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REPORTS OF ORIGINAL INVESTIGATIONS

# Elevated activated partial thromboplastin time does not correlate with heparin rebound following cardiac surgery

# Un temps de céphaline activée élevé n'est pas associé à un rebond d'héparine après une chirurgie cardiaque

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**Abstract**

**Purpose** *Exposure to cardiopulmonary bypass (CPB) is associated with postoperative coagulopathy and hemorrhage. Recent literature indicates that heparin rebound occurs almost universally following cardiac surgery. We conducted this pilot study to evaluate if the presence of residual circulating heparin following cardiac surgery can be diagnosed by elevation of activated partial thromboplastin time (APTT).*

**Method** *After obtaining Research Ethics Board approval, blood samples from 30 patients receiving heparin for CPB were evaluated at the time of intensive care unit admission and 2, 4, and 6 hr thereafter. Activated clotting time, whole blood heparin concentration (Hepcon HMS Plus, Medtronic), anti-Xa levels, and APTT were measured at each time point. Samples with prolonged APTT were subjected to mechanistic studies with heparin adsorption and 1:1 mixing.*

**Results** *Anti-Xa was elevated in 52 of the 120 blood samples ($0.08 \pm 0.08$ U · $mL^{-1}$, mean ± SD). APTT was elevated in 49 (40.8%) samples with an average of $51.4 \pm 31.9$ sec. At all time points, the APTT correlated poorly with anti-Xa levels with correlation coefficients ranging from $-0.26$ to $-0.05$. Mean APTT was modestly, but not significantly, associated with total dose of protamine with $r = 0.34$ (CI: $-0.03$, 0.62). After 1:1 mixing studies, APTT returned to normal in most (82%) samples tested.*

**Conclusion** *Circulating residual heparin is commonly presented following cardiac surgery and does not correlate with APTT. Considering that mixing studies normalize APTT in most samples, elevated APTT following CPB may reflect deficiency of coagulation factors or presence of a coagulation inhibitor such as protamine. Further studies are required to confirm this observation.*

**Resumé**

**Objectif** *La circulation extra-corporelle (CEC) peut mener à une coagulopathie, voire une hémorragie, en période postopératoire. La littérature récente indique que le rebond d'héparine survient pratiquement dans tous les cas après une chirurgie cardiaque. Nous avons réalisé cette étude pilote afin de déterminer si la présence*

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*d'héparine résiduelle dans le sang après une chirurgie cardiaque peut être dépistée par un temps de céphaline activée (aPTT) élevé.*

**Méthode** *Suite à l'approbation du Comité d'éthique de la recherche, des échantillons sanguins de 30 patients recevant de l'héparine pour la CEC ont été analysés au moment de l'admission à l'unité des soins intensifs, puis 2, 4 et 6 h plus tard. Le temps de coagulation activé (ACT), la concentration d'héparine dans le sang total (Hepcon HMS Plus, Medtronic), les taux d'anti-Xa et l'aPTT ont été mesurés lors de chaque évaluation. Les échantillons présentant un aPTT prolongé ont été soumis à des études mécanistes avec une adsorption d'héparine et un mélange à 1:1.*

**Résultats** *Le niveau d'anti-Xa était élevé dans 52 des 120 échantillons sanguins (0,08 ± 0,08 U·mL$^{-1}$, moyenne ± ET). L'aPTT était élevé dans 48 (40,8 %) des échantillons, avec une moyenne de 51,4 ± 31,9 secondes. À tous les points de mesure, l'aPTT était peu corrélé aux taux d'anti-Xa, les coefficients de corrélation allant de –0,26 à –0,05. L'aPTT moyen n'a pas été associé de façon significative avec la dose totale de protamine où r = 0,34 (IC : -0,03, 0,62). Après les études de mélange à 1:1, l'aPTT a chuté à un niveau normal dans la plupart (82 %) des échantillons testés.*

**Conclusion** *L'héparine résiduelle en circulation est un phénomène commun après une chirurgie cardiaque et n'est pas dépistée par l'aPTT. Étant donné que les études de mélange normalisent l'aPTT dans la majorité des échantillons, un aPTT élevé après la CEC pourrait indiquer une carence en facteurs de coagulation ou la présence d'un inhibiteur de la coagulation comme la protamine. D'autres études sont de mise afin de valider cette observation.*

Postoperative hemorrhage is common following cardiac surgery. Nearly 20% of patients have significant hemorrhage after surgery, and as many as 4% may require re-exploration for excessive hemorrhage.[1–3] While the costs associated with managing this hemorrhage remain staggering, ongoing blood loss also complicates clinical management in the perioperative period. There is increasing evidence that excessive bleeding requiring transfusions is independently associated with serious perioperative events, such as sepsis, acute respiratory distress syndrome, renal failure, and death.[4–6]

