchio 2009).

14.5 Management of Perioperative Bleeding and Transfusion

The management of intraoperative bleeding encompasses the maintenance of adequate oxygen delivery to tissues and the specific treatment of bleeding disorders. Early intervention will prevent the occurrence of the fatal triad of hypothermia, acidosis, and coagulopathy.

14.5.1 Anemia and Transfusion Triggers

The evaluation of intraoperative bleeding consists of a visual inspection of the surgical field, the number of swabs, an estimation of aspirated blood, measurement of hemoglobin (Hb) and hematocrit (Ht), and monitoring of body tolerance to anemia. The latter is done by monitoring oxygen delivery, mixed venous oxygen saturation, and lactic acidosis. Monitoring regional cerebral oxygen saturation helps estimate brain tolerance to anemia. ST segment monitoring and evaluation of myocardial wall motion by transesophageal echocardiography estimate the heart's tolerance to anemia.

Evidence supporting packed RBC transfusion is thin, and Hb and Ht thresholds are arbitrary. Transfusion rates in cardiac surgery patients vary across different hospitals, from 10 to 95 % (Stover et al. 1998; Snyder-Ramos et al. 2008). This wide range of practice suggests that many transfusions and their related complications could have been avoided.

Clinicians nevertheless face the challenge of identifying the ideal parameter on which to base their decision to transfuse or not. Even if the prevention and treatment of inadequate tissue oxygenation are generally accepted indications, it has yet to be proven that blood transfusion actually increases oxygen delivery to the microcirculation.

Indeed, in patients with Hb of 75–85 g/l, it has been demonstrated that the transfusion of one to two blood units, when the fraction of inspired oxygen (FiO_2) is 0.4, has little effect on intramuscular oxygen partial pressure, whereas the latter is significatively increased when the FiO_2 is raised to 1.0 (Suttner et al. 2004).

Therefore, increasing FiO_2 to 1.0 is an integral part of acute anemia management.

Combining the use of transfusion thresholds with the monitoring and understanding of physiological parameters seems to be the best available tool to optimize peripheral oxygenation (Spahn et al. 2004; Madjdpour et al. 2006).

If RBC transfusion is deliberately limited, the circulating volume should still be maintained. Crystalloids and colloids will help maintain normovolemia, but care must be taken not to worsen the hemodilution. Furthermore, the choice of the solution can worsen coagulopathy, particularly in massive hemorrhage. Colloids can be responsible for a decrease in factor VIII and von Willebrand activity, as well as a decrease in platelet adhesion (Franz et al. 2001; Gallandat Huet et al. 2000).

14.5.2 Hypothermia and Acidosis

Hypothermia is relatively common in the intraoperative period and can significatively contribute to bleeding (Arthurs et al. 2006). In vitro, viscoelastic tests show a significant decrease in clot initiation and strength from temperatures below 35 °C. At less than 16 °C, the coagulation cascade is completely inactivated. On the one hand, hypothermia decreases coagulation factor activity, and on the other, it decreases platelet activation and adhesion (Rivard et al. 2005).

The development of acidosis is the result of inadequate tissue perfusion and oxygenation, and with hypothermia it synergistically worsens coagulopathy. In vitro, the effect on aggregometry of a pH <7.0 can be compared to that of hypothermia <30 °C (Engstrom et al. 2006). Acidosis worsens coagulopathy by decreasing the activity of pH-sensitive coagulation factors, such as FVIIa (activity is decreased by 90 % in an environment with pH <7.0) (Meng et al. 2003). The use of blood units and blood-derived products can aggravate acidosis due to the fact that the pH of stored products ranges from 6.0 to 7.0.

In summary, intraoperative bleeding in cardiac surgery is related to surgical trauma but can also be caused by the development of a coagulopathy; in this case, bleeding will be diffuse. The main mechanisms of the hemostasis dysfunction are:

- Preoperative use of anticoagulants or antiaggregants
- CPB-induced thrombopenia and platelet dysfunction
- Hemodilution with a decrease of procoagulant factor levels
- Increased fibrinolysis
- Insufficient neutralization of heparin after CPB weaning
- Excess protamine
- Presence of physiological anticoagulants, inducing procoagulant factor consumption
- Hypothermia and acidosis

14.5.3 Diagnosis and Treatment of Coagulopathy

Considering the complexity of the mechanisms of hemostasis and the multifactorial pattern of postoperative coagulopathy in cardiac surgery, the therapeutic pathway should be guided by the objective measurement of the various steps contributing to coagulation. The targets are to rationalize bleeding management, to tackle the underlying coagulopathy, to avoid the potentially deleterious effects of transfusion, to improve patient outcome, and eventually to control transfusion-related costs.

