Antithrombotic therapy in cardiac surgery

[Traitement antithrombotique en chirurgie cardiaque]

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Purpose: To review the perioperative management of antithrombotic therapy in cardiac surgery, including the management of cardiopulmonary bypass (CPB) and off-pump surgery.

Methods: A review of the relevant English literature over the period 1975-2005 was undertaken, in addition to a review of international practices in antithrombotic therapy in cardiac surgery.

Principal findings: Cardiopulmonary bypass is required in most procedures and makes anticoagulation mandatory. Anticoagulation is, usually, achieved with unfractionated heparin (UFH). Unfractionated heparin is monitored by point-of-care (POC) testing, such as the activated clotting time or the determination of heparin concentration. The target values of both tests remain empirical, with no clearly validated thresholds. The target value needs to be adjusted according to the POC test, given significant variations between devices and activators. After CABG, the need for antiplatelet therapy is well demonstrated, in order to limit the risk of postoperative death or ischemic events, and improve venous graft patency. Immediately after valvular surgery, antithrombotic therapy should take into account the specific risk carried by each patient and by each prosthetic device. The risk of venous thromboembolism, though poorly defined, is also present in the postoperative period and may require additional attention. Given the frequent exposure to UFH, occurrence of heparin-induced thrombocytopenia is not infrequent in these patients and requires careful individual management.

Conclusions: Antithrombotic therapy is an essential component of cardiac surgery. Yet, with the exception of antiplatelet agents in CABG patients, antithrombotic therapy is often based on the clinical experience of medical teams more than on an evidence-based assessment of the literature.

Objectif: Revoir la gestion périopératoire du traitement antithrombotique en chirurgie cardiaque, incluant la circulation extracorporelle (CEC) et la chirurgie à cœur battant.

Méthode : Une revue des articles pertinents publiés en anglais de 1975 à 2005 a été entreprise en plus d'une revue des pratiques internationales de traitement antithrombotique en cardiologie.

Constatations principales : La circulation extracorporelle est nécessaire pour la majorité des opérations et rend l'anticoagulation obligatoire. L'anticoagulation est, habituellement, réalisée avec de l'héparine non fractionnée (HNF). L'HNF est contrôlée par des tests faits au chevet du malade comme le temps de coagulation activée ou la détermination de la concentration d'héparine. Les valeurs cible des deux tests demeurent empiriques, sans valeurs seuil clairement validées. La valeur cible doit être ajustée en fonction de chaque test de chevet à cause des variations significatives entre les instruments et les activateurs. Après le pontage aorto-coronarien (PAC), la nécessité d'un traitement antiplaquettaire a été bien démontrée, qui vise à limiter les décès postopératoires ou les incidents ischémiques et à améliorer la perméabilité du greffon veineux. Immédiatement après la chirurgie valvulaire, le traitement antithrombotique doit tenir compte du risque spécifique à chaque patient et à chaque prothèse. Le risque de thromboembolie veineuse, bien que peu défini, est aussi présent en période postopératoire et peut nécessiter une attention supplémentaire. Étant donné l'exposition fréquente à l'HNF, l'occurrence de thrombopénie induite par l'héparine n'est pas rare chez ces patients et exige une prise en charge individuelle particulière.

Conclusion : Le traitement antithrombotique est une composante essentielle de la chirurgie cardiaque. Néanmoins, à l'exception des antiplaquettaires chez les patients qui ont subi un PAC, le traitement antithrombotique repose souvent sur l'expérience clinique des équipes médicales plus que sur l'évaluation fondée sur les données de la recherche.

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ANTITHROMBOTIC therapy is a keystone for the safe conduct of effective cardiac operations. Most procedures require cardiopulmonary bypass (CPB), which induces hemostatic activation, and renders optimal anticoagulation mandatory in order to avoid both thrombotic and hemorrhagic complications. Postoperative antithrombotic therapy is also essential in order to improve coronary artery graft patency, limit the risk of thrombosis on cardiac prosthetic devices and of thrombotic complications secondary to arrhythmias. Of note, the risk of venous thromboembolic complications, though poorly defined in this context, is also present in the postoperative period. Unlike other surgeries, the use of antithrombotic agents in this context is often based on the experience of the anesthetic and surgical teams, more than on the results of large prospective controlled studies.

