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Anticoagulation monitoring during vascular surgery: accuracy of the Hemochron® low range activated clotting time (ACT-LR)

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Background. Activated clotting time (ACT) is currently used to monitor high concentrations of heparin anticoagulation. A new instrument, the Hemochron® Jr Signature device, has been specifically designed to measure ACT in low-range heparin plasma concentrations (ACT-LR). The purpose of this study was to compare ACT-LR with anti-Xa activity in patients receiving low-dose i.v. heparin during vascular surgery.

Methods. Thirty patients, undergoing arterial vascular surgery, were included in the study and received unfractionated heparin (initial dose 50 u kg^{-1}). One hundred and thirty-two pairs of blood samples were simultaneously collected during surgery to determine ACT-LR and anti-Xa activity. Pearson correlation, Kappa test, ROC curve and a specific clinical interpretation of the correlation were performed.

Results. ACT-LR ranged from 68 to 380 s, anti-Xa activity from 0 to 1.45 u ml^{-1}. We observed a strong correlation between anti-Xa activity and ACT-LR (r^2=0.87; P<0.0001). Accuracy of ACT-LR was good for anti-Xa activity up to 0.6 u ml^{-1} (Kappa, 0.94; accuracy, 97%) and 0.8 u ml^{-1} (Kappa, 0.79; accuracy, 90%), and poor for anti-Xa activity above 1 u ml^{-1} (Kappa, 0.59). A clinical interpretation of the correlation graph found 98% of measured ACT-LR values to be accurate.

Conclusion. Hemochron® Jr Signature provides measurements of ACT-LR, which are accurate for monitoring heparin anticoagulation at anti-Xa activity below 0.8 u ml^{-1}.

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Heparin-induced anticoagulation is currently used during arterial vascular surgery to prevent thrombosis and accumulation of thrombi at sites of vascular injury. Unfractioned heparin (UFH) is administered before clamping and blood flow interruption. The goals are to achieve adequate anticoagulation quickly and to maintain a steady anticoagulation concentration until cross-clamp removal. Although the risk of thrombotic events is not well established in this context there is consensus on the necessity of anticoagulation during vascular surgery.

The 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy recently recommended a fairly high concentration of anticoagulation during surgery with an initial dose of 100–150 u kg^{-1} of UFH before cross-clamping.[1] It was also recommended to supplement this dose every 50 min until circulation is re-established. But these recommendations apply only to situations where there is no monitoring of heparin anticoagulation such as activated clotting time (ACT). Curiously, no anticoagulation monitoring device was specified. With a high variability of heparin responsiveness and plasma elimination half-life,[2–4] anticoagulation monitoring may improve anticoagulation during vascular surgery. Few studies have emphasized the role of anticoagulation monitoring in this setting.[5–9]

ACT was first described by Hattersley[10] and represents a whole blood clotting time. Accelerated coagulation is

obtained by activation of the contact pathway, using either kaolin or celite as an activator. ACT measurement with point-of-care devices is currently used during procedures requiring anticoagulation, such as cardiopulmonary bypass, interventional cardiology and haemodialysis.[11 12] Maintaining adequate anticoagulation by monitoring ACT can prevent thrombosis of intravascular devices or extracorporeal circuits.[13–15] In these settings, ACT has been well correlated with anti-Xa activity.[16–18] This correlation was found in high heparin anticoagulation conditions (anti-Xa activity between 4 and 6 u ml^{-1}). However, traditional ACT measurement devices may not be accurate at lower heparin anticoagulation concentrations typically encountered in vascular surgery.

Recently, a new instrument for ACT assessment has become available, the Hemochron® Jr II Signature device (ITC, International Technidyne Corp., Edison, NJ, USA). It includes specific cartridges which provide good reproducibility to measure ACT in low anti-Xa activity settings (ACT-LR, *low range*). ACT-LR has already been compared with laboratory-based anti-Xa activity in patients undergoing extracorporeal membrane oxygenation (ECMO).[19] Several factors involved in the relationship between ACT and laboratory assay could explain the poor correlation found.