The first line of treatment consists of identifying patients at high risk of hemorrhage and applying strategies to decrease coagulation activation (Class I, level of evidence A).

The use of POC transfusion algorithms in the perioperative phase has been shown to better correlate with post-CPB bleeding than standard laboratory tests (Davidson et al. 2008; Cammerer et al. 2003). Algorithms including viscoelastic and platelet function tests in particular target the coagulation deficit and its specific treatment more precisely (Shore-Lesserson et al. 1999). This is currently the most efficient method of reducing transfusion after cardiac surgery and improving patient outcomes (Weber et al. 2012) (Class IIa, level of evidence C). A possible algorithm including the exploration of the viscoelastic properties of the clot and platelet function is proposed in Fig. 14.2.

The use of viscoelastic tests (TEG® or ROTEM®) reveals the specific contribution of coagulation factors, fibrinogen, and platelets in clot formation, as well as the influence of fibrinolysis or anticoagulation. It is important to keep in mind that platelet dysfunction caused by antiaggregants such as aspirin or thienopyridines is not revealed in viscoelastic coagulation tests (TEG® or ROTEM®) and will only be highlighted by platelet function tests using specific agonists.

In Germany, K. Goerlinger's team compared bleeding management guided by standard laboratory tests to bleeding management guided by thromboelastometry combined to multiple electrode impedance aggregometry (Weber et al. 2012). The latter, POC-guided, management group received significantly less RBC, FFP, and platelets. Interestingly, fibrinogen and PCC dosages were also inferior in the POC group, even though the frequency of use was comparable. Finally, The POC-guided

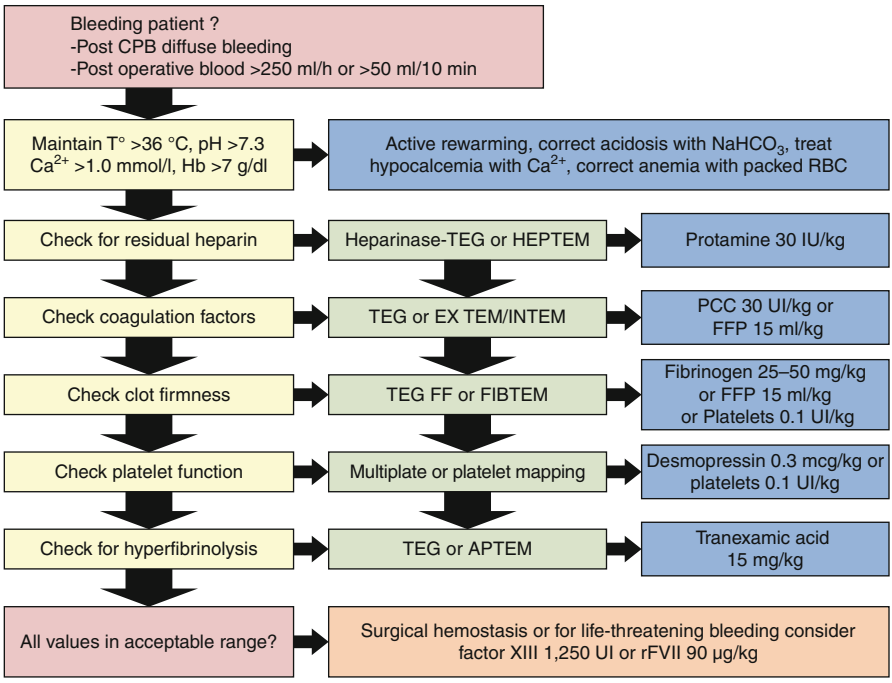

Fig. 14.2 Hemostatic therapy algorithm. *CPB* cardiopulmonary bypass, *RBC* red blood cells, *TEG* thromboelastography, *TEG FF* TEG-based functional fibrinogen assay, *EXTEM* tissue factor-activated ROTEM assay, *INTEM* ellagic acid-activated ROTEM assay, *HEPTEM* heparinized ROTEM assay, *APTEM* aprotinin-based ROTEM assay, *PCC* prothrombin complex concentrate, *FFP* fresh frozen plasma