Surgical causes of bleeding are found in less than 50% of patients undergoing re-operations for bleeding, and it is proposed that microvascular coagulopathy is the most common cause of postoperative hemorrhage. A heparin rebound phenomenon (reappearance of anticoagulant activity after adequate neutralization with protamine) can contribute to this coagulopathy.[7] Earlier studies reported an incidence of heparin rebound varying from 4% to 54%.[8–13] However, a more recent study has suggested that residual circulating heparin is present in virtually all patients following cardiac surgery.[14]

We have shown, in a recent survey, that most cardiac surgical centers in Canada do not use point of care tests in the management of postoperative cardiac surgical patients.[15] Presence of residual heparin is rarely monitored with thromboelastography, thrombin time, or other point-of-care tests. Most centers rely on laboratory assays for coagulation, namely the prothrombin time (PT) or the International Normalization Ratio (INR) and the activated partial thromboplastin time (APTT) following cardiac surgery. Moreover, the most direct measurement of heparin anticoagulant effect, the anti-Xa level, is seldom monitored in a cardiac surgery setting.

The diagnosis of circulating residual heparin remains vital, as it can easily be treated with supplemental doses of protamine. However, excess protamine may be harmful to the patient as it can have its own anticoagulant and hemodynamic effects.[16–19] Thus, it is important to diagnose the presence of circulating heparin in the postoperative cardiac surgical patient. We hypothesized that persistence of residual circulating heparin may be reflected by elevation of APTT, a test that is routinely available. Hence, we conducted a pilot study to evaluate if the presence of residual circulating heparin after cardiac surgery could be diagnosed by elevation of APTT.

## Methods

After obtaining institutional review board approval, we prospectively studied 30 adult patients scheduled for elective cardiac surgery on cardiopulmonary bypass (CPB). Patients were excluded from the study if they were <18 years of age and were unable to give written consent. Other exclusion criteria included history of any known coagulopathies, liver dysfunction, re-operations, preoperative abnormal coagulation profiles (INR $\geq$ 1.3, APTT > 33 sec), recent exposure to heparin (unfractionated or low molecular weight), warfarin, clopidogrel, or other direct thrombin inhibitors in the preceding 14 days.

Anesthesia was induced with a combination of benzodiazepine, opioid, and propofol and was maintained with oxygen, air, inhalational agent, and a muscle relaxant. A baseline activated clotting time (ACT) (Max ACT, Actalyke MAX-ACT; Array Medical, Somerville, NJ, USA) was recorded after induction of anesthesia and before surgical incision. Anticoagulation for CPB was initially induced by unfractionated heparin (Hepalean, Organon, Toronto, ON, Canada) in the dose range of 3–4 mg · kg$^{-1}$

body weight to achieve a target ACT > 480 sec. To maintain the target ACT, supplementary heparin (50–100 mg) was administered, as necessary, prior to and during CPB. Tranexamic acid (bolus: 30 mg · $kg^{-1}$, prime: 2 mg · $kg^{-1}$, infusion 2 mg · $kg^{-1}$ · $hr^{-1}$) was administered intraoperatively to all patients, as per standard protocol. All patients underwent normothermic CPB using a membrane oxygenator and biocompatible circuits (Xcoating, Terumo, Ann Arbor, MI, USA). The extracorporeal circuit was primed with ringers lactate 1000 mL, 10% pentastarch 400 mL, mannitol 40 g, 8.4% sodium bicarbonate 50 mL, and unfractionated heparin 5000 IU. Following termination of CPB, heparin was reversed with protamine sulphate (Sandoz Canada Inc., Boucherville, QC, Canada), the precise dose of which was decided by the attending anesthesiologist depending on the total dose and timing of heparin administration. Protamine was initially given as a slow bolus to return the ACT to within 10% of the baseline value. If little or no clot was seen forming on the surgical field, a further bolus (50 mg) was administered as per the discretion of the attending anesthesiologist and surgeon on visual inspection.

## Blood sampling in the Intensive care unit

Blood samples (9 mL) were drawn from arterial catheters on admission to the intensive care unit (ICU) and 2, 4, and 6 hr thereafter. The arterial transducer systems-flushes were free of heparin, and blood samples were drawn after discarding about six dead space volumes of the catheter.[20] All measurements were performed in duplicate. Samples were analyzed for ACT, whole blood heparin concentration (WBHC) (Hepcon HMS *Plus*, Medtronic), plasma anti-Xa levels, PT, and APTT (HemosIL kit, Lexington, MA, USA), as per protocol shown in Fig. 1. Briefly, anti-Xa levels were checked on all of the samples that had an elevated APTT. In order to confirm absence of residual heparin, hepadsorbed APTT was then performed on all samples that demonstrated elevated APTT but normal anti-Xa levels. Finally, 1:1 mixing studies[21] were performed on samples that demonstrated elevated APTT before and after heparin adsorption but demonstrated normal anti-Xa levels.

