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Anti-factor Xa Monitoring of Anticoagulation During Cardiopulmonary Bypass in a Patient with Antiphospholipid Syndrome

M. J. LENNON*, N. M. THACKRAY†, N. M. GIBBS‡

Department of Anaesthesia, Sir Charles Gairdner Hospital, Perth, Western Australia

SUMMARY

The activated clotting time (ACT) may be an unreliable monitor of coagulation for patients with the antiphospholipid syndrome. We describe a patient with antiphospholipid syndrome in whom adequate anticoagulation during cardiopulmonary bypass was confirmed by monitoring both the ACT and anti-factor Xa levels. The cardiopulmonary bypass was uneventful, and there were no thrombotic or bleeding complications. The use of anti-factor Xa levels provided confirmation of adequate anticoagulation (and reversal of anticoagulation) that was not possible using the ACT alone.

Key Words: ANTIPHOSPHOLIPID SYNDROME: anticoagulation, anti-factor Xa, cardiopulmonary bypass

The antiphospholipid syndrome (APS) is a term used to describe the clinical features of thrombosis, fetal loss, thrombocytopenia, or valvular heart disease, occurring in the presence of circulating antiphospholipid antibodies[1]. Patients with APS have an increased propensity for thrombosis, which places them at increased risk of peri-operative thrombotic complications[2,3]. Paradoxically, antiphospholipid antibody may cause prolongation of coagulation assays such as the activated partial thromboplastin time (APTT), prothrombin time (PT), and activated clotting time (ACT)[4]. This makes monitoring of peri-operative anticoagulation difficult, particularly if adequate anticoagulation is essential, such as during cardiopulmonary bypass (CPB). We describe a patient with APS in whom we confirmed adequate anticoagulation during CPB using anti-factor Xa levels.

CASE HISTORY

A 33-year-old, 120 kg, female patient was admitted for elective resection of a mitral valve tumour and mitral valve replacement. A transthoracic echocardiogram performed two years previously reported mitral valve prolapse. One month prior to admission she had an occlusive stroke, resulting in a right nasal hemianopia and mild dysphasia. Magnetic resonance imaging showed infarction of the temporo-occipital region. The vertebral and carotid vessels were assessed as normal and a transoesophageal echocardiogram showed a posterior mitral valve mass with the features of a fibroelastoma. A thrombophilia screen detected circulating antiphospholipid antibody. She was commenced on warfarin, aiming for an international normalized PT ratio (INR) of 3.0 to 3.5, and she was scheduled for resection of the mitral valve mass. The warfarin was discontinued six days prior to surgery and replaced with enoxaparin 100 mg subcutaneously (sc) twice daily (bd). Enoxaparin was ceased 24 hours before surgery. On the evening before surgery the patient received unfractionated heparin 5000 U sc. This was repeated on the morning of surgery (more than six hours before surgery commenced).

The preoperative haemoglobin (Hb) was 110 g/l and the platelet count was 268 x 10^9/l. The baseline APTT was prolonged at 44.5s (normal range: 21-33s). The thrombin clotting time (20.4s), INR (1.1), and fibrinogen level (4.2g/100 ml) were normal. The presence of lupus anticoagulant was confirmed using the Russell Viper Venom test (Gradipore, Sydney, Australia). Anticardiolipin antibody, measured using the ELISA method (Orgentec, Mainz, Germany), was >120 U/ml (normal <10 U/ml). Protein C, protein S,

*F.C.A.R.C.S.I., Provisional Fellow
†F.A.N.Z.C.A., Staff Anaesthetist
‡M.D., F.A.N.Z.C.A., Head of Department

Address for reprints: Dr N. M. Gibbs, Department of Anaesthesia, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, W.A. 6009.

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antithrombin III (ATIII), and factor V levels were normal.

Anaesthesia was induced with midazolam, fentanyl and propofol, and was maintained with isoflurane in oxygen or oxygen-enriched air. In addition to routine monitoring, a pulmonary artery catheter and transoesophageal echocardiography were used. Anticoagulation was monitored using the kaolin ACT (Hemochron, International Technidyne, Edison, NJ, U.S.A.) and chromogenic anti-factor Xa level (Instrumentation Laboratories, Milan, Italy). Non-pulsatile hypothermic (30°C) CPB was instituted using a membrane oxygenator and roller pump. The CPB prime consisted of 2.3l Plasmalyte 148 solution to which 100 mg porcine heparin was added.