Anticoagulation during cardiac surgery

Anticoagulation for CPB

The potent activation of coagulation induced during CPB renders an effective and profound anticoagulation mandatory. High doses of unfractionated heparin (UFH) remain the gold-standard to achieve this objective. Macromolecular heparin is formed by the combination of a core protein with a variable number of mucopolysaccharide chains. The anticoagulant activity of UFH is, primarily, related to its ability to complex with antithrombin through a specific pentasaccharide sequence. Long chains accelerate the inhibition of thrombin (anti-IIa activity or anticoagulant property). Smaller fragments, below 16 to 20 monosaccharide units, inhibit only activated factor X and reduce the generation of thrombin (anti-Xa activity or antithrombotic property). Unfractionated heparin has an anti-IIa/anti-Xa ratio of 1:1. Once the inhibition reaction is completed, heparin is released and available to promote a new antithrombin-thrombin complex. Protamine neutralizes the anti-IIa activity of UFH more efficiently than its anti-Xa activity.

Pharmaceutical grade UFH is a heterogeneous mix of polysaccharides produced either from pork intestinal mucosa or beef lung. Beef lung heparin is no longer used in European countries in order to minimize the theoretical risk of acquiring variant Creutzfeldt-Jacob disease, and its use seems mostly restricted to the USA. Unfractionated heparin has a rapid onset of action, a short but variable half-life (from 30 min for 25 IU·kg⁻¹ to 150 min for 400 IU·kg⁻¹).¹ During CPB, the *in vivo* predominant action of UFH is through its anti-IIa activity.² Most often, the initial dose of heparin, before the onset of CPB, is calculated

according to the patient's weight. North-American practice favours a dosage of 300 IU·kg⁻¹ in 67% of centres and 400 IU·kg⁻¹ in 16%.³ Additional boluses of heparin (5,000 to 10,000 IU) are, subsequently, administered either systematically (about once per hour), or according to the results of coagulation monitoring. A continuous infusion may improve the stability of the heparin concentration during CPB.⁴

The use of UFH carries a significant limitation during CPB. After a standard dose (per kg) of UFH, the activated clotting time (ACT), heparin concentration and biological half-life range from 200 to 600%.⁵ Several authors failed to observe a correlation between the dose of UFH and the anti-Xa concentration or the ACT.⁶⁻¹⁰ The pharmacokinetic and pharmacodynamic properties of UFH are highly variable, with large standard deviations, and show significant variations between individual responses according to inflammatory status, hepatic and renal functions.^{1,11,12} Considering these large differences, an appropriate and individual monitoring of the anticoagulant effect of UFH is mandatory. Such monitoring is used widely, although it has not been definitely demonstrated that it improves outcome. Moreover, the target value of a coagulation test that would translate into a hypothetical "optimal anticoagulation level" during CPB remains to be defined.

Point-of-care (POC) heparin monitoring during CPB

Heparin monitoring is usually achieved with POC tests conducted on whole blood. The anticoagulant activity of UFH is appreciated by the appearance of a clot in the sample and measured either in seconds or converted in units of activity per mL. The most common POC tests are the ACT (measured in seconds) and heparin concentration monitor (results expressed in IU·mL⁻¹).¹³ The ACT measures the clotting time of whole blood in the presence of a contact phase activator (celite or kaolin). The ACT is a good reflection of high antithrombin (anti-IIa) activity.⁶ Heparin concentration monitoring by POC tests is based on a protamine titration curve that evaluates the anti-IIa activity of heparin (anticoagulant activity). The "classic" heparin concentration test, done in coagulation laboratories and performed on plasma, measures the anti-Xa activity (antithrombotic activity) of UFH. The ACT *vs* heparin concentration debate is resolved if the clinician understands that both instruments measure a biological action of heparin, in a different way. However, an important question remains: which threshold should we target during CPB?

Monitoring of anticoagulation by the ACT during CPB

Among the various devices available, the most widely used are the Hemochron® (International Technidyne Corporation, Edison, NJ, USA) and the ACT II® (Medtronic, Medtronic, Parker, CO, United States).^{3,14} Widely accepted target values for the ACT during CPB are 480 sec (41% of centres) or 400 sec (32% of centres).³ The 480-sec threshold is based on an *in vitro* study.⁶ Importantly, this arbitrary target of eight minutes was proposed for an instrument (the manual ACT) different from those used currently. The 400-sec target is supported by an animal study demonstrating that fibrin monomers were produced when the Hemochron® celite ACT was less than 400 sec.¹⁵ Of note, preservation of fibrinogen and platelets at the end of CPB was improved significantly in animals with an ACT > 750 sec. A target value of 400–480 sec has been proposed only for the Hemochron®-based instrument.¹⁶ Modifications of the blood salvage procedure (avoiding the re-infusion of shed mediastinal blood, or return after washing and centrifugation via a cell-saving device) or the use of heparin-bound circuits could limit blood activation and reduce the amount of heparin required.^{17–21}

