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Evaluation of multiple electrode aggregometry for the perioperative assessment of aspirin therapy in cardiac surgery

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Abstract

Objective of the study: The aim of this study was to investigate the feasibility of the Multiple Electrode Aggregometry (MEA) device for reliable assessment of arachidonic acid-induced platelet function after preoperative cessation and postoperative restarting of aspirin therapy.
Methods: 102 consecutive patients undergoing coronary artery bypass grafting (CABG) were enrolled in this prospective study. After preoperative cessation for at least five days, 100 mg aspirin was restarted on the first day after surgery. Platelet function was assessed by performing Light Transmission Aggregometry (LTA) and MEA on the day before surgery (T0), four hours (T1) and five days after restarting aspirin therapy (T2). Platelet aggregation was induced using 0.5 mg/ml arachidonic acid for the LTA (ASAtest) analysis and 0.5 mM arachidonic acid (ASPItest) and 32 μM thrombin receptor activating peptide (TRAPtest) for the MEA analysis, respectively.
Results: Arachidonic acid-induced platelet aggregation was found impaired at T1 and T2 in both MEA and LTA, while platelet aggregation in TRAPtest (MEA) did not change significantly as compared to baseline. Platelet aggregation in ASPItest (MEA) was significantly correlated with the ASAtest (LTA) at pre- and postoperative measuring points.
Conclusions: MEA enables the assessment of potential residual effects of preoperatively ceased aspirin therapy. After postoperative restarting of daily aspirin therapy, MEA reliably detects aspirin non-responsiveness in a rapid and practicable manner. Therefore, MEA may be helpful to control and potentially adjust the aspirin dosage in patients following CABG surgery.

Key words: aspirin resistance, CABG, cardiac surgery, light transmission aggregometry, multiple electrode aggregometry

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Introduction

In patients with coronary artery disease, indefinite antiplatelet therapy with aspirin is associated with a significant reduction in serious ischemic vascular events [1] and aspirin is the most widely used drug in patients scheduled for elective coronary artery bypass grafting (CABG) [2]. However, due to the increased risk for transfusion and a 4-fold increase in early re-operation for bleeding [3], the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines recommend a cessation of aspirin therapy for 7-10 days before CABG [4].

The early use of aspirin following CABG has been shown to be safe and is associated with a reduced risk of death and ischemic complications involving the heart, kidneys and gastrointestinal tract [5-6]. Therefore, the recently published American College of Chest Physicians (ACCP) guidelines recommend (re)-starting daily aspirin therapy (75-100 mg) following CABG within the first 6-48 hours following surgery [7].

Several authors suggest a higher recurrence rate of cardiovascular events in patients with persistent platelet reactivity despite aspirin therapy [8-9]. Depending on both aspirin dosages and performed platelet function tests, the prevalence of aspirin resistance is reported to vary between 0.4 and 83.3 % [10]. Three recently published meta-analyses revealed that the average prevalence of laboratory aspirin resistance was between 25 and 27 % [11-13]. The high prevalence of the so-called aspirin resistance is alarming.

With respect to the important clinical benefits associated with a sufficient antiplatelet therapy following coronary artery bypass grafting (CABG) [7], a sensitive and specific method for monitoring the therapeutic inhibition of platelet function at the bedside would be desirable.

LTA is considered to be the gold standard for assessing platelet response to agonists such as arachidonic acid or adenosine diphospate (ADP) [14] and has already been used to assess drug response to aspirin [15] or clopidogrel [16]. However, complex logistical demands in the performance of LTA hinder its wide clinical use [17]. A simple, fast and standardized method to assess platelet function in patients treated with aspirin would be a valuable alternative. Multiple Electrode Aggregometry (MEA) has recently been developed for the rapid assessment of platelet response to different agonists such as arachidonic acid, ADP, collagen or thrombin-receptor activating peptide [18] and thus might be an applicable method for the assessment of aspirin influence on platelet function.

In the present study, the gold standard for platelet function testing, LTA, and the new point-of-care device MEA were used to i) assess aspirin-induced platelet inhibition and ii) identify patients with aspirin resistance after restarting daily antiplatelet therapy with 100 mg aspirin following elective CABG.

Methods

Study population and intervention

This study complies with the declaration of Helsinki and was approved by the local Scientific and Ethic Review Board. All patients gave written informed consent. One hundred two (n=102) consecutive patients scheduled for CABG at the Department of Thoracic and Cardiovascular Surgery of J.-W. Goethe University Hospital Frankfurt, Germany, were enrolled in this study. All patients had received daily aspirin therapy (100 mg/d) prior to surgery for at least one month. Eligibility criteria were that i) patients were scheduled for elective CABG without valve surgery, ii) patients had ceased antiplatelet therapy with aspirin at least five days prior to surgery and iii) daily antiplatelet therapy with 100 mg aspirin was restarted on the first postoperative day. Exclusion criteria were preoperative antiplatelet therapy with clopidogrel or other antiplatelet medication and chronic renal insufficiency. Extracorporeal circulation (ECC) was performed using a tubing set in an open extra-

corporeal circuit with a Maquet Quadrox Oxygenator, including an arterial 40 µm filter and a 4 l cardiotomy reservoir (Maquet GmbH, Rastatt, Germany). During ECC, patients were treated with moderate hypothermia (32 °C). Postoperatively, patients were admitted to the ICU. Sedation was performed with a continuous infusion of 4-5 mg/kg/h of propofol (Propofol, Fresenius Kabi GmbH, Bad Homburg, Germany), according to institutional standards. The continuous infusion of propofol was reduced and patients were extubated by the decision of the physician on ward following institutional protocol. In order to prevent thromboembolic complications, weight-adapted low-molecular-weight-heparin (Nadroparin-Calcium, Fraxiparin®, GlaxoSmithKline, Munich, Germany) was administered subcutaneously 12 hours after surgical intervention according to institutional standards. Based on institutional standards, antiplatelet therapy with 100 mg/d aspirin was restarted at the morning of the first postoperative day.

