Letter to the Editor
Diagnostic Hematology

Ann Lab Med 2025;45:105-108
https://doi.org/10.3343/alm.2024.0216
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Endogenous Thrombin Potential Level Helps Predict High Blood Loss in Patients Undergoing Cardiac Surgery

Yujin Jung, M.D.[1,*], Jae Woong Choi, M.D., Ph.D.[2,*], Ho Young Hwang

Dear Editor,

Excessive bleeding is a major complication in 10% of patients undergoing cardiac surgery [1, 2]. Cardiopulmonary bypass (CPB) can disrupt hemostasis by activating the contact system when blood contacts an artificial surface, affecting postoperative bleeding. Increased postoperative bleeding heightens mortality rates and risks of other adverse effects, including stroke, re-exploration, hospitalization, and mechanical ventilation requirements [2, 3]. Accurate prediction of blood loss following cardiac surgery could enhance patient prognosis.

Coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT) and rotational thromboelastometry, are administered pre- and postoperatively to assess hemostasis; however, their clinical utility in predicting postoperative bleeding is controversial [4-7]. The thrombin generation assay (TGA), which helps measure thrombin volume, reflects the balance of pro- and anticoagulant activities and, therefore, the overall hemostasis status. We previously demonstrated that the preoperative endogenous thrombin potential (ETP) helps predict high blood loss within 24 hrs postoperatively [8].

In this study, we aimed to accurately predict blood loss following cardiac surgery to enhance patient prognosis. Accordingly, we enrolled 89 patients at Seoul National University Hospital (Seoul, Korea) who underwent heart or aortic surgery with CPB from June 2021 to May 2022. This included patients undergoing heart valve replacement (N=45), aorta replacement (N=21), and combined valve and aorta replacement (N=23). The diagnoses included aortic valve stenosis (N=34), bicuspid aortic valve (N=28), aortic aneurysm (N=12), aortic arch aneurysm (N=4), aortic valve regurgitation (N=3), ascending aorta aneurysm (N=2), aortic stenoinsufficiency (N=2), and infective endocarditis, aortic dissection, aortic coarctation, and annuloaortic ectasia (N=1 each). The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2104-231-1217). Written informed consent was obtained from all participants. The median patient age was 70 yrs (interquartile range [IQR]), 63–77). TGA was performed using blood samples collected pre-surgery (T0) and immediately (T1),

1 day (T2), and 3 days (T3) post-surgery to measure ETP, lag time, peak height, time-to-peak, velocity index, and start tail, using a thrombinoscope (Thrombinoscope, Maastricht, The Netherlands). Thrombin generation curves were analyzed using the Thrombinoscope software (Diagnostica Stago, Asnières-sur-Seine, France). Data on total blood loss volume (BLV) (i.e., total output until chest drain removal), PT, aPTT, and CPB time were retrieved from electronic medical records. The median time for chest drain removal was 4 days (IQR, 3–7). MedCalc v20.215 (MedCalc Software, Ostend, Belgium) was used to determine optimal cut-off values from ROC curves, and logistic regression and *t*-tests were performed using SPSS v26.0 (SPSS, Chicago, IL, USA).

Patients were divided into low- (≤1,467 mL, N=45) and high- (>1,467 mL, N=44) blood-loss groups based on the median BLV [8]. ETP levels at T0 and T2 were significantly lower in the high-blood-loss group than in the low-blood-loss group (Fig. 1). The levels of other TGA factors did not differ between the two groups at any time point.

The ETP level at T2 decreased with increasing CPB time (Pearson's correlation coefficient, r=–0.322, P=0.003) (data not shown). A low ETP level (≤1,191.57 nM·min) pre-surgery had a significantly increased odds ratio (OR) for high blood loss risk (Table 1). We also measured ETP from pre- to 3 days post-surgery. Pre-surgery ETP levels helped predict total blood loss until chest drain removal beyond the first 24 hrs. Low ETP levels at T2 (≤813.12 nM·min) and T3 (≤1,268.23 nM·min) had high ORs. Low start-tail levels were significantly predictive at T0 and T3. PT and aPTT do not have high predictive value for clinically significant bleeding events [9]. In our study, aPTT remained