The ACT values obtained by different monitors or with different activators cannot be interchanged, particularly during anticoagulation with heparin.²² A comparative study in patients undergoing percutaneous coronary angioplasty showed that the results of the ACT II® were 130 sec shorter than those of the Hemochron® ACT. In the therapeutic range, the mean difference in results between the two devices was 30%.²³ Another recent study, which compared two POC devices (Hemochron Response®, International Technidyne Corporation, Parker, CO, USA and Aktalike®, Array Medical, Somerville, NJ, USA) to the older Hemochron 801® showed that the ACTs measured with the Aktalike® were 18% shorter than those measured with the Hemochron 801® ($P = 0.0001$).²⁴ The ability to detect a clot in the blood sample is, obviously, different between instruments and has an impact on the final result.

The ACT values depend not only on the type and amount of coagulation activator used (celite or kaolin) but also on the presence of other drugs. Aprotinin increases the celite-based ACT in a dose-dependent manner, while the measure of the kaolin-based ACT (Hemotec, Medtronic-HemoTec, Englewood, CO, USA) is not prolonged.^{25–27} The increase of the celite ACT may, possibly, reflect aprotinin's own anticoagulant effect, in addition to that of heparin.²⁸ When aprotinin is used during CPB, the recommended

empirical target value for the celite ACT is at least 750 sec, while it is 450 sec for the kaolin-ACT.²³ It is important to note that the target of 750 sec is based on *in vitro* data and that the threshold of 450 sec for the kaolin-ACT has not been validated by clinical studies.²⁹ Tranexamic acid does not modify ACT values, making anticoagulation easier to manage when POC monitors are used to monitor heparin effect.³⁰

For clinical purposes and until randomized trials become available, UFH should be administered to keep the celite Hemochron® above 400 sec. In patients receiving aprotinin a target of 750 sec or more should be used. Reinterpretation of the results from Young *et al.*¹⁵ suggests that a safer threshold of more than 750 sec should, probably, be used in the majority of patients.

An ACT is, usually, obtained before the onset of CPB (baseline ACT), five minutes after the administration of heparin, every 30 min during the procedure, and after the neutralization of heparin with protamine. The optimal time to determine the baseline ACT is immediately after the surgical incision.³¹

Overall, the optimal target value of the ACT remains empirical, even when using the most common device (Hemochron® celite) as no large prospective study has clearly validated a threshold. Importantly, the target value applied during CPB needs to be individualized, as no single number can be applied to all POC monitors and activators. An evidence-based approach to optimal anticoagulation during cardiac surgery would require clinical studies, evaluating bleeding and thrombotic complications. These studies should also take into account the important variation of the results obtained during CPB or off bypass surgery and differences between devices and activators.¹⁶ Until randomized clinical trials become available, the clinician will have to apply an empirical threshold, adapted to the POC monitor being used.

Monitoring of heparin concentration during CPB

During CPB, heparin activity (usually described as heparin concentration) can be determined by the protamine neutralization test in activated whole blood.^{32–34} Heparin concentration during CPB is most often determined by POC monitors such as the Hepcon HMS® (Medtronic, Parker, CO, USA). As for ACT monitors, the time for formation of a clot is measured. This result is translated in units per mL, based on a predetermined heparin/protamine neutralization ratio that varies from 0.8 to 1.3. The chosen ratio in the test tube depends on the type and lot of heparin used by the clinician. A clinical dosage of heparin or protamine can be proposed by the instru-

ment, based on the estimated blood volume. These numerous assumptions can introduce a large bias in the final measure and limit the extrapolation of results between centres.

The protamine neutralization test is different from the measurement of chromogenic anti-Xa activity of heparin conducted on plasma. The correlation between the protamine titration method and the enzymatic determination of heparin levels remains controversial.³⁴⁻³⁶ While they may correlate, the results are not interchangeable.

The optimal heparin concentration during CPB has not been well established. The North American practice is to maintain a concentration of at least 3.0 IU·mL⁻¹ (in 64% of centres) or 3.5 IU·mL⁻¹ (in 19% of centres).³ These concentrations remain empirical, and their maintenance has no clinical advantage over an ACT-based management.^{37,38}

The instrument may also determine an individualized target concentration of heparin. Prior to CPB (with its associated hypothermia, hemodilution and consumption of coagulation factors), a value of heparin concentration is correlated to a target kaolin ACT. During CPB, a heparin concentration will be used as a surrogate for the ACT to adjust heparin and protamine dosages. Contrary to an arbitrary target, the heparin concentration determined in this manner is different from patient to patient. This practice is associated with the administration of a larger dose of heparin, a smaller dose of protamine (protamine/heparin ratio of 0.7) and a significant reduction in the transfusion of hemostatic blood products (plasma, platelet concentrates and cryoprecipitate).³⁹ However, a more recent study has not been able to confirm these favourable results.³⁷