## Laboratory and point of care tests

The ACT (Max ACT, Actalyke MAX-ACT; Array Medical, Somerville, NJ, USA) was performed by dispensing blood 0.5 mL into the MAX-ACT tube, filling the tube to the indicated line, and gently shaking the tube side to side before inserting it into the two wells of an Actalyke device. As per standard policy, routine quality control was performed daily. The Hepcon HMS *Plus* (Medtronic) was used for measuring whole blood heparin concentration after performing stringent quality controls as per manufacturer's instructions. The method involves adding known quantities of protamine to a blood sample with unknown quantities of heparin. The protamine in each channel neutralizes a specific amount of heparin. Both excess heparin and excess protamine act as anticoagulants, and the first channel to clot is the channel in which the amount of protamine most closely neutralizes all of the heparin. Since low concentrations of residual heparin were anticipated in our patients, cartridges with the range estimated to be appropriate for the expected heparin concentration (red, four channel) were used initially. The cartridge was inserted into the Hepcon device to stabilize at approximately 37°C. When the measured heparin concentration was at the limit of detection of the chosen cartridge, the concentration was confirmed with the use of a cartridge with a more appropriate range. Plasma anti-Xa levels were measured in the laboratory by an automated chromogenic assay. In this assay, heparin is analyzed as a heparin-antithrombin complex after adding purified human antithrombin to the plasma sample. Factor Xa is then added in excess to the sample and is neutralized by the heparin–antithrombin complex. Residual Xa level is quantified with

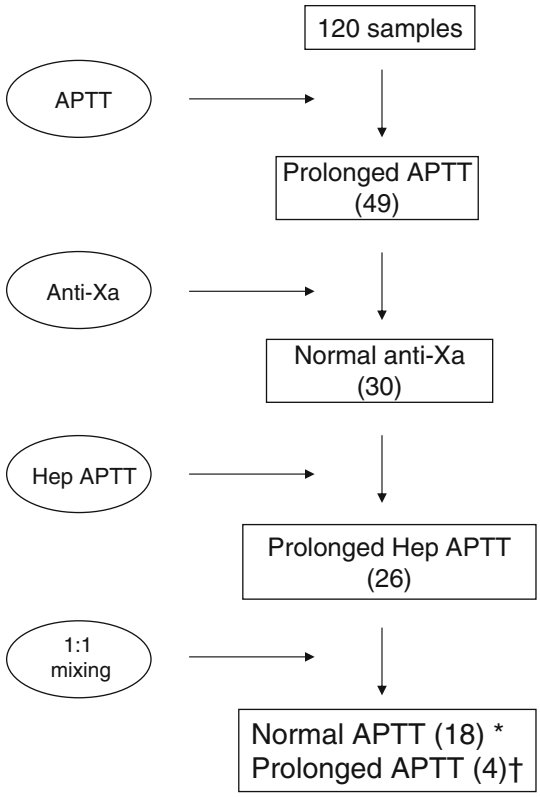


**Fig. 1** Protocol for evaluating blood samples (see text for details). * Four samples could not be evaluated due to insufficient quantities of plasma remaining. † Four of 22 samples tested with 1:1 mixing studies showed partial correction of APTT. Hep APTT = Hepadsorbed activated partial thromboplastin time

a synthetic chromogenic substrate (lower limit of detection 0.01 U · $mL^{-1}$). For standardization, the hospital laboratory had established its own mean and standard deviation and had a quality control program to monitor testing. For the analysis of PT and APTT (HemosIL, Lexington, MA, USA), whole blood was collected into sodium citrate vacutainer tubes (3.2%), centrifuged at 1500*g* to recover platelet free plasma, aliquoted, and tested as per manufacturer's instructions. Hepadsorbed APTT (Inotech Biosystems International Inc., Rockville, MD, USA) was conducted after incubating patients' plasma with the heparin adsorbent (ECTEOLA) for one minute as per instructions. In order to further distinguish the cause of elevated APTT (factor deficiency or presence of inhibitor), 1:1 mixing studies were carried out on selected samples by incubating the patient plasma with an equal volume of plasma donated by normal donors, and the APTT test was repeated immediately afterwards. Since factor levels of 50% of normal are sufficient to produce a normal APTT, the 1:1 mixing would result in correction of abnormality if it was caused by deficiency of one or more coagulation factors. On the other hand, if an inhibitory antibody was present, after that the mixing procedure would result in little or no correction of APTT.[21]

A total of 30 patients were enrolled in this pilot study. Spearman rank correlation coefficients[22] and their respective 95% confidence intervals based on Fisher's *z* transformation[23] were calculated between APTT and anti-Xa, INR for each time point. Similarly, Spearman rank correlations were used to evaluate the relationship between mean APTT and perioperative factors, including duration of CPB, aortic cross clamp time, heparin–protamine dose, blood loss, and transfusions. Univariable logistic regression was used to evaluate the association between various parameters in patients who suffered from excessive hemorrhage (>1000 mL at 18 hr). Results are presented as mean ± SD. A $P$ value <0.05 was considered to be statistically significant. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

## Results

Of 37 patients (120 blood samples) who were screened, 32 patients met eligibility criteria and were subsequently enrolled. Two patients had to return to the operating room (OR) within 4 hr of ICU admission and could not complete the study. The demographic profile of patients is outlined in Table 1.