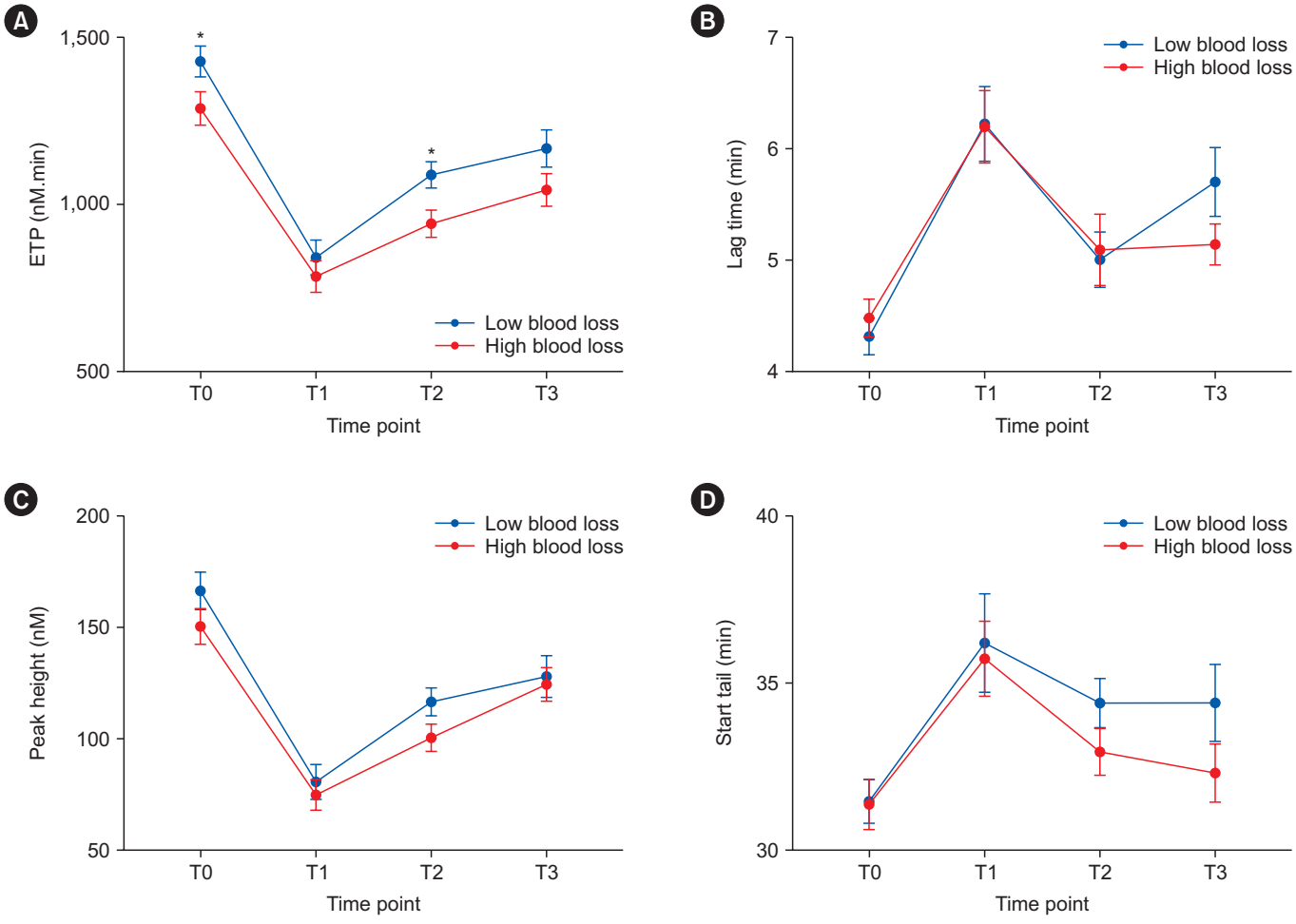

Fig. 1. Comparison of TGA results between the low- (N=45) and high- (N=44) blood-loss groups. (A) ETP, (B) lag time, (C) peak height, and (D) start tail. The groups were compared using independent *t*-tests, and only significant results (*P<0.05) are shown.
Abbreviations: TGA, thrombin generation assay; ETP, endogenous thrombin potential; T0, pre-surgery; T1, immediately post-surgery; T2, 1 day post-surgery; T3, 3 days post-surgery.

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Table 1. Predictive value of coagulation markers for risk of high blood loss

