Enhanced Thrombin Generation After Cardiopulmonary Bypass Surgery

Susanne Lison, MD,* Wulf Dietrich, MD, PhD,* Siegmund Braun, MD,† Johannes Boehm, MD,† Tibor Schuster, MS,§ Anna Englhard, MD,* Anna Perchuc, PhD,¶ Michael Spannagl, MD, PhD,* and Raimund Busley, MD#

BACKGROUND: Thrombin generation has a key role in the pathophysiology of hemostasis. Research has focused on the intraoperative course of hemostasis, while little is known about postoperative hemostatic activation. Thrombin generation assays quantify the potential for thrombin generation ex vivo and may be useful for determining hypercoagulability. The thrombin dynamics test (TDT) assesses the initial kinetics of thrombin formation. We hypothesized that there would be an increase in thrombin generation as well as thrombin capacity after cardiac surgery.

METHODS: Two hundred twenty patients undergoing primary coronary artery bypass grafting or aortic valve replacement (AVR) surgery were prospectively enrolled. Patients undergoing AVR received warfarin beginning on the second postoperative day. In addition to prothrombin fragment (F1+2), TDT, d-dimer, and troponin T were assessed. Blood samples were obtained preoperatively, at the end of the operation, 4 hours postoperatively, and the morning of postoperative days (PODs) 1, 3, and 5. The primary end point was the change of thrombin dynamics on POD 1.

RESULTS: In all patients, F1+2 peaked at the end of the operation and remained significantly elevated until POD 5. Compared with baseline and after an initial decrease, TDT was found to be significantly elevated on POD 1. After coronary artery bypass graft, TDT remained significantly elevated, whereas in AVR patients with warfarin treatment, TDT was significantly reduced on PODs 3 and 5.

CONCLUSIONS: After cardiac surgery, thrombin generation continues, accompanied by a high thrombin-generating capacity and elevated fibrinogen levels. This constellation suggests a marked procoagulopathic state in the postoperative period with the potential to aggravate the risk of thromboembolic complications. Warfarin treatment after AVR significantly reduced thrombin-generating capacity. (Anesth Analg 2011;112:37–45)

Thrombin formation is the key regulatory step that maintains intravascular hemostasis in patients undergoing cardiac surgery.1–4 Once formed, thrombin converts fibrinogen into fibrin and is the most potent physiological platelet activator, leading to platelet aggregation. Thrombin also activates factor XIII and terminates its physiological platelet activator, leading to platelet aggregation.1,2 It is usually determined by measuring the thrombin-generating capacity. (Anesth Analg 2011;112:37–45)

Authors’ affiliations are listed at the end of the article.

Accepted for publication August 30, 2010.

Supported solely by the Medical Faculty of the Technische Universität München and the Deutsches Herzzentrum München, Munich, Germany. Clinical trial registration: ClinicalTrials.gov NCT00396760 (http://www.clinicaltrials.gov).

Conflicts of Interest: See Disclosures at the end of the article.

The authors WD and RB formerly held positions at the German Heart Center Munich. AP is currently affiliated with August-Lenz-Stiftung am Institut für Prophylaxe und Epidemiologie der Kreislaufkrankheiten, Ludwig Maximilians Universität, Munich, Germany.

Address correspondence and reprint requests to Wulf Dietrich, MD, PhD, Working Group of Perioperative Hemostasis, Ludwig Maximilians Universität, Winthirstr. 4, 80639 Munich, Germany. Address e-mail to wulf.dietrich@t-online.de.

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DOI: 10.1213/ANE.0b013e3181f6d4d0

January 2011 • Volume 112 • Number 1

www.anesthesia-analgesia.org

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formation and inhibition of thrombin using “slow” thrombin substrates over a period of up to 1 hour. The thrombin dynamics test (TDT) uses a “fast” chromogenic substrate (i.e., a substrate that is rapidly converted by thrombin) to detect initial thrombin-formation kinetics. This test was applied in the present investigation to describe the dynamics of thrombin generation during and after cardiac surgery.

The aim of this study was to evaluate the activation of plasmatic coagulation in cardiac surgery with special emphasis on the postoperative period. We hypothesized that cardiac surgery leads to a prothrombotic state postoperatively that may be partly independent of the degree of intraoperative hemostatic activation.