The purpose of our study was 2-fold: (i) to test the relation between ACT-LR measurements and anti-Xa activity; (ii) to evaluate medical decisions based on ACT-LR monitoring during vascular surgery.

Materials and methods

Patients and procedure

Thirty consecutive patients, undergoing arterial vascular surgery, were included in the study. Additional inclusion criteria were (i) age (>18 yr); (ii) ASA physical status (I–III). Exclusion criteria were (i) documented heparin allergy; (ii) chronic renal failure with a clearance below 30 ml min^{-1} (Cockroft formula). The study protocol was approved by the Hospital Ethics Committee. Written, informed consent was obtained from all patients.

All patients were premedicated 1 h before surgery with cetirizine (1 mg kg^{-1}). Anaesthesia was induced with sufentanil (0.2 μg kg^{-1}), propofol (2 mg kg^{-1}), atracurium (0.5 mg kg^{-1}) and maintained with isoflurane (0.6–1%) and supplements of these drugs. All patients were equipped with an arterial catheter, according to the standard protocol of our hospital. Anticoagulation was achieved with 50 u kg^{-1} of bovine sodium heparin (Choay Sanofi-Synthélabo, Paris, France) injected before artery clamping and blood flow interruption. Supplemental 25 u kg^{-1} heparin doses were administered every 60 min until cross-clamp removal. Heparin reversal was obtained with protamine, 50 u kg^{-1} (Choay Sanofi-Synthélabo, Paris, France), injected after cross-clamp removal. None of the patients received aminocapric acid or aprotinin.

Blood samples and ACT-LR measurements were collected at various steps as follows: (i) at baseline; (ii) 5 min after heparin bolus; (iii) during cross-clamp: 15, 30, 45, 60 and 90 min after the initial bolus injection; and (iv) at 5 min after protamine infusion. Samples were drawn from an arterial line with no heparin added to the flush solution. Five millilitres of fresh whole blood were collected to measure anti-Xa activity. Vacutainer® tubes (Becton Dickinson, Meylan, France) containing sodium citrate were used and 1 ml of fresh whole blood was collected to measure ACT-LR.

ACT-LR measurement

ACT-LR (*low range*) measurements were performed according to the manufacturer's instructions, using the portable Hemochron® Jr II Signature device (ITC, NJ, USA). Specific cartridges containing celite (low range) were inserted into the instrument for 1 min prewarming at 37°C. Celite was used as a contact pathway activator to accelerate coagulation.

Measurement of anti-Xa activity

Anti-Xa activity was immediately determined in citrated plasma. Thereby, the intensity of inhibition of the hydrolysis of a chromogenic substrate by factor Xa was determined in presence of heparin–antithrombin complexes (Hyphen-Biomed, Andresy, France).

Statistical analysis

Data were expressed as mean (SD). Spearman's correlation was used to assess the relation between ACT-LR and anti-Xa activity. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive accuracy of ACT-LR for anti-Xa activity. Three different anti-Xa activity settings were defined. As guidelines recommend therapeutic anti-Xa activity of 0.6–0.7 u ml^{-1} in venous and arterial thrombosis,[1 20] 0.6, 0.8 and 1 u ml^{-1} were tested. For each anti-Xa activity target, sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated. Areas under the ROC curves were calculated for each threshold. Finally, the degree of concordance between ACT-LR and anti-Xa activity was studied using the Kappa coefficient. Excellent concordance was defined as Kappa coefficient between 0.81 and 1. Good concordance was defined as Kappa coefficient between 0.8 and 0.61. Below these values concordance was considered low.