group received less rFVIIa. The conventional group, on the other hand, showed more blood loss, a lower PaO_2/FiO_2 index, prolonged postoperative ventilation, an increased rate of undesirable events, and a higher 6-month mortality rate. These results confirm that a POC-guided approach is superior to an approach based on standard laboratory tests. Whereas standard tests provide only quantitative information on hemostasis, POCs rapidly provide qualitative information, allowing the clinician to act faster and target a specific problem.

It should be noted that, even if controlling a bleeding defect is advisable, picking out the main culprit is difficult. This is due to the multitude of potential mechanisms causing the coagulopathy. Luckily, there is rarely a need to target a single factor or specific clotting or fibrinolysis pathway. Indeed, acting on one part of the clotting pathway is often sufficient to compensate for the disorder present elsewhere in it.

Our pharmacological array allows us to promote hemostasis and fibrin formation (and to slow down fibrinolysis) by interfering in the delicate balance between coagulation activation and physiological anticoagulation (Mannucci and Levi 2007). Nevertheless, the use of pharmacological agents carries the potential risk of thrombotic complications. A transfusion algorithm is shown in Fig. 14.2.

The use of fibrinogen, factor XIII, PCC, desmopressin, recombinant factor VII, and antifibrinolytics is discussed in Chaps. 11 and 12.

14.5.4 Heparin and Protamine

Antagonization of heparin's anticoagulant effects after CPB weaning is achieved with protamine. Protamine is an alkaline arginine-rich (70 %) polypeptide extracted from salmon sperm. It neutralizes heparin by binding to its acidic sulfate group, preventing interaction with AT III. Controversy exists about which dose of protamine should be administered after CPB. Dosing regimens range from 0.8 to 1.3 mg of protamine for 100 IU of heparin. The calculation is often based on the initial or total dose of heparin, without taking its elimination into account. This can lead to a relative overdose of protamine with deleterious effects on coagulation and platelet function, since protamine itself has anticoagulant as well as antiaggregant properties. Protamine enhances endothelial release of t-PA and binds to thrombin, inhibiting its capacity to convert fibrinogen into fibrin. Furthermore, protamine-heparin complexes transiently decrease platelet count and function.

Ideally, the protamine dose should be based on the plasma heparin level (Despotis et al. 1995; Jobes et al. 1995). After protamine administration, a residual heparin effect can be caused by insufficient antagonization or heparin rebound – a reappearance of anticoagulant activity after adequate neutralization. Residual heparin effects can be responsible for pathological bleeding (Frick and Brogli 1966). Considering its low sensitivity to low plasmatic heparin concentrations, ACT is an inadequate measure for the detection of residual heparin effects. It is advisable to use specific heparinase-based tests (ROTEM® HEPTEM or heparinase-TEG®).

14.5.5 Side Effects of Protamine

The undesired effects of protamine administration are mainly hemodynamic and can be classified into three types.

The type I effect – the most frequent – is hypotension caused by mast cell release of histamine and can be prevented by injecting protamine slowly (over 5 min).

Type II effects are classified as type IIa, anaphylaxis; type IIb, nonimmune-dependent anaphylactoid reactions; and type IIc, delayed, non-cardiogenic pulmonary edema probably linked to direct drug toxicity. Although type IIa reactions can occur at any dosage and speed of infusion, careful titration is recommended with high-risk patients (past exposure to protamine, insulin-dependent diabetes treated with Hagedorn insulin, fish allergy, personal history of vasectomy) (Nybo and Madsen 2008).

A type III reaction consists of severe pulmonary vasoconstriction (probably mediated by activation of complement by pulmonary macrophages) causing acute right ventricular failure and systemic hypotension. This pulmonary hypertension can be short lived or long enough to justify going back on the CPB circuit until the hemodynamic parameters normalize. This phenomenon can be prevented by slow administration of diluted protamine.