As for the determination of the optimal ACT value, only studies addressing clinical outcomes would be valuable. A recent prospective study indicated that heparin monitoring with the Hepcon HMS® device led to maintenance of higher heparin levels, but postoperative bleeding was not decreased.³⁷ There is no evidence that an ACT-based administration of heparin is better than a heparin concentration-based management.⁴⁰ This important question should be addressed before considering the addition of antithrombin concentrates in order to achieve “adequate” prolongations of the ACT, as suggested recently.⁴¹

Heparin resistance and antithrombin concentrates

Heparin resistance is defined as an insufficient prolongation of the ACT after the administration of heparin. The definition of heparin resistance varies between studies: either an ACT under 600 sec after the infu-

sion of 600 IU·kg⁻¹ or an ACT under 480 sec after the infusion of 450 IU·kg⁻¹.^{42,43} In such cases, antithrombin deficiency is suspected as a large part of the anticoagulant activity of heparin requires the presence of antithrombin. During CPB, antithrombin levels are frequently around 60% of normal (due to hemodilution, elimination of the heparin-antithrombin and antithrombin-proteases complexes). It was suggested initially that heparin resistance was more frequent in patients receiving heparin prior to surgery, but this was not confirmed subsequently.^{41,44} Acquired antithrombin deficiency can lead to decreased inhibition of thrombin and factor Xa activity by heparin.⁴⁵⁻⁴⁷

Predictably, antithrombin infusion results in ACT prolongation.⁴¹ Interestingly, treatment with antithrombin could also decrease hemostatic activation markers. It has been suggested that antithrombin repletion could be specially beneficial in children, where CPB induces severe hemodilution.^{46,47} However, no clinical study has yet demonstrated a clinical benefit or evaluated the cost/benefit ratio of this additional form of anticoagulation. Moreover, as the ideal target ACT during CPB is not well defined, the infusion of antithrombin should not aim to solely increase the ACT but should be supported by a clear demonstration of improved clinical outcomes.

Anticoagulation for beating heart (off-pump) surgery

Initially, the absence of exposure to a CPB circuit supported the use of a “vascular surgery” target of 250 sec for the ACT. Usually, a bolus of 100 IU·kg⁻¹ of UFH is administered. However, a more recent approach favours higher thresholds. In interventional cardiology, the maintenance of an ACT of 300 to 400 sec provides the best balance between the rate of bleeding and thrombotic complications. A recent study compared a more aggressive anticoagulation management to a control group where the ACTs were maintained > 300 sec (heparin dose of 150 IU·kg⁻¹).⁴⁸ The experimental group received an initial bolus of heparin of 300 IU·kg⁻¹ and ACT values were maintained higher than 400 sec. This protocol was associated with a reduced rate of postoperative graft thrombosis (5.2% vs 1.3%, $P < 0.05$). Based on limited data and extrapolating from interventional cardiology, the ACT should probably be maintained at more than 400 sec with an appropriate dose of UFH.

Postoperative antithrombotic therapy

The period after cardiac surgery carries both a high risk of bleeding and thrombotic complications. Given the increasing age and the high prevalence of atherosclerotic disease in this population, postoperative

arterial thrombotic events such as myocardial infarction and stroke are a major concern. Specific arterial complications consist of peripheral embolization in non-sinus rhythm patients, graft occlusion in CABG and valve thrombosis in valvular surgery. Venous complications such as deep vein thrombosis (DVT) or pulmonary embolism may also occur in the postoperative course, as in other major surgical procedures. The aim of postoperative antithrombotic therapy is to minimize the rate of adverse thrombotic events (arterial or venous), without an excessive increase in bleeding rate and exposure to transfusions.

Antiplatelet therapy in the prevention of graft occlusion and other arterial complications after CABG

The risk of early graft closure, mostly restricted to saphenous vein grafts, is real and clearly multifactorial.⁴⁹ In the absence of antithrombotic therapy, the percentage of venous graft patency, evaluated between the first month to 24 months after CABG surgery ranges from 19.7 to 91% (mean 75.3%).⁴⁹ In contrast, the rate of the internal mammary artery graft patency is high, from 92 to 100% at three months to three years after surgery, even in the absence of antiplatelet therapy.^{50, 51} Acetyl salicylic acid (ASA) therapy improves the rate of venous graft patency.^{52–55} The early introduction of ASA (on the day of surgery) is more effective than a late one (after three days), suggesting that graft occlusion is an early thrombotic process mediated by platelet aggregation.^{56–58} Acetyl salicylic acid 75 to 325 mg within six hours after the operation, or as soon as possible in the case of bleeding, is recommended.^{49,52,59,60} It should be noted that two out of three studies evaluating a low dose of ASA (100–150 mg) showed no clinical benefit. In contrast, three out of four studies report an improved graft patency rate with 325 mg of ASA.