As statistical correlation neither include clinical significance of accuracy nor describe the type of eventual estimation errors, the clinical relevance of the ACT determination was examined using a graph derived from the error grid analysis (EGA). This concept was initially developed to assess the accuracy of home blood glucometers.[21] The EGA takes into account the clinical implications

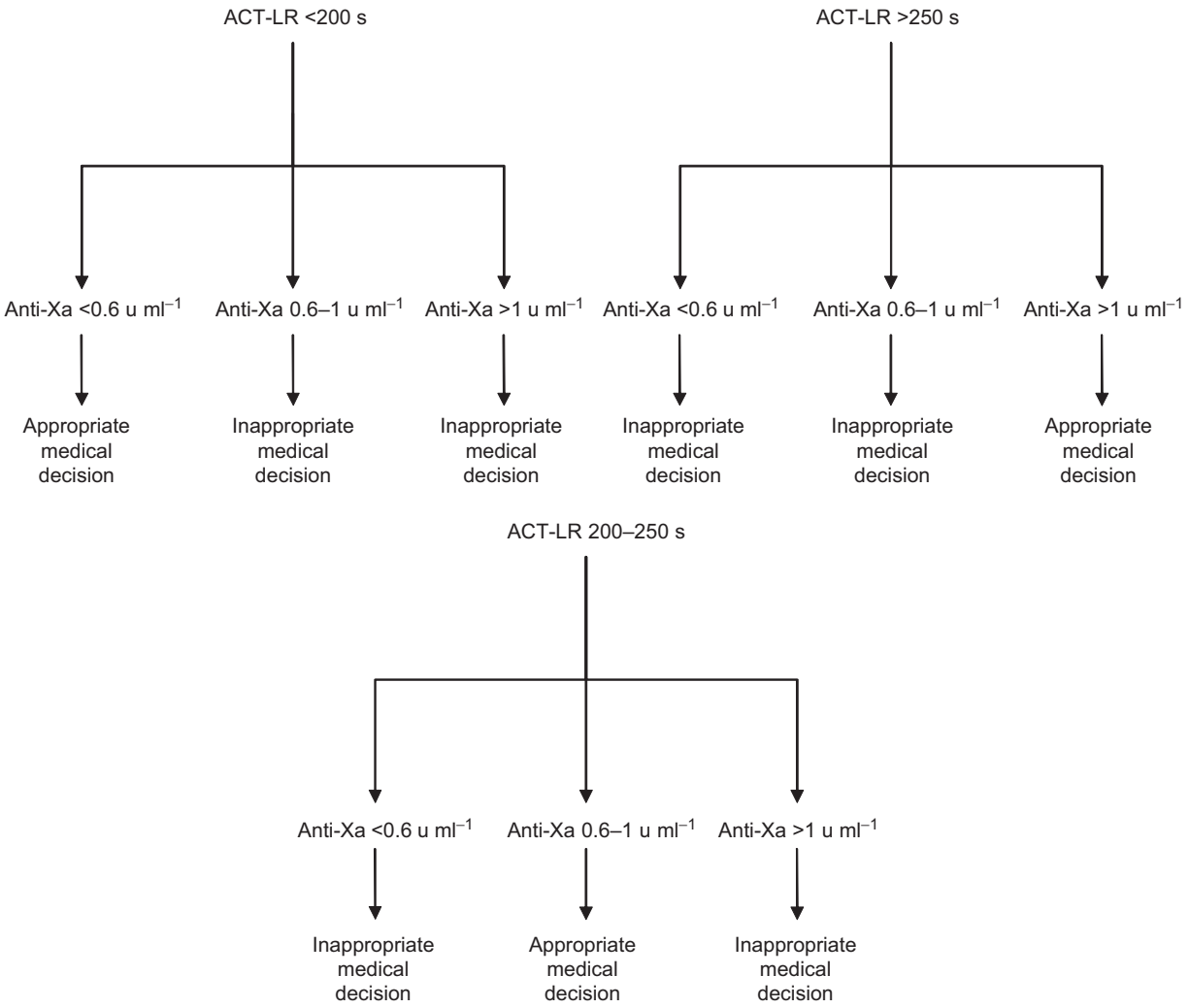

Fig 1 Relevance of clinical decisions based on ACT-LR values during vascular surgery; the error grid analysis graph was obtained with these assumptions. ACT-LR, activated clotting time low range.