Overall, anti-Xa was elevated in 52 of 120 samples evaluated, with at least one elevated value observed in 26 of 30 patients (0.08 ± 0.08 U · $mL^{-1}$). For comparison, the usual therapeutic range for systemic anticoagulation to achieve an APTT that is 2 to 2.5 times normal equates to a heparin range from 0.3 to 0.7 U · $mL^{-1}$; conventional heparin levels for CPB are usually in the range of 3–5 U · $mL^{-1}$. The APTT was elevated in 49 of the 120 samples (at least one elevated value observed in 26 of 30 patients) with an average of 51.4 ± 31.9 sec (normal ≤33 sec). APTT correlated poorly with anti-Xa levels at all time points with correlation coefficients ranging from −0.26 to −0.05 (Table 2). However, better correlations were observed between APTT and INR ranging from 0.16 to 0.70 at all four time points. When tested for whole blood heparin concentrations via Hepcon, all but two blood samples showed absence of circulating heparin. Both of these samples with elevated WBHC (0.14 ± 0.06 U · $mL^{-1}$) had normal APTT but elevated anti-Xa levels. Taken together, these results suggest that both the APTT and WBHC are relatively insensitive assays for heparin relative to the gold standard anti-Xa.

Further tests were carried out to find the cause of prolonged APTT (Fig. 1). Anti-Xa levels were checked in these samples and were found elevated in only 19 of the 49 samples (38.8%). Hepadsorbed APTT was then carried out on all 30 samples that had elevated APTT and non-detectable plasma anti-Xa levels. In 26 of these samples (86.6%), hepadsorbed APTT was elevated, confirming lack

**Table 1** Demographic profile of patients enrolled in the study

| | |
|---|---|
| No. of patients | 30 |
| Gender | Male (22), Female (8) |
| Type of surgery | CABG (19), Valve replacement (6), combined (5) |
| Age (yrs) | 67.7 ± 11.8 |
| Weight (kg) | 81.6 ± 15 |
| Euroscore | 4.4 ± 2.8 |
| CPB time (min) | 100.8 ± 36.3 |
| ACC time (min) | 71.2 ± 30.3 |
| Heparin protamine ratio | 1.4 ± 0.5 |

*CABG* coronary artery bypass graft; *CPB* cardiopulmonary bypass; *ACC* aortic cross clamp

Values represent mean ± SD

**Table 2** Spearman rank correlations between APTT and anti-Xa, INR

| Time (hr) | Correlation coefficients | |
|---|---|---|
| | APTT; anti-Xa *r* (CI 95%) | APTT; INR *r* (CI 95%) |
| 0 | −0.26 (−0.56, 0.12) | 0.70 (0.45, 0.84) |
| 2 | −0.26 (−0.57, 0.11) | 0.48 (0.14, 0.71) |
| 4 | −0.22 (−0.54, 0.15) | 0.16 (−0.22, 0.49) |
| 6 | −0.05 (−0.40, 0.32) | 0.47 (0.13, 0.71) |

*APTT* activated partial thromboplastin time; *INR* International Normalization Ratio; *CI* confidence intervals

of residual heparin in the samples. Twenty-two of these 26 samples (with elevated APTT and negative anti-Xa levels) were then subjected to 1:1 mixing studies (the remaining four samples could not be analyzed due to insufficient quantities of plasma remaining). After mixing patient samples with an equal volume of normal pooled donor plasma, the APTT returned to normal values in 18 of the 22 samples (81.8%). Partial correction of APTT (>25%) was observed in the remaining four samples.

Spearman rank correlations evaluating the association between mean APTT and other intraoperative characteristics are presented in Table 3. A significant association with OR transfusions ($r = 0.58$, $P < 0.01$) and a modest association with total protamine dose administered ($r = 0.34$, $P = 0.06$) was obtained. Univariable logistic regression was carried out for variables that could potentially be associated with excessive hemorrhage (>1000 mL in the first 18 hr) following surgery. With the exception of increasing age, none of the other variables was found to be significantly associated with excessive hemorrhage in this patient cohort (Table 4).