In a case of protamine allergy, a 5 mg/kg dose of platelet factor 4 (PF4) and 5–7 mg/kg of heparinase have been proposed as alternatives for the reversal of a dose of 300 UI/kg of heparin (Dehmer et al. 1995; Michelsen et al. 1996).

When no treatment is available, omitting heparin neutralization will cause heavy bleeding (up to 5 l in 13 h (Campbell et al. 1984)) which can lead to a consumption coagulopathy. In order to reduce the need for allogeneic blood transfusion, it is recommended, in this specific case, to recycle blood collected from chest tubes in a cell salvage device.

14.6 Heparin-Induced Thrombocytopenia (HIT) in Cardiac Surgery

14.6.1 Pathophysiology of HIT

Unfractionated heparin remains the gold standard for anticoagulation in cardiac surgery, with or without CPB, given its easy titration, safety margin, reversibility, and low cost. However, its use carries the risk of developing heparin-induced thrombocytopenia (HIT). Heparin binds to PF4 and 50 % of cardiac surgery patients develop antibodies (Ab) to these heparin-PF4 complexes (anti-heparin-PF4 Ab). In 1–5 % of these patients, the anti-heparin-PF4 Ab will activate platelets by binding its Fc fragment to the platelet FcRII receptor (Warkentin et al. 2000).

The anti-heparin-PF4 Ab-mediated platelet activation and the resulting release of proclotting factors increase the production of thrombin. The continuing exposure, or reexposure, to heparin can lead to venous thrombosis (17–55 % of cases) (Warkentin and Kelton 1996; Warkentin et al. 2000) or arterial thrombosis (3–10 % of cases) (Warkentin and Kelton 1996). Although rare, it can also cause anaphylactoid reactions after intravenous injection, cutaneous necrosis at the site of injection, adrenal hemorrhage, or disseminated intravascular coagulation (DIC).

In cardiac surgery, the most common complication of untreated or unrecognized HIT is arterial thrombosis, which carries an associated mortality of 5–10 %.

14.6.2 Diagnosis of HIT

The diagnosis of HIT is based on a typical clinical presentation and the presence of anti-PF4 Ab in patients treated with UFH or LMWH (although it is ten times less frequent with the latter). HIT typically appears between the fifth and tenth day of heparin treatment or within 24 h if anti-heparin-PF4 Ab are still circulating after prior sensitization (<100 days). Less frequently, HIT can occur up to 3 weeks after the cessation of heparin. In cardiac surgery, the pattern of HIT differs from the thrombocytopenia generally seen after CPB: a patient who undergoes CPB generally experiences a platelet drop immediately on arrival in the intensive care unit; subsequently, the platelet count starts recovering, reaching preoperative values

around 5–6 days after the operation (Pouplard et al. 2005). In this setting, HIT is more often represented by a continuous drop in platelet count or a very late recovery (Pouplard et al. 2005).

An easy tool for the clinical diagnosis of HIT is the 4Ts score (Table 14.2). A low 4Ts score implies a very low probability of the patient actually having a HIT (0–0.3 %) (Lo et al. 2006; Pouplard et al. 2007); however, some patients with a high 4Ts score (24–61 %) do not have HIT at all (Lo et al. 2006; Pouplard et al. 2007). In cardiac surgery, the usefulness of the 4Ts score is limited because 2 of the 4 Ts are always present after the procedure anyway (Thrombocytopenia and other causes) and a third (Time) is unreliable.

HIT is associated with a daily thrombosis rate of 5 % (Lubenow et al. 2005). Thus, considering the long laboratory turnaround times for HIT tests and the nondiagnostic presence of isolated anti-PF4 Ab, a fast *clinical* diagnosis of HIT is imperative.