of any treatment decision based on ACT-LR measurements and is based on the assumption represented on Figure 1. The lower threshold was chosen in respect to therapeutic anti-Xa activity used in venous or arterial thrombosis or acute limb ischaemia.[20] Six zones are described on the EGA regression graph (Fig. 4). Upper and lower zones A represent ACT values that either deviated less than 10% from the values obtained with the linear regression equation, or were below 200 s when anti-Xa activity was below 0.6 u ml^{-1}. An ACT value in zone A is accurate and a clinical decision based on this value would be safe. Upper and lower zones C represent ACT values, not reflecting anti-Xa activity. An ACT value in zone C is not accurate and a clinical decision based on it could be dangerous. Zone C is labelled as 'erroneous treatment'. Upper and lower zones B represent ACT values which deviate more than 10% from values obtained with the linear regression equation, but are outside zone C. An ACT value in zone B is moderately accurate and an erroneous clinical decision based on it would be safe. Zone B is labelled as 'benign errors'.

Statistics were computed with StatView 5.0 (SAS Institute, Cary, CA, USA) and SPSS 10.0 (SPSS France, Paris, France). $P<0.05$ was considered significant.

Results

Blood samples were obtained from 30 consecutive patients [mean age, 69 (10) yr, 4 women, 26 men] included in the protocol. Surgical procedures were carotid endarterectomy (12 patients), infrarenal aorta surgery (10 patients) and peripheral vascular surgery (8 patients). Mean duration of arterial cross-clamp was 25 (10) min for carotid endarterectomy and 68 (23) min for aorta and peripheral vascular surgery. Thirteen patients received aspirin and nine patients received heparin up to the morning of surgery. No thrombotic event occurred during or after the intervention.

A total of 264 duplicate anti-Xa activity and Hemochron® ACT-LR measurements were obtained simultaneously

Table 1 Mean ACT-LR and anti-Xa activity during vascular surgery. Data are mean (SD). Units of measurements are seconds for ACT and u ml^{-1} for anti-Xa activity. ACT-LR, activated clotting time low range

Measurements	Carotid endarterectomy (n=12)		Aorta and peripheral vascular surgery (n=18)	
	ACT-LR	Anti-Xa activity	ACT-LR	Anti-Xa activity
Baseline	152 (33)	0.1 (0.1)	158 (13)	0.1 (0.1)
5 min	275 (58)	1.2 (0.2)	270 (25)	0.9 (0.2)
15 min	257 (48)	0.9 (0.2)		
30 min			240 (21)	1.1 (0.2)
45 min			243 (28)	1 (0.2)
60 min			240 (61)	0.7 (0.1)
90 min			206 (8)	0.6 (0.1)
After protamine	160 (19)	0.2 (0.1)	166 (17)	0.2 (0.1)

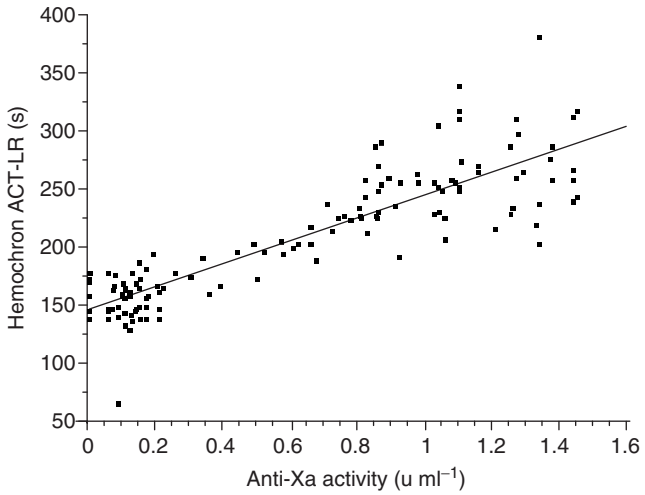

Fig 2 Linear regression analysis between ACT-LR measurements and anti-Xa activity. Bold line = regression line. ACT-LR, activated clotting time low range.