**Table 3** Spearman rank correlations between mean APTT and other intraoperative variables

| Variable | *r* (CI 95%) | *P* value |
|---|---|---|
| Age (yrs) | 0.26 (−0.11, 0.57) | 0.16 |
| Weight (kg) | −0.29 (−0.59, 0.08) | 0.12 |
| CPB time (min) | 0.18 (−0.20, 0.50) | 0.35 |
| ACC time (min) | 0.25 (−0.12, 0.56) | 0.17 |
| Total heparin dose | 0.22 (−0.15, 0.54) | 0.23 |
| Highest ACT | −0.10 (−0.44, 0.27) | 0.60 |
| Total protamine dose | 0.34 (−0.03, 0.62) | 0.06 |
| Heparin protamine ratio | −0.12 (−0.46, 0.25) | 0.52 |
| Residual pump blood | 0.04 (−0.34, 0.42) | 0.83 |
| Blood loss (6 hr) | 0.07 (−0.30, 0.42) | 0.70 |
| Blood loss (18 hr) | 0.15 (−0.22, 0.48) | 0.43 |
| OR transfusions | 0.58 (0.27, 0.78) | <0.01 |
| ICU transfusions | −0.06 (−0.43, 0.33) | 0.77 |

*ACC* aortic cross clamp; *ACT* activated clotting time; *OR* operating room; *ICU* intensive care unit; *CI* confidence intervals

## Discussion

This study shows that residual circulating heparin, as measured by anti-Xa levels, is commonly present in patients following cardiac surgery. The APTT is also commonly elevated in the postoperative period; however, it does not correlate with anti-Xa levels.

APTT remains the most frequently used method to monitor anticoagulation with heparin in contemporary medical practice.[24] Various studies have measured APTT following cardiac surgery and have found it to be commonly elevated.[25–34] Some have found a positive correlation between APTT and postoperative hemorrhage following cardiac surgery.[26,28,30,35–39] Very few studies, in fact, have specified their transfusion algorithms for the management of hemorrhage,[26–28,40] thus making it difficult to ascertain how elevated APTT was interpreted and dealt with in most studies.

The APTT test results can be influenced by several factors, for example, blood collection techniques, citrate concentration, and platelets can artifactually alter the results of this test.[41–43] Apart from the use of heparin, hirudin analogues, and argatroban,[42] the APTT may also be prolonged by a deficiency of coagulation factors (congenital or acquired), including lupus anticoagulant, monoclonal

**Table 4** Logistic regression for various variables that could be associated with excessive hemorrhage following CPB

| Variable | Hemorrhage <1000 mL Mean (SD) [$n = 25$] | Hemorrhage >1000 mL Mean (SD) [$n = 5$] | Odds ratio (CI) | *P* value |
|---|---|---|---|---|
| Age (yr) | 65.6 (11.4) | 78.4 (8.2) | 0.85 (0.73, 0.99) | 0.04 |
| Weight (kg) | 82.9 (15.4) | 74.7 (12.4) | 1.04 (0.97, 1.1) | 0.27 |
| CPB time (min) | 95.5 (25.7) | 127.2 (67.5) | 0.98 (0.95, 1.01) | 0.13 |
| ACC time (min) | 66.7 (21.1) | 93.6 (56.7) | 0.98 (0.95, 1.01) | 0.11 |
| Heparin ($U \cdot kg^{-1}$) | 506.9 (152.7) | 496.4 (161.8) | 1.0 (0.99, 1.01) | 0.89 |
| Highest ACT | 744.5 (306.1) | 841.4 (417.2) | 1.0 (0.99, 1.00) | 0.54 |
| Protamine ($mg \cdot kg^{-1}$) | 3.92 (1.71) | 4.30 (0.80) | 0.88 (0.51, 1.50) | 0.63 |
| Mean APTT (sec) | 36.1 (13.7) | 43.8 (12.1) | 0.97 (0.91, 1.03) | 0.28 |
| Mean ACT (sec) | 121.7 (9.15) | 123.8 (14.9) | 0.98 (0.89, 1.08) | 0.67 |
| Mean anti-Xa | 005 (0.05) | 0.04 (0.05) | 1.1 (0.85, 1.35) | 0.56 |
| Mean INR | 1.21 (0.13) | 1.34 (0.15) | 0.01 (<0.001, 2.61) | 0.09 |

*ACC* aortic cross clamp; *ACT* activated clotting time; *CPB* cardiopulmonary bypass; *APTT* activated partial thromboplastin time; *INR* International Normalization Ratio; *CI* confidence interval

gammopathy, and dysfibrinogenemia. An APTT ratio of 1.5–2.5 times the control value equates to protamine titrated heparin levels of 0.2–0.4 U · $mL^{-1}$.[44] However, in this study, APTT did not correlate with anti-Xa levels (chromogenic assay) or with WBHC (protamine titration method). Weak correlation between APTT and heparin concentration has also been reported during vascular surgery after lower doses of heparin.[45] The degree of prolongation of APTT in response to heparin can vary amongst different APTT methods and, based on this observation, it is recommended that the therapeutic range for each reagent be determined relative to plasma concentrations of heparin.[41] For this study, calibration for APTT was carried out as per Clinical and Laboratory Institute (CLSI) guidelines[44]; therefore, other explanations need to be sought for prolongation of APTT in our patient cohort.