**METHODS**

After IRB approval (Ethical Committee, Medical Faculty of the Technische Universitaet Muenchen, Munich, Germany) and written informed consent, 220 patients older than 18 years and scheduled for primary coronary artery bypass graft (CABG) or aortic valve replacement (AVR) surgery were prospectively enrolled in this study. Exclusion criteria were emergency operation, known previous exposure to aprotinin, warfarin treatment within 5 days of the operation, or refusal of allogeneic blood transfusion. Aspirin or thienopyridine therapy did not lead to exclusion. Demographic data, medical and surgical history, medications, and outcomes were recorded by trained research staff using defined protocols in a purpose-built case report form. This nonindustry sponsored study was supported by the Department of Anaesthesiology of the Deutsches Herz-Zentrum Muenchen, Munich, Germany. Quantitative data about blood loss and transfusion requirements are published elsewhere.

In all patients, standard anesthesia was performed using sufentanil and midazolam supplemented with sevoflurane inhalation; neuromuscular blockade was achieved and maintained by either pancuronium bromide or vecuronium. During CPB, nonpulsatile pump flow was used with moderate systemic hypothermia of 32°C. CPB was performed using a membrane oxygenator, an open cardiotomy reservoir, and uncoated tubing systems. The oxygenator was primed with a total volume of 1500 mL crystalloid solution. Myocardial protection consisted of administration of either cold crystalloid or blood cardioplegia. Intraoperative cell salvage of shed blood was used for all patients.

The patients were randomly assigned to receive either aprotinin (Trasylol Bayer AG, Leverkusen, Germany) or tranexamic acid (Cyklokapron; Pfizer Pharma GmbH, Berlin, Germany) during surgery. The anesthesiologist was blinded to group allocation. Patients received either 2 × 10^6 kIU aprotinin over 10 minutes, followed by a continuous infusion of 5 × 10^5 kIU aprotinin/h for the duration of surgery with an additional bolus of 2 × 10^5 kIU aprotinin to the CPB priming, or 2 g tranexamic acid followed by a continuous infusion of 1 g/h and an additional bolus of 2 g to the CPB circuit.

For CPB, the patients received anticoagulation with porcine heparin 375 U/kg; 10,000 U of heparin was added to the priming solution. The degree of heparinization was determined by measuring the kaolin activated clotting time (Hemochron 800; Intern Technidyne Corp., Edison, NJ) every 30 minutes, with a target activated clotting time of 480 seconds. After termination of CPB, heparin was reversed by protamine chloride in a ratio of 1:1 of the initial heparin dosage.

The trigger for transfusion of allogeneic blood was a hematocrit <18% during CPB or <21%–24% postoperatively or if physiological signs (tachycardia >100/min with adequate volume load and pain care and/or tachypnea with >25 breaths per minute and/or a decrease in central venous oxygen saturation below 65%) of the patient indicated a need for improved oxygen supply. Postoperatively, patients’ lungs were ventilated in the intensive care unit until warmed to 37°C, oxygenation and hemodynamics were sufficient, and blood loss was <100 mL/h. A standard 12-lead electrocardiography was applied postoperatively on the morning of the first, third, and fifth postoperative days (PODs).

After prosthetic AVR, all patients received oral warfarin treatment beginning the second day after the operation.

**Blood Sampling**

Blood samples were obtained before induction of anesthesia, at the end of the operation, 4 hours postoperatively, and the morning of PODs 1, 3, and 5. After discarding the first 10 mL, blood was collected in citrated plastic tubes (sodium citrate 0.106 mol/L; Sarstedt, Numbrecht, Germany) without stasis from an arterial catheter or a central venous catheter. Blood samples were centrifuged immediately (10 minutes, 3000g); the plasma was frozen in multiple aliquots of platelet-poor plasma and stored at −80°C. All measurements were performed directly after thawing the plasma.