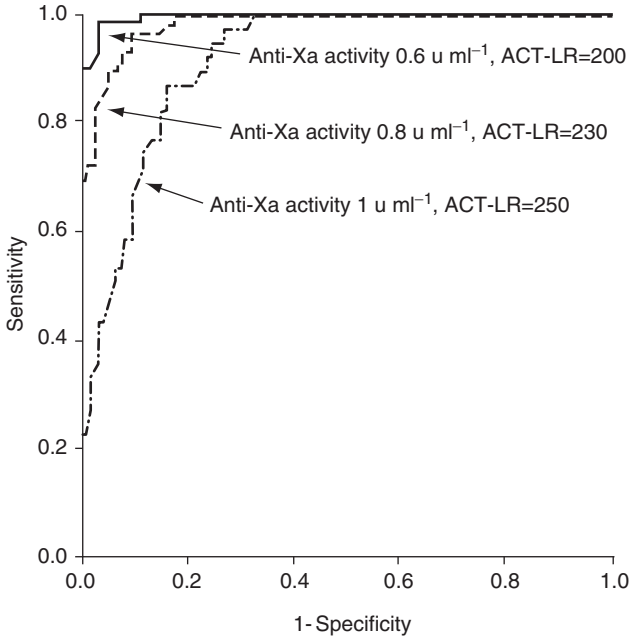

Fig 3 ROC curves for ACT-LR in predicting three different anti-Xa activity: 0.6, 0.8, 1 u ml^{-1}. For each threshold, optimal ACT-LR regarding Kappa values are represented.

from 132 blood samples. Hemochron® ACT-LR ranged from 68 to 380 s, anti-Xa activity from 0 to 1.45 u ml^{-1}.

ACT-LR and anti-Xa activity are reported in Table 1. Results for carotid surgery, and aortic and peripheral vascular surgery are presented separately.

Taking into account all determinations, significant correlation was observed between ACT-LR obtained with Hemochron® Jr Signature and anti-Xa activity (n=132; y=148.4+99.67 x, r^2=0.87, P<0.001) (Fig. 2).

The ROC curves for ACT-LR predicting anti-Xa activity are shown in Figure 3 and the different characteristics of each test are presented in Table 2. For an anti-Xa activity above 0.6 u ml^{-1}, the optimum ACT-LR cut-off was 200 s (Fig. 3), with an excellent concordance (Kappa, 0.94), 128 blood samples (97%) were correctly classified by the Hemochron® system. For an anti-Xa activity above 0.8 u ml^{-1}, the optimal cut-off was 230 s (Fig. 3), with a good concordance (Kappa, 0.79), 119 blood samples (90%) were correctly classified. For an anti-Xa activity above 1 u ml^{-1}, however, the optimum cut-off was 250 s (Fig. 3), with poor concordance (Kappa, 0.59) and only 110 blood samples (83%) were classified correctly.

The EGA-derived graph is represented in Figure 4. One hundred and two ACT values (77%) fell into zone A (clinically accurate), while 28 (21%) fell into zone B (benign errors). Two ACT values (2%) fell into zone C (erroneous treatment).

Discussion

ACT was initially described to assess the degree of heparin-induced anticoagulation during procedures such as cardiopulmonary bypass interventional, cardiology and haemodialysis.[14 22 23] In all these settings high-concentration anticoagulation is mandatory. Anticoagulation monitoring is not systematically used during vascular surgery. Traditionally, ACT measurement devices are not powerful on low concentrations of anticoagulation (anti-Xa activity below 1 u ml^{-1}). We report the first study evaluating the Hemochron® ACT-LR monitoring during arterial vascular surgery. Our results show good correlation between ACT-LR and anti-Xa activity. In this particular setting ACT-LR measurements provide correct estimation of anti-Xa activity in more than 95% of total cases. Accuracy of Hemochron® ACT-LR seems to be best for anti-Xa activity below 1 u ml^{-1}. Assessment of ACT-LR appears to be appropriate to evaluate heparin-induced anticoagulation during vascular surgery.