Mixing studies suggested that elevated APTT could have been related to a deficiency of coagulation factors, and these results are further supported by the observation that APTT was found to have good correlation with INR. Consumption of coagulation factors has been well described in cardiac surgery,[30,46,47] as has the dilution of factors resulting from red cell transfusion and volume expanders. In addition, altered blood flow during CPB might have resulted in decreased synthetic function of coagulation factors by the liver. Taken together, these effects could contribute to a modest depletion of multiple factors manifested as prolonged INR and APTT in the postoperative period. The 1:1 mixing studies carried out in this investigation could not rule out the effect of another inhibitor (anticoagulant). Interestingly, APTT had a modest association, though not statistically significant, with the amount of protamine administered to patients. Excess protamine can prolong APTT,[48–50] hence, we speculate that elevated APTT in our patients may have been related, at least in part, to an excessive protamine dose in an attempt to reverse heparin. Further work is needed to clarify the effect of protamine on APTT in the cardiac surgery setting.

Protamine is frequently administered to cardiac surgical patients in the postoperative period. It is difficult to ascertain how commonly this occurs, although there is suggestion that more than 20% of patients may be administered additional protamine to neutralize residual heparin.[14] We have recently shown that the majority of cardiac surgery centers in Canada do not have written guidelines for administering hemostatic infusions, including protamine, in the postoperative period.[15] Since APTT is still used as a surrogate marker of coagulation abnormalities in the postoperative period and is clearly an insensitive assay for residual heparin, caution should be exercised before administering protamine based on the results of APTT.

In this study, residual heparin, as measured by anti-Xa levels, did not correlate with whole blood heparin concentrations via Hepcon HMS *Plus*. Although good correlation has been observed intraoperatively between these two methods,[45] Hardy *et al.* have also shown a lack of agreement between the two methods during cardiac surgery.[51] This discrepancy may have occurred for a variety of reasons. Lack of agreement between the chromogenic assay and the Hepcon device can occur due to the inhibitory effect of heparin on platelet function, an important component of the latter technique using whole blood rather than plasma. It is also important to consider that the Hepcon instrument could only measure discrete results (0.0, 0.4, 0.8, 1.2 U · $mL^{-1}$) with the specific cartridge used for this study and could not differentiate the in-between or particularly low levels of heparin detected by the anti-Xa assay. Besides, measurement of heparin through a protamine titration assay is based on inhibiting clotting at the factor IIa level, whereas the chromogenic assay measures the inhibition reaction at the Xa level. Nevertheless, the Hepcon instrument has been recommended as a useful point-of-care test after cardiac surgery.[52] Since Hepcon HMS *Plus* measures heparin through a protamine titration assay, it is possible to contemplate that this may more accurately represent the fraction of heparin amenable to reversal with protamine. The primary reason for documenting residual heparin postoperatively must be to facilitate its reversal with supplemental protamine—hence, based on the observation that completely diverse results were observed on analysis of residual heparin levels through anti-Xa levels and the protamine titration assay, further investigations are required to evaluate the most relevant method for measuring residual heparin following cardiac surgery.

This study has several imitations. Of all hemostatic transfusions, only red cell concentrates were transfused according to guidelines accepted in the ICU. Decisions to transfuse coagulation factors or platelets were left to the attending surgeons and physicians in the ICU. Recently, lack of existing guidelines has been identified as a major issue in Canadian cardiac surgical centers.[15] Similarly, no guidelines were followed for administering additional doses of heparin or protamine during surgery. Nine of the 30 patients received supplemental protamine in the ICU, and this consisted of a single bolus dose of 50 mg administered intravenously. However, there was a time lag of at least 40 min between the supplemental protamine dose and APTT testing, and considering that protamine has a short half life of about seven minutes,[53] it is possible that such small doses may not have affected the ensuing set of laboratory results.

We conclude that anti-Xa levels and APTT are frequently elevated following cardiac surgery. Elevation of APTT does not correlate with plasma anti-Xa levels by the chromogenic assay or whole blood heparin concentrations

as measured by Hepcon HMS *Plus*. Further, elevated APTT may reflect deficiency of coagulation factors or protamine excess following CPB, and more studies are needed to confirm this observation.

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**Conflicts of interest** None declared.