**Thrombin Dynamics Test**

The TDT (Pefakit, in-TDT; Pentapharm, Basel, Switzerland) allows for the rapid detection of thrombin-formation kinetics in platelet-poor plasma by activation of the intrinsic coagulation pathway and optical detection of clots in standard coagulation analyzers. The assay is commercially available from Pentapharm, Basel, Switzerland using intrinsic coagulation activation, i.e., via factors XII, XI, IX, VIII, X, V, and ultimately thrombin. Analyses were performed on the Behring Coagulation System Analyzer (BCS; Siemens, Marburg, Germany). Briefly, coagulation is triggered by the addition of 60 µL activator reagent to 60 µL platelet-poor plasma (contact phase activator based on ellagic acid and phospholipids), diluted 1:3 in 0.9% saline. After incubation for 180 seconds at 37°C, 60 µL of reagent containing CaCl₂, fibrin polymerization inhibitor (H-Gly-Pro-Arg-Pro-OH) that allows for undisturbed optical detection, and a chromogenic substrate (H-D-CHG-Ala-Arg-pNa2AcOH) is added. Thrombin formation is detected with a “fast” chromogenic substrate, i.e., a substrate that is readily converted by thrombin and releases p-nitroaniline; color intensity is continuously recorded at 405 nm over 4 to 10 minutes. The peak value of the first derivative representing the maximum velocity of the conversion of the thrombin substrate is determined. This parameter characterizes the dynamics of
thrombin formation and is expressed as a percentage of thrombin formation of a normal control population.

Further laboratory tests determined activated partial thromboplastin time (aPTT) (Pathromtin SL; Dade Behring, Marburg, Germany) (reference range, 25–37 seconds); prothrombin time (PT) (%) (Innovin, Dade Behring) (reference range, 70%–120%); antithrombin (Berichrom Antithrombin SL; Dade Behring, Marburg, Germany) (reference range, 25–37 seconds); thromboplastin time (aPTT) (Pathromtin SL; Dade Behring, Marburg, Germany) (reference range, 25–37 seconds); fibrinogen with a modification of the Clauss method (Multifibren, Dade Behring) (reference range, 180–350 mg/dL); and thrombin activation, determined by fibrin monomer (Asserachrom Fibrin Monomer; Dade Behring) (reference range, 80%–120%); and D-dimer (Asserachrom D-Dimer Plus Assay, Dade Behring) (reference range, 0.01–0.5 mg/mL).

Myocardial infarction was defined as the new occurrence of Q waves on electrocardiogram or an increase in troponin T with a postoperative cutoff >1.58 ng/mL. ischemic stroke was confirmed by computed tomography after clinical findings.

### Sample Size and Power Considerations

Study design and calculation of sample size were initially based on 24-hour blood loss as reported previously by Dietrich et al. A sample size of 220 was deemed sufficient for detecting changes in TDT values of at least 2.5% from baseline to POD 1, with 80% power, assuming a common standard deviation of 6%.

### Statistical Analysis

The primary end point of the investigation was the change in thrombin dynamics on the first POD as compared with preoperative values. Secondary end points were changes in thrombin dynamics and prothrombin fragment F<sub>1+2</sub> levels up to the fifth POD. Additionally, we analyzed the influence of 2 different intraoperative antifibrinolytic treatments as well as postoperative warfarin treatment on these parameters. Distributions of quantitative data are described by reporting the median with 25th to 75th percentiles. Categorical variables are reported as percentages.

The Friedman test was used to evaluate longitudinal changes in quantitative measurements over time. In the case of a statistically significant Friedman test, the nonparametric post hoc multiple comparison analysis by Daniel was applied to assess the significance of changes in each time point compared with baseline values. In addition, analysis of patients divided in subpopulations (CABG and AVR) or subgroups (aprotinin and tranexamic acid), respectively, was performed in the same manner. To assess intergroup differences at single predetermined time points, the Mann-Whitney U test was used. In all statistical comparisons, a P value <0.05 was considered statistically significant. The Pearson correlation coefficient (r) was used to quantify bivariate correlation of quantitative measurements at distinct time points.

### RESULTS

Two hundred twenty patients were enrolled in this study. CABG was performed in 134 patients; 86 patients had AVRs. All patients underwent first-time cardiac surgery. Demographic and procedural data are summarized in Tables 1 and 2.

In all patients, thrombin dynamics (median; 25th–75th percentile) were significantly reduced postoperatively (83%; 77%–87%, P < 0.05) compared with baseline (97%; 93%–101%,) (Table 3; Figs. 1 and 2). On POD 1, a significant increase in thrombin dynamics was found (100%; 96%–103%, P < 0.05) (Table 3; Figs. 1 and 2). Separate analysis of the aprotinin and tranexamic acid subgroups on POD 1 revealed a decreased TDT in the aprotinin subgroup compared with the tranexamic acid subgroup (aprotinin subgroup 99%; 94%–102% vs tranexamic acid subgroup 101%; 96%–105%, P < 0.05) (Fig. 3).