The optimum anticoagulation required for vascular surgery with arterial clamping remains to be determined. For percutaneous coronary intervention the optimum

Table 2 Accuracy of ACT-LR. Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value

	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	Area under the ROC curve	Kappa values
ACT 200 s to estimate anti-Xa activity >0.6 u ml^{-1}	97	97	97	97	97	0.99	0.94
ACT 230 s to estimate anti-Xa activity >0.8 u ml^{-1}	81	97	96	87	90	0.98	0.79
ACT 250 s to estimate anti-Xa activity >1 u ml^{-1}	69	91	73	89	83	0.91	0.59

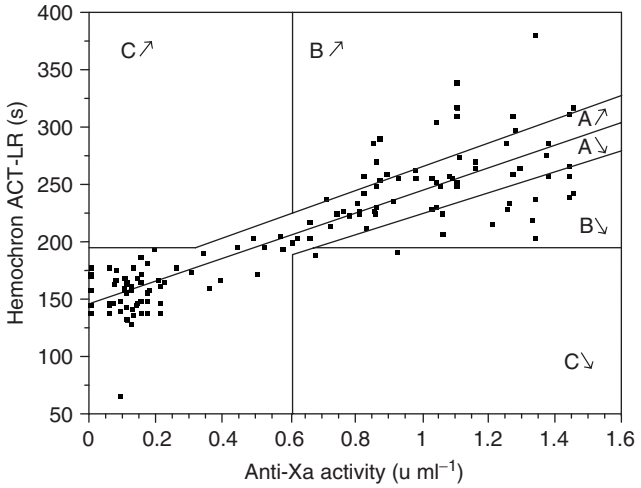

Fig 4 Specific relationship between Hemochron® ACT-LR measurements and anti-Xa activity. Pearson's correlation and error grid analysis graph showing the categorization of ACT-LR in six zones describing the clinical implications of estimate errors. The median slope represents the linear regression slope. The upper divergent diagonal represents a 10% overestimation and the lower a 10% underestimation. Other zones are defined as described in Materials and methods. ACT-LR, activated clotting time low range.

concentration of ACT is defined and linked to outcome.[13] Target values during cardiopulmonary bypass have also been evaluated.[14 15] Target values for anticoagulation, recommended in similar situations, may be useful to estimate the required dose of heparin during surgical cross-clamp. For venous thrombosis or acute arterial ischaemia, the desired anti-Xa activity concentration is 0.3–0.7 u ml^{-1}, with a recommended initial heparin dose of 50–80 u kg^{-1}.[24] After these assumptions, we tested three concentrations of anti-Xa activity (0.6, 0.8 and 1 u ml^{-1}) to evaluate the ability of the Hemochron® JR Signature to detect therapeutic ranges. These choices are subjective, but consistent with clinical practice. The assumption of target values for anticoagulation has allowed biological and clinical evaluation of ACT-LR during vascular surgery.

In this study, heparin anticoagulation was determined by assessing the anti-Xa activity. Although the usual therapeutic doses of heparin could be monitored by the activated partial thromboplastin time (APTT),[20] anti-Xa activity seems to be more directly linked to heparin-induced anticoagulation. Indeed there is a wide variation in APTT results among different laboratories.[25] The APTT results depend on the laboratory method used, and could range from 48 to 108 s at therapeutic heparin plasma concentration.[26 27] For this reason, the use of anti-Xa activity instead of APTT would be more relevant in clinical practice.