Coagulation markers	OR	95% CI	*P*
Pre-surgery			
ETP (≤1,191.57 nM·min vs. >1,191.57 nM·min)	3.47	1.25–9.61	0.017
Lag time (>3.79 min vs. ≤3.79 min)	0.59	0.21–1.61	0.300
Peak height (≤131.49 nM vs. >131.49 nM)	2.08	0.79–5.46	0.136
Time-to-peak (≤6.67 min vs. >6.67 min)	0.15	0.02–1.27	0.081
Velocity index (≤45.56 nM/min vs. >45.56 nM/min)	0.53	0.21–1.38	0.194
Start tail (≤3 2 min vs. >32 min)	2.96	1.17–7.50	0.022
PT (>upper limit of normal vs. ≤upper limit of normal)	1.81	0.40–8.16	0.442
Immediately post-surgery			
ETP (≤476.18 nM·min vs. >476.18 nM·min)	2.56	0.61–10.74	0.198
Lag time (≤5.8 min vs. >5.8 min)	1.86	0.79–4.37	0.154
Peak height (≤62.88 nM vs. >62.88 nM)	1.81	0.74–4.46	0.195
Time-to-peak (≤8.67 min vs. >8.67 min)	1.56	0.60–4.02	0.361
Velocity index (≤13.44 nM/min vs. >13.44 nM/min)	2.04	0.82–5.07	0.123
Start tail (≤37 min vs. >37 min)	1.47	0.63–3.45	0.376
PT (>upper limit of normal vs. ≤upper limit of normal)	1.92	0.17–22.14	0.601
aPTT* (>upper limit of normal vs. ≤upper limit of normal)	0.76	0.18–3.12	0.700
One day post-surgery			
ETP (≤813.12 nM·min vs. >813.12 nM·min)	5.53	1.63–18.75	0.006
Lag time (≤4.67 min vs. >4.67 min)	1.35	0.58–3.14	0.486
Peak height (≤96.66 nM vs. >96.66 nM)	3.36	1.31–8.61	0.012
Time-to-peak (>7.33 min vs. ≤7.33 min)	1.72	0.63–4.70	0.287
Velocity index (≤26.82 nM/min vs. >26.82 nM/min)	1.94	0.80–4.69	0.142
Start tail (≤30.85 min vs. >30.85 min)	2.55	0.86–7.57	0.093
PT (>upper limit of normal vs. ≤upper limit of normal)	3.09	1.15–8.27	0.025
Three days post-surgery			
ETP (≤1,268.23 nM·min vs. >1,268.23 nM·min)	3.87	1.54–9.76	0.004
Lag time (≤7 min vs. >7 min)	6.74	1.34–33.93	0.021
Peak height (≤121.97 nM vs. >121.97 nM)	1.65	0.71–3.84	0.248
Time-to-peak (≤14.67 min vs. >14.67 min)	9.85	1.07–90.39	0.043
Velocity index (>13.71 nM/min vs. ≤1 3.71 nM/min)	3.63	0.90–14.73	0.071
Start tail (≤27 min vs. >27 min)	4.59	1.18–17.87	0.028
PT (>upper limit of normal vs. ≤upper limit of normal)	1.55	0.53–4.57	0.426

*The aPTT value was higher than the upper normal reference limit in nine of the 89 patients immediately after surgery and in one at T2 or two at T0 and T3. Age- and sex-adjusted logistic regression was used to assess the risk of high blood loss (>1,467 mL). TGA markers were dichotomized at an optimal cut-off point determined from an ROC curve. PT and aPTT were dichotomized at the upper limit of normal.
Abbreviations: TGA, thrombin generation assay; ETP, endogenous thrombin potential; PT, prothrombin time; aPTT, activated partial thromboplastin time; CI, confidence interval; OR, odds ratio.

within the normal range in most patients, except at T1. In a subset of patients, PT exceeded the upper limit of normal at T2 (N=63) and T3 (N=17). PT values exceeding the upper normal limit at T2 had a significantly high OR for high blood loss risk.

In conclusion, we highlight the significance of pre- and postoperative ETP levels as predictors for significant blood loss until chest drain removal. Consequently, pre- and postoperative ETP levels are robust predictors of total BLV. Thus, TGA is a reliable

follow-up assay for monitoring postoperative bleeding. Future research employing test results for various coagulation factors is essential to substantiate these findings. Although TGA is not a routine clinical test, its development for bedside application could render it valuable for identifying patients at increased risk of bleeding following surgery with CPB.

ACKNOWLEDGEMENTS

None.

AUTHOR CONTRIBUTIONS

Conceptualization: Kim KH and Kim HK; Methodology: Jung Y, Choi JW, Hwang HY, Kim KH, and Kim HK; Investigation: Jung Y, Choi JW, Hwang HY, Gu JY, and Kim KH; Visualization: Jung Y; Funding acquisition: Kim HK; Project administration: Kim HK; Supervision: Kim KH and Kim HK; Writing – original draft: Jung Y; Writing – review & editing: Jung Y, Choi JW, Hwang HY, Gu JY, Kim KH, and Kim HK.

CONFLICTS OF INTEREST

None declared.

RESEARCH FUNDING

This research was supported by a grant of Korean Cell-Based Artificial Blood Project funded by the Korean government (The Ministry of Science and ICT, The Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (grant number: HX23C1718).

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https://doi.org/10.3343/alm.2024.0216