All patients with prosthetic AVR began oral warfarin anticoagulation on POD 2 and demonstrated significantly attenuated thrombin dynamics on the third and fifth PODs compared with baseline (P < 0.05) and compared with patients without warfarin treatment after CABG (P < 0.05).

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 220)</th>
<th>Aprotinin (n = 110)</th>
<th>TA (n = 110)</th>
<th>CABG (n = 134)</th>
<th>AVR (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>66 (30.1)</td>
<td>28 (25.5)</td>
<td>38 (34.5)</td>
<td>22 (16.4)</td>
<td>44 (51.2)</td>
</tr>
<tr>
<td>Age (%)</td>
<td>70 (64–76)</td>
<td>69 (63–75)</td>
<td>71 (64–77)</td>
<td>70 (64–75)</td>
<td>64 (71–46)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>62 (28.2)</td>
<td>28 (25.5)</td>
<td>34 (30.9)</td>
<td>52 (38.8)</td>
<td>10 (11.6)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3 (1.4)</td>
<td>3 (2.7)</td>
<td>0 (0)</td>
<td>2 (1.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>60 (27.3)</td>
<td>33 (30)</td>
<td>27 (24.5)</td>
<td>44 (32.8)</td>
<td>16 (18.6)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>27 (12.3)</td>
<td>15 (13.6)</td>
<td>12 (10.9)</td>
<td>24 (17.9)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Hemoglobin preoperatively (g/dL)</td>
<td>13.5 (12.4–14.6)</td>
<td>13.6 (12.5–14.6)</td>
<td>13.2 (12.3–14.7)</td>
<td>13.6 (12.5–15.0)</td>
<td>13.1 (12.4–13.9)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60 (48–70)</td>
<td>69 (43–68)</td>
<td>62 (49–70)</td>
<td>60 (47–70)</td>
<td>64 (50–70)</td>
</tr>
<tr>
<td>EuroScore</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>Preoperative risk score</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>75 (34.1)</td>
<td>36 (32.7)</td>
<td>39 (35.5)</td>
<td>45 (33.6)</td>
<td>30 (34.9)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>141 (64.1)</td>
<td>70 (63.6)</td>
<td>71 (64.5)</td>
<td>86 (64.2)</td>
<td>55 (64)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>4 (1.8)</td>
<td>4 (3.6)</td>
<td>0 (0)</td>
<td>3 (2.2)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Values are n (%) or median (25th–75th percentiles). Preoperative risk score was calculated according to the Cleveland Clinic Risk Score.

TA = tranexamic acid; CABG = coronary artery bypass graft; AVR = aortic valve replacement; BMI = body mass index; MI = myocardial infarction; EF = left-ventricular ejection fraction; NYHA = New York Heart Association.
Table 2. Procedural Data

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 220)</th>
<th>Aprotinin (n = 110)</th>
<th>TA (n = 110)</th>
<th>CABG (n = 134)</th>
<th>AVR (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>134 (60.9)</td>
<td>66 (60.0)</td>
<td>68 (61.8)</td>
<td>210 (185–250)</td>
<td>175 (146–210)</td>
</tr>
<tr>
<td>AVR</td>
<td>86 (39.1)</td>
<td>44 (40.0)</td>
<td>42 (38.2)</td>
<td>83 (71–99)</td>
<td>88 (74–102)</td>
</tr>
<tr>
<td>OP duration (min)</td>
<td>200 (165–235)</td>
<td>195 (165–235)</td>
<td>200 (170–234)</td>
<td>210 (185–250)</td>
<td>175 (146–210)</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>85 (72–101)</td>
<td>88 (73–102)</td>
<td>83 (71–98)</td>
<td>83 (71–99)</td>
<td>88 (74–102)</td>
</tr>
<tr>
<td>Time on ventilator (min)</td>
<td>520 (380–715)</td>
<td>548 (406–724)</td>
<td>480 (373–689)</td>
<td>435 (345–675)</td>
<td>530 (409–706)</td>
</tr>
<tr>
<td>ICU stay (d)</td>
<td>1.0 (1.0–1.0)</td>
<td>1.0 (1.0–1.0)</td>
<td>1.0 (1.0–1.8)</td>
<td>1.0 (1.0–1.8)</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>9 (8–12)</td>
<td>9 (8–12)</td>
<td>9 (8–12)</td>
<td>9 (8–11)</td>
<td>10 (8–13)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>3 (1.4)</td>
<td>2 (1.8)</td>
<td>1 (0.9)</td>
<td>2 (1.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Mortality within 30 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rethoracotomy for bleeding</td>
<td>5 (2.3)</td>
<td>2 (1.8)</td>
<td>3 (2.7)</td>
<td>2 (1.5)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Blood loss 24 h (mL)</td>
<td>500 (300–713)</td>
<td>500 (300–700)</td>
<td>565 (300–800)</td>
<td>600 (400–800)</td>
<td>340 (250–588)</td>
</tr>
<tr>
<td>Packet cells, allogenic (yes)</td>
<td>119 (54)</td>
<td>52 (47.3)</td>
<td>67 (60.9)</td>
<td>67 (50)</td>
<td>52 (60.5)</td>
</tr>
<tr>
<td>Platelets total (yes)</td>
<td>4 (1.8)</td>
<td>0</td>
<td>4 (3.6)</td>
<td>3 (2.2)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Fresh frozen plasma total (yes)</td>
<td>20 (9.1)</td>
<td>10 (9.1)</td>
<td>10 (9.1)</td>
<td>17 (12.7)</td>
<td>3 (3.5)</td>
</tr>
</tbody>
</table>