## References

1. *Unsworth-White MJ, Herriot A, Valencia O, et al*. Resternotomy for bleeding after cardiac operation: a marker for increased morbidity and mortality. Ann Thorac Surg 1995; 59: 664–7.
2. *Sellman M, Intonti MA, Ivert T*. Reoperations for bleeding after coronary artery bypass procedures during 25 years. Eur J Cardiothorac Surg 1997; 11: 521–7.
3. *Munoz JJ, Birkmeyer NJ, Dacey LJ, Birkmeyer JD, Charlesworth DC, Johnson ER, et al*. Trends in rates of reexploration for hemorrhage after coronary artery bypass surgery. Northern New England Cardiovascular Disease Study Group. Ann Thorac Surg 1999; 68: 1321–5.
4. *Karkouti K, Wijeysundera DN, Yau TM, et al*. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004; 44: 1453–62.
5. *Koch CG, Li L, Van Wagoner DR, Duncan AI, Gillinov AM, Blackstone EH*. Red cell transfusion is associated with an increased risk for postoperative atrial fibrillation. Ann Thorac Surg 2006; 82: 1747–56.
6. *Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, et al*. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008; 358: 1229–39.
7. *Paparella D, Brister SJ, Buchanan MR*. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med 2004; 30: 1873–81.
8. *Shore-Lesserson L, Reich DL, DePerio M*. Heparin and protamine titration do not improve haemostasis in cardiac surgical patients. Can J Anaesth 1998; 45: 10–8.
9. *Jobes DR, Aitken GL, Shaffer GW*. Increased accuracy and precision of heparin and protamine dosing reduces blood loss and transfusion in patients undergoing primary cardiac operations. J Thorac Cardiovasc Surg 1995; 110: 36–45.
10. *Despotis GJ, Summerfield AL, Joist JH, et al*. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg 1994; 108: 1076–82.
11. *Martin P, Horkay F, Gupta NK, Gebitekin C, Walker DR*. Heparin rebound phenomenon—much ado about nothing? Blood Coagul Fibrinolysis 1992; 3: 187–91.
12. *Gravlee GP, Rogers AT, Dudas LM, et al*. Heparin management protocol for cardiopulmonary bypass influences postoperative heparin rebound but not bleeding. Anesthesiology 1992; 76: 393–401.
13. *Esposito RA, Culliford AT, Colvin SB, Thomas SJ, Lackner H, Spencer FC*. Heparin resistance during cardiopulmonary bypass. The role of heparin pretreatment. J Thorac Cardiovasc Surg 1983; 85: 346–53.
14. *Teoh KH, Young E, Blackall MH, Roberts RS, Hirsh J*. Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery? J Thorac Cardiovasc Surg 2004; 128: 211–9.
15. *Taneja R, Fernandes P, Marwaha G, Cheng D, Bainbridge D*. Perioperative coagulation management and blood conservation in cardiac surgery: a Canadian survey. J Cardiothorac Vasc Anesth 2008; 22: 662–9.
16. *Barstad RM, Stephens RW, Hamers MJ, Sakariassen KS*. Protamine sulphate inhibits platelet membrane glycoprotein Ib-von Willebrand factor activity. Thromb Haemost 2000; 83: 334–7.
17. *Mochizuki T, Olson PJ, Szlam F, Ramsay JG, Levy JH*. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. Anesth Analg 1998; 87: 781–5.
18. *Nybo M, Madsen JS*. Serious anaphylactic reactions due to protamine sulfate: a systematic literature review. Basic Clin Pharmacol Toxicol 2008; 103: 192–6.
19. *Nielsen VG*. Protamine enhances fibrinolysis by decreasing clot strength: role of tissue factor-initiated thrombin generation. Ann Thorac Surg 2006; 81: 1720–7.
20. *Palermo LM, Andrews RW, Ellison N*. Avoidance of heparin contamination in coagulation studies drawn from indwelling lines. Anesth Analg 1980; 59: 222–4.
21. *Santoro S, Eby C*. Laboratory evaluation of hemostatic disease. In: Hoffman R, editor. Hematology-Basic Principles and Practice. 3rd ed. Philadelphia: Churchill Livingstone; 2000. p. 1841–9.
22. *Armitage P, Berry G*. Statistical Methods in Research, vol. 2. Oxford: Backwell Scientific Publications; 1987.
23. *Snedecor G, Cochran G*. Statistical Methods, vol. 6. Iowa: The Iowa State Press; 1967.
24. *Hirsh J, Warkentin TE, Shaughnessy SG, et al*. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119: 64S–94S.
25. *Ramsey G, Arvan DA, Stewart S, Blumberg N*. Do preoperative laboratory tests predict blood transfusion needs in cardiac operations? J Thorac Cardiovasc Surg 1983; 85: 564–9.
26. *Nuttall GA, Oliver WC, Beynen FM, Santrach PJ, Strickland RA, Murray MJ*. Determination of normal versus abnormal activated partial thromboplastin time and prothrombin time after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1995; 9: 355–61.
27. *Despotis GJ, Filos KS, Zoys TN, Hogue CW Jr, Spitznagel E, Lappas DG*. Factors associated with excessive postoperative blood loss and hemostatic transfusion requirements: a multivariate analysis in cardiac surgical patients. Anesth Analg 1996; 82: 13–21.
28. *Nuttall GA, Oliver WC, Ereth MH, Santrach PJ*. Coagulation tests predict bleeding after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1997; 11: 815–23.
29. *Chavez JJ, Weatherall JS, Strevels SM, Liu F, Snider CC, Carroll RC*. Evaluation of a point-of-care coagulation analyzer on patients undergoing cardiopulmonary bypass surgery. J Clin Anesth 2004; 16: 7–10.
30. *Blome M, Isgro F, Kiessling AH, et al*. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost 2005; 93: 1101–7.
31. *Bishop CV, Renwick WE, Hogan C, Haeusler M, Tuckfield A, Tatoulis J*. Recombinant activated factor VII: treating postoperative hemorrhage in cardiac surgery. Ann Thorac Surg 2006; 81: 875–9.