Prior to CPB, the baseline ACT was 147s (normal range 91-151s) and anti-factor Xa level was 0.4 U/ml. Heparin 3 mg/kg (1 mg=100U) was administered, resulting in an ACT of 517s and an anti-factor Xa level of 7.6 U/ml. After 50 minutes of CPB the ACT was 424s. A further 100 mg of heparin was given intravenously (IV), because our target ACT was >480s. However, the anti-factor Xa level, measured at the same time, remained above our target of 4.0 U/ml. After 70min of CPB the ACT was 499s and the anti-factor Xa level was 6.6 U/ml. After separation of CPB before the administration of protamine, the ACT was 388s. At this time the anti-factor Xa level was 7.5 U/ml. After administration of protamine 750 mg (1.3 mg per mg of heparin used) over 15 minutes, the ACT decreased to 146s, and the anti-factor Xa level to 0.2 U/ml. The changes in ACT and anti-factor Xa levels in response to heparin and protamine are shown in Figure 1.

The patient underwent excision of the mass, which involved both mitral valve leaflets, and prosthetic

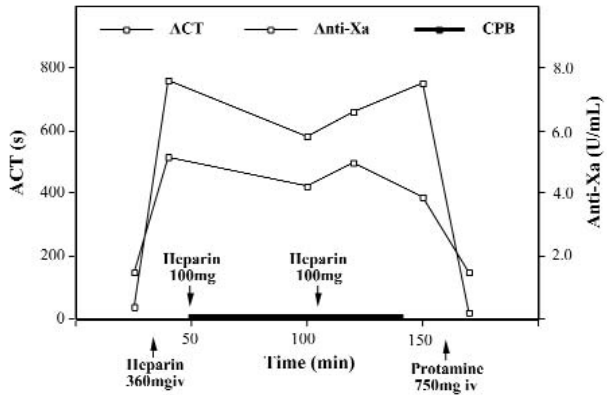

FIGURE 1: Changes in activated clotting time (ACT) and anti-factor Xa levels (Anti-Xa) in response to heparin and protamine. The thick black line represents the period of cardiopulmonary bypass (CPB). The first heparin dose during CPB (down arrow) represents the heparin added to the CPB prime.

mitral valve replacement. No allogeneic blood transfusion was required. Postoperatively the patient was transferred to an intensive care unit where blood loss was minimal (250 ml over 24h). Histology revealed a chronically scarred mitral valve with multiple foci of calcification and superimposed thrombus formation. There was no active rheumatic heart disease. Anticoagulation with warfarin was recommenced 24 hours postoperatively.

Unfractionated heparin 7.5 mg sc 8 hourly was given until the INR was in the target range (3.0-3.5). The patient was discharged from the hospital on day 7 on long-term warfarin anticoagulation.

DISCUSSION

The antiphospholipid syndrome occurs in about 2% of the population. It is most commonly associated with systemic lupus erythematosis, but may also occur following acute viral infections, other autoimmune diseases, certain malignancies, or exposure to drugs such as procainamide, phenothiazines, and hydralazine[5]. It may also occur in the absence of a concomitant disease. In all cases it is associated with the presence of an antiphospholipid antibody.

Surgical patients with the APS are at increased risk of thrombotic complications due to their disease process, and bleeding complications due to perioperative anticoagulation. Careful monitoring of their coagulation status is required peri-operatively. Cardiopulmonary bypass presents a particular challenge due to the thrombotic risks and the extent of anticoagulation required. During CPB, anticoagulation is usually monitored by the ACT[6]. However, there have been several reports of a prolonged baseline ACT in cardiac patients (up to 430s), which makes use of the ACT alone, unreliable[7,8]. For example, an ACT of 430 s might be considered adequate anticoagulation, but could occur in the absence of any heparin effect[7]. Therefore, alternative methods for ensuring adequate anticoagulation are required. Additional concerns include thrombocytopenia, which occurs in up to 50% of APS patients, and low AT III levels which may influence response to heparin administration (independent of the antiphospholipid antibody)[1].