Values are n (%) or SD or median (25th–75th percentiles).
TA = tranexamic acid; CABG = coronary artery bypass graft; AVR = aortic valve replacement; OP = operation; CPB = cardiopulmonary bypass; ICU = intensive care unit.

Table 3. Laboratory Data (All Patients)

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin (g/dL)</th>
<th>Fibrinogen (mg/dL)</th>
<th>D-dimer (mg/dL)</th>
<th>Troponin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>Opend</td>
<td>4 h Opend</td>
<td>POD 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.5 (12.4–14.6)</td>
<td>10.5 (9.6–11.4)</td>
<td>10.8 (9.9–11.8)</td>
<td>10.8 (9.9–11.8)</td>
</tr>
<tr>
<td></td>
<td>0.13 (0.09–0.21)</td>
<td>0.17 (0.12–0.23)</td>
<td>0.14 (0.10–0.21)</td>
<td>0.15 (0.11–0.21)</td>
</tr>
<tr>
<td></td>
<td>0.01 (0.01–0.01)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>97 (93–101)</td>
<td>83 (77–88)</td>
<td>96 (91–100)</td>
<td>100 (96–103)</td>
</tr>
<tr>
<td></td>
<td>98 (92–104)</td>
<td>70 (62–81)</td>
<td>92 (82–100)</td>
<td>95 (86–103)</td>
</tr>
<tr>
<td></td>
<td>32.7 (30.3–35.5)</td>
<td>47.8 (38.2–58.9)</td>
<td>34.7 (31.3–40.1)</td>
<td>34.5 (31.9–38.2)</td>
</tr>
<tr>
<td></td>
<td>74 (68–80)</td>
<td>58 (51–63)</td>
<td>65 (58–72)</td>
<td>74 (65–81)</td>
</tr>
</tbody>
</table>

Values are median (25th–75th percentiles).
Preop = before the operation; Opend = at the end of the operation; POD = postoperative day; F1 2 = prothrombin fragment; TDT = thrombin dynamics test; PT = prothrombin time; aPTT = activated partial thromboplastin time; AT = antithrombin.

(Fig. 4). In addition to these findings, in the AVR subpopulation, the PT was significantly decreased compared with baseline (97%; 92%–103%) on POD 3 (60%; 33%–94%; P < 0.05) and POD 5 (31%; 23%–45%; P < 0.05) as well as in comparison to patients after CABG on PODs 3 and 5 (P < 0.05).