In patients already receiving ASA before CABG, the discontinuation of treatment before CABG is matter of debate. The preoperative use of ASA was found to increase postoperative blood loss, transfusion requirements and early reoperation for bleeding.^{61–63} However, these findings were inconsistent and of a weak magnitude.⁶⁴ Recent guidelines indicate that cessation of aspirin and other platelet inhibitors seven to ten days before CABG in stable patients and low-risk plaque morphology could be prudent to decrease the risk of postoperative bleeding and transfusion.⁶⁰ However, a recent large prospective case-control study showed that the preoperative use of ASA was associated with a decreased risk of mortality, without a significant increase of hemorrhage, and that the benefits of ASA outweigh the risk of bleeding.⁶⁵ A

recent observational study showed that early (i.e., within 48 hr) ASA therapy after CABG was associated with a reduction of 44 to 70% in the frequency of early death, and of major adverse events related to the heart, brain, kidney and gastrointestinal tract.⁶⁶

Clopidogrel, another antiplatelet agent, has also been proposed after CABG, as an alternative for patients who are allergic to ASA. The recommended dose is a loading dose of 300 mg, six hours after surgery, followed by 75 mg *id.*⁵² The benefits and risks of clopidogrel were analyzed recently in patients undergoing CABG for non-ST elevation acute coronary syndrome.⁶⁷ The benefits of clopidogrel (re-introduced after six to 25 days after surgery) outweighed the bleeding risk. However, data indicate that the use of clopidogrel within three to five days before surgery is associated with increased bleeding.^{67, 68} Therefore, cessation of clopidogrel at least five days before surgery, when possible, is clearly recommended. When clopidogrel has not been stopped before surgery (for example, emergency procedure), the use of antifibrinolytics (aprotinin, epsilon-aminocaproic acid or tranexamic acid) could be proposed, since such treatments decrease postoperative blood loss and transfusion requirements, without increasing early graft closure.^{69–77} More recently, it was emphasized that ASA or clopidogrel resistance was common after CABG, suggesting the possible need for adjusted dosage or alternative therapy in such patients.^{78–80} The combination of ASA with dipyridamole or vitamin K antagonists is not recommended for the prevention of postoperative graft thrombosis.⁵²

Antithrombotic therapy after valvular surgery

Patients undergoing valve surgery are at risk of developing valvular and arterial thrombosis. This risk is especially high in patients with a mechanical prosthetic heart valve, justifying life-long oral anticoagulation, but is also increased in patients with biological heart valves or after valve repair. Guidelines for long-term anticoagulation in these patients have been proposed by scientific societies such as the American College of Cardiology/American Heart Association, the European Society of Cardiology, and the American College of Chest Physicians.^{81–83} Life-long oral anticoagulation is required for all patients with a mechanical valve prosthesis, aiming for a target international normalized ratio (INR) of the prothrombin time greater than 2. The definitive target value will vary according to the position of the valve (higher target values are required for mitral prostheses compared to aortic), the type of prosthesis (higher target values are required for first generation prostheses