32. *Welsby IJ, Jiao K, Ortel TL, et al*. The kaolin-activated thrombelastograph predicts bleeding after cardiac surgery. J Cardiothorac Vasc Anesth 2006; 20: 531–5.
33. *Chong SK, Kum SP, Mi JY, Kyoung OK*. Effects of intravascular volume therapy using hydroxyethyl starch (130/0.4) on postoperative bleeding and transfusion requirements in children undergoing cardiac surgery: a randomized clinical trial. Acta Anaesthesiol Scand 2006; 50: 108–11.
34. *Niranjan G, Asimakopoulos G, Karagounis A, Cockerill G, Thompson M, Chandrasekaran V*. Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on-versus off-cardiopulmonary bypass: a randomised trial. Eur J Cardiothorac Surg 2006; 30: 271–7.
35. *Mohr R, Martinowitz U, Golan M, Ayala L, Goor DA, Ramot B*. Platelet size and mass as an indicator for platelet transfusion after cardiopulmonary bypass. Circulation 1986; 74: III153–8.
36. *Khuri SF, Wolfe JA, Josa M, et al*. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. J Thorac Cardiovasc Surg 1992; 104: 94–107.
37. *Essell JH, Martin TJ, Salinas J, Thompson JM, Smith VC*. Comparison of thromboelastography to bleeding time and standard coagulation tests in patients after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1993; 7: 410–5.
38. *Gravlee GP, Arora S, Lavender SW, et al*. Predictive value of blood clotting tests in cardiac surgical patients. Ann Thorac Surg 1994; 58: 216–21.
39. *Nuttall GA, Oliver WC Jr, Beynen FM, Dull JJ, Murray MJ, Nichols WL*. Intraoperative measurement of activated partial thromboplastin time and prothrombin time by a portable laser photometer in patients following cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1993; 7: 402–9.
40. *Miller BE, Mochizuki T, Levy JH, et al*. Predicting and treating coagulopathies after cardiopulmonary bypass in children. Anesth Analg 1997; 85: 1196–202.
41. *Olson JD, Arkin CF, Brandt JT, et al*. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. Arch Pathol Lab Med 1998; 122: 782–98.
42. *Nelson DE*. Current considerations in the use of the APTT in monitoring unfractionated heparin. Clin Lab Sci 1999; 12: 359–64.
43. *Adcock DM, Kressin DC, Marlar RA*. Effect of 32% vs. 38% sodium citrate concentration on routine coagulation testing. Am J Clin Pathol 1997; 107: 105–10.
44. *Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J*. Establishing a therapeutic range for heparin therapy. Ann Intern Med 1993; 119: 104–9.
45. *Murray DJ, Brosnahan WJ, Pennell B, Kapalanski D, Weiler JM, Olson J*. Heparin detection by the activated coagulation time: a comparison of the sensitivity of coagulation tests and heparin assays. J Cardiothorac Vasc Anesth 1997; 11: 24–8.
46. *Despotis GJ, Joist JH, Hogue CW Jr, et al*. More effective suppression of hemostatic system activation in patients undergoing cardiac surgery by heparin dosing based on heparin blood concentrations rather than ACT. Thromb Haemost 1996; 76: 902–8.
47. *Bevan DH*. Cardiac bypass haemostasis: putting blood through the mill. Br J Haematol 1999; 104: 208–19.
48. *Inagaki M, Goto K, Katayama H, Benson KT, Goto H, Arakawa K*. Activated partial thromboplastin time-protamine dose relation in the presence and absence of heparin. J Cardiothorac Anesth 1989; 3: 734–6.
49. *Carr ME Jr, Carr SL*. At high heparin concentrations, protamine concentrations which reverse heparin anticoagulant effects are insufficient to reverse heparin anti-platelet effects. Thromb Res 1994; 75: 617–30.
50. *Perkash A*. A comparison of the quantitative action of protamine and heparin on blood coagulation. Significance in clinical and laboratory usage. Am J Clin Pathol 1980; 73: 676–81.
51. *Hardy JF, Belisle S, Robitaille D, Perrault J, Roy M, Gagnon L*. Measurement of heparin concentration in whole blood with the Hepcon/HMS device does not agree with laboratory determination of plasma heparin concentration using a chromogenic substrate for activated factor X. J Thorac Cardiovasc Surg 1996; 112: 154–61.
52. *Shore-Lesserson L*. Transfusion algorithms: more than just alphabet soup? J Cardiothorac Vasc Anesth 1997; 11: 813–4.
53. *Butterworth J, Lin YA, Prielipp R, Bennett J*. James R The pharmacokinetics and cardiovascular effects of a single intravenous dose of protamine in normal volunteers. Anesth Analg 2002; 94: 514–22.