14.6.3 Treatment of HIT

After cardiac surgery, patients with strongly suspected or confirmed HIT, whether or not complicated by thrombosis, should be treated with an alternative, nonheparin anticoagulant such as danaparoid, lepirudin, argatroban, fondaparinux, or bivalirudin (Linkins et al. 2012). Any treatment with VKA must be interrupted until the platelet count has substantially recovered (usually, to at least 150×10^9/l). VKA

Table 14.2 Estimating the pretest probability of HIT with the 4Ts score: low probability, 0–3 points; moderate probability, 4–5 points; and high probability, 6–8 points

	Score = 2	Score = 1	Score = 0
Thrombocytopenia	>50 % fall or $>20 \times 10^9$/l	30–50 % fall or $10–20 \times 10^9$/l	<30 % fall or $<10 \times 10^9$/l
Timing of platelet count fall or thrombosis (day 0 = first day of most recent heparin exposure)	Platelet fall days 5–10 after start of heparin Platelet fall within 1 day and exposure to heparin within past 5–30 days	Platelet fall > day 10 Platelet fall within 1 day and exposure to heparin within past 31–100 days Platelet fall days 5–10 but not clear (e.g., missing counts)	Platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae)	Confirmed new thrombosis Skin necrosis at injection site Anaphylactoid reaction to IV heparin bolus Adrenal hemorrhage	Recurrent venous thrombosis in patient receiving therapeutic anticoagulants Suspected thrombosis (awaiting confirmation) Erythematous skin lesions at heparin injection sites	Thrombosis suspected
OTher causes of Thrombocytopenia	No alternative explanation for platelet fall is evident	Possible other cause is evident	Probable other cause is evident

therapy can only be resumed with low maintenance doses (maximum 5 mg of warfarin or 6 mg of phenprocoumon), and the nonheparin anticoagulant has to be continued until the platelet count has reached a stable plateau and the international normalized ratio (INR) has reached the intended target range. There must be a minimum overlap of 5 days between nonheparin anticoagulation and VKA therapy before the nonheparin anticoagulant is withdrawn (Linkins et al. 2012).

14.6.4 Cardiac Surgery in Patients with HIT

Patients with a history, or a severe suspicion, of previous HIT should be tested for anti-heparin-PF4 Ab. These usually disappear about 100 days after the last exposure to heparin. If anti-heparin-PF4 Ab are no longer present, cardiac surgery can be performed using standard UFH (Warkentin et al. 2008), but after receiving protamine, no further doses of heparin should be administered, and the prophylaxis of thrombotic events should be based on alternative anticoagulants. Conversely, if active antibodies are still present, the operation should be postponed (if feasible) until they disappear. An algorithm for the management of patients with HIT who need cardiac surgery is presented in Fig. 14.3.

Different strategies have been proposed for patients with active antibodies whose cardiac surgery cannot be postponed. A first possibility is to replace heparin with another anticoagulant, such as argatroban (Edwards et al. 2003; Furukawa et al. 2001), lepirudin (Koster et al. 2000a; Riess et al. 2007), or bivalirudin (Koster et al. 2000a, 2007; Dyke et al. 2007). However, caution should be applied in patients with impaired renal function, especially when bivalirudin or, in particular, lepirudin is used.

In patients with acute HIT, there is no direct evidence supporting the use of one alternative nonheparin anticoagulant over another. Although off-label, bivalirudin is

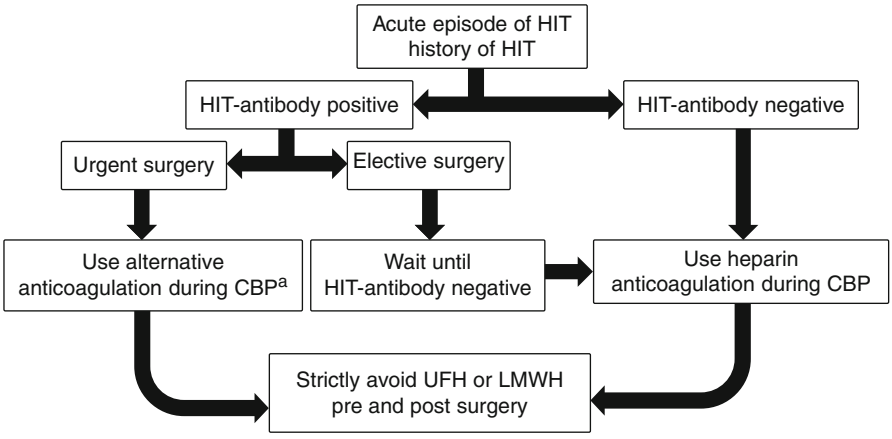

Fig. 14.3 Heparin-induced thrombocytopenia (HIT) management algorithm. *CBP* cardiopulmonary bypass, *UFH* unfractionated heparin, *LMWH* low-molecular-weight heparin. [a]See text for details