Several anticoagulation strategies have been proposed in previous case reports. Initial reports used a standard (3 mg/kg)[9] or increased dose of heparin (5 mg/kg)[10] and ignored the ACT. Sheikh and colleagues used a heparin dose sufficient to "double" the baseline ACT[7]. Ducart and co-workers measured the heparin concentration by means of protamine titration and maintained the heparin concentration

greater than 2.5 mg/ml[8]. Others have determined the heparin—ACT response curve prior to surgery (by adding known amounts of heparin to the patient's blood in vitro)[11,12]. In addition, the use of anti-factor Xa levels as a secondary confirmatory measure of adequate anticoagulation during CPB has been described[11,12].

The use of anti-factor Xa levels may be considered the gold standard for monitoring heparin therapy[13]. Until recently, it has been impractical to monitor anti-factor Xa levels during CPB due to the length of time required to perform the test. However, the test can now be performed within 20 minutes. Moreover, in the future it may be possible to measure anti-factor Xa levels at the point of care. Another advantage of monitoring anti-Xa levels is that it provides a measure of heparin effect, rather than heparin concentration. During CPB, it is more important to monitor heparin effect than concentration, because many factors influence the relationship between concentration and effect (e.g., AT III level)[5].

We elected to use both the ACT and anti-factor Xa levels to confirm adequate anticoagulation in our patient. If the baseline ACT had been prolonged, or if the ACT had not responded predictably to the heparin dose, we could have used the anti-factor Xa level to confirm adequate anticoagulation prior to the institution of CPB. This would have involved a delay of only 10 to 20 minutes. However, following a standard dose of heparin (3 mg/kg IV), the ACT increased from 147s to 517s. Given that the post-heparin ACT was triple the baseline ACT, and that an additional 100 mg of heparin was present in the CPB pump prime, we anticipated that adequate anticoagulation for CPB was ensured. Nevertheless, we confirmed adequate anticoagulation by measuring anti-factor Xa levels. Our target anti-factor Xa level was greater than 4.0 U/ml, which is said to indicate adequate anticoagulation[11,12]. If inadequate anti-factor Xa levels had been present, we would have administered further doses of heparin. Post-CPB, a total of 750 mg protamine IV was given to reverse the heparin. This resulted in a return of the ACT to the pre-heparin level (146s) and a return of the anti-factor Xa level to 0.2 U/ml. These findings were consistent with complete neutralisation of heparin.

The ACT levels in our patient appeared to be relatively unaffected by the patient's antiphospholipid antibody. However, it was only possible to reach this conclusion because we had another concurrent measure of anticoagulation. Relatively normal ACT responses have also been observed by others[12]. Different effects on coagulation tests may be due to different anti-phospholipid antibodies[14]. Antiphospholipid antibodies include anti-cardiolipin antibody type A and type B, and lupus anticoagulant. Lupus anticoagulant is actually a misnomer and refers to the effect of the antibody on coagulation tests. These antibodies may occur together or in isolation. Unfortunately, it is not possible to predict the effect of the antibodies on all coagulation tests. Our patient exhibited many of the clinical features of APS, and had positive lupus anticoagulant and anti-cardiolipin antibodies. However, her APTT was only slightly prolonged, and her other coagulation tests appeared normal.

The use of the ACT alone may be safe for monitoring anticoagulation during CPB in some patients, but there is always a possibility of inadequate anticoagulation due to an artifactually prolonged ACT. The use of a higher than usual dose of heparin is also unsatisfactory, due to the increased risk of bleeding complications postoperatively. Measuring a heparin concentration—ACT response curve in vitro preoperatively may assist the determination of correct heparin dose. Nevertheless it is preferable to measure heparin effect rather than concentration during CPB. Therefore, we recommend using both the ACT and anti-factor Xa levels for monitoring of anticoagulation during CPB for patients with APS.

In summary, we describe a case in which adequate anticoagulation during CPB was ensured by monitoring both the ACT and anti-factor Xa levels. The ACT response to heparin was normal, and the patient had no thrombotic or bleeding complications. The use of anti-factor Xa levels provided confirmation of adequate anticoagulation, which was not possible using ACT alone.

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