Molecular markers of hemostasis are summarized in Table 3 and Figure 5. Prothrombin fragment F1 2, a parameter of prothrombin cleavage, peaked immediately after surgery and remained significantly elevated throughout the postoperative period (P < 0.05). After CABG, significantly elevated prothrombin fragment F1 2 levels were found on POD 5 compared with warfarin-treated patients after AVR (after CABG 301 pmol/L; 222–389 pmol/L vs after AVR 198 pmol/L; 159–273 pmol/L, P < 0.05). No significant difference in postoperative prothrombin fragment F1 2 levels was found between patients treated with aprotinin and those treated with tranexamic acid. Levels of fibrinogen were significantly decreased at the end of surgery and 4 hours postoperatively but later increased significantly above baseline on POD 1 (P < 0.05). Levels increased further during the residual observation period and reached a median of 693 mg/dL (584–778 mg/dL) on POD 5 (P < 0.05 vs baseline). Plasmin-dependent fibrin degradation as measured by D-dimer levels showed a minimal increase at the end of surgery and increased further in the postoperative period. Antithrombin was significantly reduced at the end of surgery and 4 hours postoperatively (P < 0.05).

For the first POD, a positive but weak correlation was found between thrombin dynamics and prothrombin fragment F1 2 levels (r = 0.18).

In all patients, troponin T values (Table 3) were significantly increased in the postoperative course compared with baseline and peaked 4 hours after the operation (P < 0.05). Nine patients showed an increase above the defined cutoff of 1.58 ng/mL postoperatively; 5 of these patients had elevated values above 1.58 ng/mL on POD 1. No correlation was found between troponin T and TDT. No Q wave myocardial infarction was observed.

Three patients (1.4%) died either in the hospital or within 30 days after the operation. One patient died of ischemic stroke on POD 5. The other patient died of multiorgan failure on POD 42. The third patient experienced sudden cardiac death after discharge on POD 14 (Table 2).
DISCUSSION

Our study revealed a pronounced hypercoagulable state after cardiac surgery as demonstrated by increased prothrombin fragment $F_{1+2}$, accompanied by a high thrombin-generating capacity and increased fibrinogen levels. The majority of studies evaluating hemostasis and cardiac surgery focus on hemostatic changes during the course of CPB and the immediate postoperative period. Hemostatic markers of the activation and activity of prothrombin (prothrombin fragment $F_{1+2}$ and thrombin-antithrombin complex, respectively) increase during surgery and peak after protamine administration. The current study supports previous research demonstrating alterations in hemostasis up to 30 days after surgery. Prothrombin fragment $F_{1+2}$, as an index of continuing thrombin generation, peaked immediately after surgery and remained significantly elevated until POD 5. On the contrary, TDT, as a marker of thrombin-generating capacity, decreased immediately after the operation but increased again up to POD 1 in all patients. Fibrinogen showed a similar course with significantly reduced values postoperatively and a considerable and significant increase starting on POD 1 and continuing until POD 5. D-dimer values showed only a minimal increase at the end of the operation as well as 4 hours after the operation. However, one must consider that all patients were treated with high-dose antifibrinolytics.

When thrombin is finally formed, prothrombin fragment $F_{1+2}$ is cleaved from the prothrombin molecule. Therefore, during and immediately after surgery, prothrombin fragment $F_{1+2}$ should be enhanced. Thrombin generation capacity reflects the potential amount of thrombin that is reduced during and early after surgery because of the consumption of clotting factors and hemodilution. This situation contributes to the possible risk of the widely documented increased bleeding tendency in the perioperative period.

In patients with acute coronary syndrome, but without surgical intervention, high levels of thrombin generation are predictors of an increased risk of an unfavorable outcome.
Activation of hemostasis during cardiac surgery may present a comparable “hemostatic constellation.” CPB results in a significant enhancement of thrombin generation and activation of fibrinolysis, despite adequate heparinization. In addition to an increased perioperative bleeding tendency, impaired hemostasis after CPB also leads to prothrombotic effects. Increased levels of hemostatic activation are associated with evidence of postoperative organ dysfunction after cardiac surgery. Our results demonstrate continuing thrombin activity until the fifth POD after cardiac surgery, data that may explain the clinical findings of postoperative ischemic events such as myocardial infarction, graft occlusions, ischemic stroke, or venous thromboembolism. However, the number of patients in the present study was too small to demonstrate an association between hemostatic activation and adverse outcome.

The kinetics of thrombin formation are of fundamental importance for the hemostatic process in vivo and are not reflected by routine coagulation tests such as aPTT or PT. Thrombin generation capacity is a general “function test” providing a global picture of plasmatic hemostasis by showing the potential rate of thrombin production. Hemker and Beguin once compared prothrombin fragment F1 + F2 to a smoke detector that reports a fire, whereas the thrombin generation test would depict the risk of fire. Thrombin generation tests have been used to assess hypocoagulable states such as clotting factor deficiencies (e.g., hemophilia), hypercoagulable states such as thrombosis and coronary disease, and it is also used to monitor different antithrombotic therapies.