compared to recent devices), and the cardiac context (higher target values are required in the presence of arrhythmia or auricular dilatation). The European and American recommendations are, overall, identical for aortic valve prostheses (INR between 2 and 3 for second generation prostheses in the absence of auricular dilatation or arrhythmia). For mitral valve prostheses, the European guidelines recommend higher INR values than the American ones (3–4.5 and 2.5–3.5, respectively). For biological mitral valves, oral anticoagulation is recommended during the first three months after surgery.⁸³ Whether biological aortic valve prostheses require oral anticoagulation during the first three months remains a matter of debate. A recent study suggests that warfarin is not more effective than ASA with regards to early cerebral ischemic events, bleeding and survival.⁸⁴ Whatever the long-term target value at which the INR should be maintained, the need for early antithrombotic therapy after surgery is recognized, since thrombotic events can occur in the very first days after surgery. Initially, heparins are used to achieve therapeutic levels of anticoagulation. As the risk of bleeding is high in the first days after surgery, heparin is usually started six hours after surgery, or later in the case of bleeding. A vitamin K antagonist is initiated 24 to 48 hr after chest drainage tubes are removed. Unfractionated heparin is most often prescribed after valve surgery, since low molecular weight heparins (LMWH) have not been evaluated extensively in these conditions. The dose of UFH is adjusted according to coagulation monitoring (usually the activated partial thromboplastin time; aPTT), aiming for an aPTT 1.5 to 3 longer than control. Unfractionated heparin must be continued until the INR is in the therapeutic range. Given the difficulties and cost of UFH management during the period between the end of surgery and effective anticoagulation with a vitamin K antagonist, an increasing number of cardiac surgery units use LMWH, although the available evidence of their efficacy and safety is still limited. A non-randomized study of 208 patients undergoing mechanical heart valve implantation showed that LMWH (mostly enoxaparin 200 UI·kg⁻¹ per day) was as safe and effective as UFH.⁸⁵ No difference in the rate of bleeding or thrombotic complications was observed with enoxaparin in a small cohort (29) of patients, but two bleeding complications were reported in another 12 patients.^{86,87} Therefore, the use of LMWH in the immediate postoperative period after heart valve surgery remains controversial. If LMWH are used, anti-Xa activity must be monitored carefully, and the dosage should be adapted according to the renal function of the patient.

Other indications for heparin or vitamin K antagonists

Anticoagulation using heparin or vitamin K antagonists can be required in patients with atrial fibrillation after CABG. New-onset postoperative atrial fibrillation occurs in 30% of patients with a peak incidence on the second to third postoperative day. Postoperative atrial fibrillation is associated with a two- to threefold increase in postoperative risk for stroke.⁶⁰ The risk of aggressive anticoagulation in such patients (mediastinal bleeding) has to be weighed against the possible reduction of neurological complications. Alternatively, electrical or pharmacological cardioversion, without anticoagulation, can be attempted, especially if a left atrial thrombus has been excluded.⁶⁰ Beyond the early postoperative period, cardioversion can be attempted in patients receiving *iv* heparin. If atrial fibrillation persists more than 48 hr, warfarin anticoagulation is recommended for at least four weeks.⁸⁸ Also, long-term (three to six months) anticoagulation is suggested for patients with recent anterior-apical myocardial infarction and persistent wall-motion abnormality.⁶⁰

Heparin or vitamin K antagonists can also be required to prevent the risk of venous thromboembolism, which is present after CABG, but remains poorly defined. In the absence of heparin prophylaxis, the incidence of DVT was 22% in the prospective study by Goldhaber *et al.*⁸⁹ The incidence of pulmonary embolism ranges from 0.6 to 9.5%.^{90–92} Eighteen to 40% of pulmonary embolisms were fatal. A recent observational study, from three Italian rehabilitation institutions serving 19 cardiac surgery units, indicates that despite short-duration (< three days) heparin prophylaxis after CABG (mainly LMWH) in 63% of the patients, deep venous thrombosis was present in 17.4% of cases. Proximal vein thrombosis accounted for 2.6% of cases, and pulmonary embolism was observed in 0.7%. Ninety-one percent of the DVT were diagnosed on admission, and 50% were localized in the saphenous vein contralateral to the harvest site.⁹³ Overall, these data suggest that CABG is associated with a moderate but significant risk of venous thromboembolism. The efficacy of mechanical prevention seems poor.^{89,93} The safety and efficacy of LMWH have not been evaluated in this context, but LMWH should probably be considered in the postoperative period, especially in patients with additional risk factors such as prolonged length of stay and female gender.⁹³

Management of heparin-induced thrombocytopenia (HIT)

Cardiac surgery patients commonly receive UFH treatment either during CPB and/or in the postoperative period, putting them at relatively high risk for HIT.

Heparin-induced thrombocytopenia is an immune-mediated disorder resulting from the production of immunoglobulin G (IgG) antibodies that recognize the heparin-platelet factor 4 (PF4) complex.^{94,95} This multimolecular complex of IgG-PF4-heparin can bind to the immunoglobulin fragment c (Fc) platelet receptor, leading to platelet activation. The thrombotic risk remains elevated for days to weeks, even after heparin has been stopped.⁹⁶ Heparin antibodies triggered by the recent heparin exposure are transient.⁹⁷ The overall frequency of HIT after cardiac surgery is approximately 2 to 3%.^{98,99} However, immunoglobulin seroconversion after cardiac surgery is present in 30% to 50% of patients, indicating that only a minority of antibody-positive patients develop thrombocytopenia. Heparin-induced thrombocytopenia has been shown to be more frequent when UFH from beef lung rather than from porcine gut is used.¹⁰⁰ Heparin from pork intestinal mucosa is the recommended formulation to be used during cardiac surgery.¹⁰¹ Low molecular weight heparin, which is not commonly used during heart surgery because of its long half-life and poor neutralization by protamine, carries a lower risk of HIT than UFH.¹⁰²