Table 14.3 Alternative anticoagulation with bivalirudin for urgent cardiac surgery in patients diagnosed with HIT

Drug	Start	Bolus	Infusion	Monitoring	Additional doses	Stop
Bivalirudin (Koster et al. 2007)	Before cannulation	1 mg/kg IV and 50 mg in CPB prime	2.5 mg/kg/min	ACT >400 s or 2.5 times of baseline value	During CPB: 0.1–0.5 mg/kg IV After weaning: 50 mg in *CPB* followed by 50 mg/h infusion	10–15 min before weaning

For details, see text

the only one that is supported by prospective multicenter cohort studies of patients with HIT, who require urgent cardiac surgery, and indirectly by small randomized heparin-controlled trials in patients without HIT (Dyke et al. 2007; Koster et al. 2007, 2009). This hirudin-derived peptide does not cross-react with anti-PF4 Ab. Bivalirudin is a reversible thrombin inhibitor with a half-life of 25 min; it is eliminated by plasmatic proteolysis and renal excretion (20 %) and can be ultrafiltrated.

Bivalirudin is administered with an initial bolus of 1 mg/kg IV, followed by an infusion of 2.5 mg/kg/h (Koster et al. 2007) (Table 14.3). Targeting an ACT >300 s (or 2.5 times the baseline), additional 0.1–0.5 mg/kg boluses can be given. The infusion should be stopped 10–15 min before weaning. In the case of CPB, 50 mg has to be added to the priming volume, and due to bivalirudin's metabolic properties, its use demands certain changes. First, surgery has to be normothermic. Second, since stasis of blood can enhance the enzymatic breakdown of bivalirudin, the following modifications of the CBP circuit are recommended:

- The use of a closed-circuit CPB when possible or replacing cardiotomy suction by a citrate anticoagulated cell saver.
- Avoiding hemofiltration during CPB.
- Inserting shunt lines from arterial filter to the cardiotomy reservoir.
- Intermittent flushing of soft venous reservoirs.
- After weaning from CPB, add a bolus of 50 mg followed by a continued infusion of 50 mg/h in the circuit.
- After weaning, once return on bypass is excluded, process the blood in the circuit with a citrate anticoagulated cell saver for reinfusion.

In the case of CABG surgery, assessments of graft patency or leakage must be performed with unheparinized normal saline. When grafting an internal mammary artery, the vessel should be transected as late as possible before grafting.

Another strategy involves combining heparin with a short-acting potent antiplatelet agent, such as a prostacyclin analog (e.g., epoprostenol, iloprost) (Antoniou et al. 2002) or a glycoprotein (GP) IIb/IIIa inhibitor (e.g., tirofiban) (Koster et al. 2000b) to attenuate platelet activation (Table 14.4). Prostacyclin analogs inhibit platelet activation by increasing adenylate cyclase activity and have very short half-lives (6 min for epoprostenol and 15–30 min for iloprost). The most important side effect reported is profound hypotension. Tirofiban has a half-life of about 2 h and is eliminated by renal and biliary excretion.

Table 14.4 Anticoagulation with platelet inhibitors and heparin for urgent cardiac surgery in patient diagnosed with HIT

Drug	Start	Bolus	Infusion	Heparin	Monitoring	Additional doses	Stop
Prostacyclin (Antoniou et al. 2002)	After induction of anesthesia	Avoid	6–12 ng/kg/min	100–300 UI/kg when HIPA negative	ACT HIPA test	Increase perfusion by 6 ng/kg/min until HIPA negative	20 min after protamine
Tirofiban (Koster et al. 2001)	Before cannulation	10 mcg/kg	0.15 mcg/min	300 UI/kg after tirofiban bolus	ACT >480 s	None	1 h before end of CPB

HIPA heparin-induced platelet aggregation

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