TDT is a fairly new modification of the thrombin-generating assay described by Hemker et al. In contrast to the original assay, TDT focuses on the physiologically relevant initial phase of thrombin generation. Thus, a “fast” thrombin substrate is used, which increases the speed of the test. Additionally, it is an easily applicable method that is performed on standard automated hemostasis instrumentation.

Only a few studies examined TDT, and no data are found concerning TDT after cardiac surgery. Similar to our results, Tanaka et al. demonstrated a reduced thrombin generation compared with prebypass values by using the...
found an increased prothrombotic state (as measured by prothrombin fragment F$_{1+2}$) after on-pump as well as off-pump coronary surgery, which lasted as long as 1 month after the operation.

Interestingly, when started on POD 2, warfarin decreased TDT as well as PT and increased aPTT on PODs 3 and 5. PT and aPTT only detect the onset time of thrombin formation, whereas thrombin generation tests in general quantify the thrombin generation potential and therefore provide information in addition to PT in warfarin therapy. In the CABG subpopulation, TDT values were higher in comparison to the warfarin-treated patients. Particularly, in regard to increased prothrombin fragment F$_{1+2}$ levels, this result reveals a pronounced hypercoagulable state. Currently, postoperative antithrombotic prophylaxis is often disregarded in cardiac surgery. Future studies must evaluate whether more aggressive antithrombotic therapy may reduce thromboembolic events in cardiac surgery.

After aprotinin administration, less pronounced TDT values were observed at the end of surgery and on POD 1 in the aprotinin group compared with the tranexamic acid group. Aprotinin has anticoagulant properties that might preserve hemostasis by inhibiting the contact pathway during and directly after surgery.

This study has several limitations. First, because of the small number of patients and the low incidence of complications, our study could not demonstrate an association between adverse events or troponin T increases with elevated TDT values. Second, at the time of the study, only an intrinsic activator of TDT was commercially available for measurements. Extrinsic activation, indicating factor VII and factor X activity and mainly activated by tissue factor, might provide additional information about a procoagulatory state. Third, blood samples were obtained discontinuously with a total of 6 samples during a study period of 5 days. Therefore, we might have missed peaks of prothrombin fragment F$_{1+2}$ levels or TDT during the study period. Fourth, even though TDT values were significantly increased on POD 1 in all patients and stayed increased on PODs 3 and 5 in patients without warfarin treatment, it should be noted that TDT values stayed within the range of normal during the whole observational period.

In conclusion, this study demonstrated enhanced thrombin generation and a high thrombin capacity after cardiac surgery. These observations confirm the hypothesis that hemostatic alterations after cardiac surgery result in a prothrombotic state, which potentially increases the risk of thrombotic complications. This hypercoagulable milieu might be partly independent of CPB and partially related to surgical stress.

**AUTHOR AFFILIATIONS**

From the *Working Group of Perioperative Hemostasis, Ludwig Maximilians Universitaet, Munich; †Department of Clinical Chemistry, and ‡Department of Cardiac Surgery, Deutsches Herzzentrum Muenchen, Munich; §Department of Medical Statistics and Epidemiology, Klinikum Rechts der Isar, Technische Universitaet Muenchen, Munich, Germany; ‡Department for Research & Development, Pentapharm Ltd.,
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Basel, Switzerland; and Department of Anesthesiology, Behandlungszentrum Vogtareuth, Vogtareuth, Germany.

DISCLOSURES
SL, WD, and MS received speaker honoraria from Bayer Corp. WD was a paid consultant at the FDA advisory committee meetings in September 2006 and September 2007 in Washington DC. RB was a member of an advisory board for aprotinin. AP worked in the Department of Research & Development at Pentapharm Ltd., Basel, Switzerland in the course of her dissertation at the University of Basel, Switzerland. No other potential conflicts of interest relevant to this article are reported.

ACKNOWLEDGMENTS
We thank Mrs. Seggebrock for assistance in data collection and review of patients’ records and Mrs. Kramer for technical assistance in collecting and analyzing blood samples. Drug preparation and randomization were performed by the pharmacist, Mrs. Graf.

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