One major finding in this study was a positive and significant correlation between anti-Xa activity and ACT-LR. Previous studies have already described good correlation between ACT and anti-Xa activity, specially during cardiac surgery.[11] On the other hand, no correlation had been reported for low concentrations of anticoagulation between Hemochron® Jr ACT-LR values and anti-Xa activity during ECMO.[19] Our different results could be explained by physiological factors during ECMO, such as intense coagulopathy, hypothermia and haemodilution. This study confirms that low anti-Xa activity is the most appropriate setting for Hemochron® Jr II Signature device with low-range cartridges. Secondarily, we tested its ability to differentiate three different concentrations of anticoagulation. With anti-Xa activity above 0.6 or 0.8 u ml^{-1}, the corresponding ACT-LR target values were 200 and 230 s, respectively, for adequate anticoagulation. Within these thresholds, 97 and 90% of ACT-LR values were found to be in accordance with anti-Xa activity. PPV (97 and 96%, respectively) and Sp values (both 97%) make ACT-LR a valuable tool to detect dangerous under-anticoagulation. Based on ACT-LR values, rapid correction could be started safely, helping the physician to maintain optimum anticoagulation during surgery. However, low accuracy was observed for anti-Xa activity above 1 u ml^{-1}, ACT-LR does not seem to be accurate for monitoring heparin anticoagulation in this range.

Furthermore, analysis of the EGA-derived graph showed ACT-LR measurements to be clinically reliable. ACT-LR values were in perfect agreement with anti-Xa activity in 77% of total cases, making a consequent medical decision safe. In 21% of total cases, ACT-LR values were in zone B, considered as 'benign errors'. Despite the mild inaccuracy of ACT measurements, consequent clinical decisions would not be dangerous. Indeed, the only consequence was an over-anticoagulation which could induce postoperative bleeding in the absence of protamine administration. Nevertheless, as reported,[28] the risk of postoperative bleeding is low even if heparin-induced anticoagulation is not routinely reversed. Finally, only

2% of all ACT-LR measurements, in zone C, were failures which could potentially lead to an inappropriate treatment.

There are, however, some reservations concerning our study. The patients included were heterogeneous. Almost half of the patients took platelet antagonist treatment up to the day of surgery. All patients undergoing endarterectomy received aspirin preoperatively without discontinuation, as recommended by recent guidelines.[1] Although activation of coagulation during vascular surgery results from stimulation of both intrinsic and extrinsic pathways, local platelet activation may occur after application of cross-clamp. Indeed, increased platelet aggregation has been found after coronary artery flow interruption.[29] We hypothesized that platelet antagonist agents decrease this activation and take part in the prevention of thrombus formation. As previously described, Hemochron® ACT is not correlated with any platelet antagonist agent treatment.[30] Also, anti-aggregation induced by platelet antagonists is not taken into account in ACT-LR values. For this reason, it seems reasonable to individualize populations of patients who receive antiplatelet agents in future studies.

To achieve anticoagulation before cross-clamp application, we used a heparin dose of 50 u kg^{-1}, which is below the recommended dose of 100–150 u kg^{-1}.[1] Consequently, only low anti-Xa activity were studied. If a higher dose had been used, a poorer correlation between ACT-LR measurements and anti-Xa activity might have been found. These choices are arguable, but the optimal dose of heparin during vascular surgery remains undetermined. We have been using this dose for years in our hospital without notable adverse events. We based our choice of concentration of anticoagulation during cross-clamp on therapeutic recommendations for venous and arterial thrombosis. Although heparin-induced anticoagulation is linked to cardiac outcome,[31] no study has investigated the links between different anti-Xa activity during vascular surgery and outcome. Also a further study will be needed to evaluate the use of Hemochron® ACT-LR as an anticoagulation monitor for doses higher than 50 u kg^{-1}.

Finally, ACT-LR measurements must be directly compared with other methods of point-of-care testing of heparinization such as conventional ACT and APTT.

In conclusion, our study has demonstrated the accuracy of Hemochron® ACT-LR anticoagulation monitoring during vascular surgery with the use of small doses of heparin (50 u kg^{-1}). ACT-LR and anti-Xa activity are well correlated and ACT-LR is clinically relevant for low anti-Xa activity. After cross-clamping, target ACT-LR values correlated with anti-Xa activity and can be used to titrate heparin up to the required concentration of anticoagulation.

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