A proportional fall in platelet count of more than 30 to 50% from the highest preoperative value, five to ten days after heart surgery, with or without thrombosis, suggests HIT.^{103,104} Significant levels of HIT antibodies usually occur only after the fifth postoperative day or later, so thrombocytopenia during the first four postoperative days is only rarely attributable to HIT. The risk of thrombosis is high, with 40 to 75% of patients developing this complication.⁹⁶ In cardiac surgery patients developing HIT, arterial is more frequent than venous thrombosis (mainly lower limb arteries).^{98,104} Saphenous vein graft occlusion is a prominent manifestation of HIT¹⁰⁵ since it is present in 38% to 81% of the cases with an associated mortality of 28%.^{98,99} Deep vein thrombosis (especially associated with central venous catheters) and pulmonary embolism are also common.¹⁰⁶

Laboratory testing

Platelet aggregation assays have limited sensitivity and specificity for detecting HIT antibodies.^{94,107} An enzyme-linked immunosorbent assay (ELISA) detecting anti PF4-heparin antibodies is highly sensitive for HIT, meaning that a negative result usually rules out the condition. However, ELISA has a moderate positive predictive value, particularly if the test result is weakly positive. A high rate of sub clinical HIT antibodies after cardiac surgery, without thrombocytopenia, is observed. The serotonin-release test is more predictive of HIT but the test can only be performed

in highly specialized centres.¹⁰⁸ All these assays are carried out in reference laboratories, and the results are rarely obtained without delay. This means that the decision to stop heparin and to switch to an appropriate antithrombotic therapy has to be taken on the basis of a decline of the platelet count and the clinical context (typically five to ten days after surgery, with or without thrombosis or other clinical manifestation).

Alternative anticoagulant therapies

Alternative anticoagulant therapies are: 1) hirudins and other direct thrombin inhibitors (Lepirudin in the United States, Canada, European Union, Australia and New Zealand; Bivalirudin in the United States; Argatroban in the United States and Canada); and 2) danaparoid, a factor Xa inhibitor available in the European Union, Canada, Australia and New Zealand.

Direct thrombin inhibitors

Hirudin is naturally produced by the salivary gland of the medicinal leech. Lepirudin (Refludan®, Berlex Montville NJ, USA and Pharmion, Cambridge, UK) is available by recombinant technology. Hirudin forms an irreversible complex with thrombin, inhibiting all procoagulant actions of thrombin. No antidote is available. In patients with a normal renal function, the half-life is approximately 80 min, and hirudin levels decline quickly after stopping the infusion. When renal function is impaired, the half-life increases to up to more than 200 hr. Drug accumulation can cause severe bleeding and ultrafiltration may be required (using appropriate filters).^{109,110} Lepirudin has been used during CPB at high doses. It can only be monitored by the ecarin clotting time (ECT) since the ACT and aPTT do not correlate with the concentration of hirudin. The goal is to achieve stable intraoperative hirudin levels of 3.5 to 4 µg·mL⁻¹.¹¹¹ Dosing schedules and treatment protocols are presented in detail elsewhere.¹¹²

Bivalirudin (Angiomax® (ICS, Louisville, KY, USA) is a synthetic peptide modelled after hirudin which, unlike lepirudin, interacts reversibly with thrombin and has a short half-life (25 min). Its clearance is mediated by proteolytic cleavage by plasma enzymes (including thrombin). Clearance is also reduced when renal function is impaired. Bivalirudin has been used successfully for anticoagulation during both off-pump and on-pump cardiac surgery in patients with acute or previous HIT.¹¹³⁻¹¹⁵ Clots can be observed in the pericardial cavity and should not be interpreted as a sign of insufficient systemic anticoagulation. Ecarin clotting time is recommended for intraoperative monitoring during CPB.¹¹⁵

Argatroban is a direct thrombin inhibitor, eliminated by the liver with a half-life of 40 to 50 min. No specific antidote is available. Argatroban interferes with the prothrombin time and INR, which can be confusing when vitamin K antagonists are used. It has been used successfully during CPB in dogs, but clinical experience in humans is too limited¹¹⁶ to be recommended.

Danaparoid

Danaparoid (Orgaran®, Organon, Oss, The Netherlands) is a glycosaminoglycan with predominant anti-factor Xa activity, and low cross-reactivity with HIT antibodies. It has a long half-life (25 hr) and no antidote is available, making postoperative bleeding a major concern after CPB. Only the anti-factor Xa levels can be used to monitor danaparoid levels required for CPB. Fixed dose or weight-adjusted regimens have been proposed, with a target anti-factor Xa level of $1.5 \pm 0.3 \text{ U} \cdot \text{mL}^{-1}$.^{117,118}

Heparin and tirofiban

An interesting alternative treatment by UFH and the short-acting platelet glycoprotein IIb-IIIa antagonist tirofiban (Aggrastat®, Merck and co, Frankfurt, Germany) has been proposed by Koster *et al.* in 2001.¹¹⁹ In a report on 47 patients with HIT and CPB, this strategy (UFH bolus $400 \text{ IU} \cdot \text{kg}^{-1}$ and tirofiban, bolus $10 \mu\text{g} \cdot \text{kg}^{-1}$, followed by a continuous infusion $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) resulted in satisfying results, with no excessive bleeding and no thrombotic complications. Only three patients presented a severe thrombocytopenia before CPB, and received platelet concentrates. Hirudin was used as pre- and post-CPB antithrombotic treatment. The important advantage of this strategy is to avoid the use of specialized biological tests such as the ECT. Further, this strategy could be used in patients with an impaired renal function, given the short half-life of the medications, and the possibility of eliminating tirofiban by ultrafiltration.¹²⁰

Cardiac surgery in patients with previous HIT

Heparin-induced thrombocytopenia antibodies are transient and usually become undetectable by 100 days (median 50 days) after exposure to heparin. Antibody formation does not recur more often in a patient with a previous history of HIT who is re-exposed to heparin.^{97,121,122} Unfractionated heparin is the drug of choice for anticoagulation during CPB in patients with a history of HIT who no longer have circulating HIT antibodies using one or more sensitive assays (washed platelet activation assay or PF4-heparin

antibodies).^{121,123} Importantly, the preoperative or postoperative use of heparin must be avoided completely (catheterization) and alternative methods of anticoagulation should be used.

Cardiac surgery in patients with acute or subacute HIT

A patient with a recent episode of HIT who has detectable HIT antibodies can develop rapid onset HIT if exposed to UFH.^{97,122} Non-urgent cardiac surgery must be postponed for more than 100 days. If cardiac surgery cannot be delayed and heparin anticoagulation is still contraindicated, several approaches should be considered. The use of heparin-coated CPB circuitry must be avoided. For CABG surgery, an off-pump technique should be considered as only one third or one half of the usual heparin dose is needed. Relatively low doses of danaparoid or recombinant hirudin may be used in these cases.^{124,125}

The use of a non-heparin anticoagulant depends on patient factors (renal or hepatic failure), availability of non-heparin anticoagulants, and the accessibility of appropriate coagulation monitoring. Specialized monitoring (ECT, anti-Xa activity) is mandatory when using alternative anticoagulants. Recently, recommendations have been published concerning alternative anticoagulant approaches, in order of preference: 1) bivalirudin for intraoperative anticoagulation during CPB (if ECT is available) or during off-pump surgery; 2) lepirudin for intraoperative anticoagulation (if ECT is available and the patient has a normal renal function); 3) UFH plus an antiplatelet agent, eposprestenol or anti GPIIb-IIIa (tirofiban) if ECT monitoring is not available or in the presence of renal insufficiency that precludes lepirudin use; or 4) danaparoid if anti-factor Xa monitoring is available.^{101,119,126} Overall a team approach is mandatory, associating the surgeon, anesthesiologist and hematologist.

Management of HIT after cardiac surgery

When HIT is suspected, UFH as well as low molecular weight heparin, even in small doses used to flush invasive catheters should be stopped urgently and another antithrombotic treatment substituted. Heparin cessation by itself is associated with a high rate of thrombosis (25% to 50%) with 5% of fatal events.^{95,96} Prophylactic platelet transfusions should be avoided, since infused platelets may react with HIT antibodies and trigger an acute thrombus formation. Vitamin K antagonists should be avoided in the initial phase of HIT, until platelet count is normalized, since they cause hypercoagulability through protein C depletion within the first hours after administration.

Screening for venous thrombosis should be performed in order to detect occult lower limb DVT. When acute limb ischemia occurs, surgical thrombectomy may be considered concomitantly with fast-acting alternative anticoagulant therapy.

Conclusion

Overall, antithrombotic therapy in cardiac surgery raises specific concerns with respect to the choice, dosing, time of onset of antithrombotic agents, and their relative safety and efficacy in this context. As UFH remains widely used in cardiac surgery, HIT is not a rare event, which requires a cautious and multidisciplinary approach.

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