Blood sampling

During the study period, blood samples for conventional coagulation analyses (aPTT, INR, hematocrit, fibrinogen, platelet count), MEA and LTA were taken at the following time points: the evening before CABG (T0), 4 hours after restarting daily antiplatelet therapy on the first postoperative day (T1) and on the evening of the 5th postoperative day (T2).

At T0, blood was drawn by clean venous puncture from an antecubital vein, and at T1 and T2, blood was drawn from an intraoperatively placed central venous line. The first 10 ml of blood were discarded. Then, blood was collected for MEA analysis into hirudin-anticoagulated 4.5 ml tubes (Dynabyte, Munich, Germany) and into 10 ml citrate-anticoagulated tubes (Saarstedt, Nümbrecht, Germany) for conventional coagulation and LTA analyses, respectively.

Platelet function assays

Light Transmittance Aggregometry (LTA)

LTA was performed on the Behring Coagulation Timer (BCT®, Dade Behring, Südingen, Switzerland). The BCT®, a fully automatic machine, detects platelet aggregate formation in platelet rich plasma (PRP) by monitoring changes in light transmission (monochromatic light, wavelength: 620 nm) at 37 °C. Platelet aggregation was induced by 0.5 mg/ml arachidonic acid (ASA, Moelab GmbH, Hilden, Germany), which was introduced automatically into the PRP (135 µl of plasma). The extent of induced aggregation was defined by the slope of the aggregation curve obtained from the change in light transmission over time. The maximum aggregation response (MaxAggr), which is seen approximately 90 seconds after the addition of the agonist, was recorded. Light transmission was measured in the PRP at the beginning and at the time of MaxAggr and was compared to that in platelet poor plasma (PPP). Maximum aggregation was calculated from the following formula:

$$\text{Maximum aggregation [\%]} = 100\% * \frac{(\text{start aggr PRP} - \text{max. aggr PRP})}{(\text{start aggr PRP} - \text{aggr PPP})}$$

Reference ranges for arachidonic acid-induced platelet aggregation are 78-96 % [19]. Thus, aspirin-induced suppression of platelet aggregation (aspirin responder) in LTA was defined by a maximum aggregation of <78 %.

Multiple Electrode Aggregometry (MEA)

MEA was performed using the Multiplate® analyzer, a novel whole blood impedance aggregometer (Dynabyte, Munich, Germany). The device has 5 test cells for parallel testing, and each test cell incorporates two independent sensor units. The method is based on the aggregation of activated platelets onto metal sensor wires in the test cell, thus increasing the electrical impedance between the wires [18]. For measurement, 300 µl of preheated saline (37 °C) and 300 µl of hirudin-anticoagulated whole blood were placed into the test cell, and the sample was stirred using a Teflon-coated electromagnetic stirrer (800 rpm) over a three-minute incubation period. Platelet aggregation was initiated by addition of arachidonic acid (ASPItest, 0.5 mM) or thrombin receptor activating peptide (TRAP-6, TRAPtest, 32 µM) using commercially available reagents (Dynabyte, Munich, Germany). Increased impedance due to the attachment of platelets to the electrodes was continuously and separately measured by each sensor unit over 6 minutes. Data were transformed to arbitrary aggregation units (AU) and plotted as two separate aggregation curves against time. Aggregation measured by MEA was quantified as the area under the aggregation curve (AUC, AU*min). Reference ranges for healthy subjects obtained from the manufacturer were 745-1361 AU*min for the ASPItest and 941-1563 AU*min for the TRAPtest.

Statistical analysis

The Wilcoxon signed rank test was used to detect the differences between pre- and postoperative measurement points. Spearman rank order correlations were performed to quantify the association between platelet aggregation in MEA and LTA. Receiver operating characteristic (ROC) curves were performed to investigate the ability of MEA to predict therapeutic platelet inhibition as approved by LTA (ASAtest < 78 %). The area under the ROC curve (AUC), sensitivity (true-positives/[true-positives + false-negatives]), and specificity (true-negatives/[true-negatives + false-positives]) of the assays were calculated.

Depending on the distribution of the data (Kolmogorov-Smirnov-Test), values were expressed as mean ± standard deviation or median (25^{th}/75^{th} percentiles). The level of statistical significance was set to $p < 0.05$. Statistical analysis was performed using SigmaStat 3.5 and SigmaPlot 11 (Systat Software GmbH, Erkrath, Germany) software.

Results

Of the 102 patients studied, 79 (77.5%) were men. The mean age was 67.8 ± 9.4 years, and the mean body mass index was 28.3 ± 3.9 kg/m^2. None of the patients suffered from significant chronic renal failure, since routinely performed preoperative measurements of renal function were within normal ranges in all patients (Creatinine 1.15 ± 0.48 mg/dl; Urea 47.4 ± 26.2 mg/dl). Patients ceased aspirin therapy 6.4 ± 1.2 days prior to elective CABG and aspirin therapy (100 mg/day) was restarted 16 ± 4 hours after admission to ICU. None of the patients was treated with clopidogrel or antiplatelet medications other than aspirin. None of the patients had previously undergone cardiac surgery.

The duration of surgery and extracorporeal circulation was 199 ± 64 min and 74 ± 46 min, respectively. The intraoperative blood loss (cell saver volume) was 560 ± 310 ml and the postoperative blood loss (mediastinal tubes) within the first 12 hours after admission to the intensive care unit (ICU) was 600 ± 400 ml. In patients with persistent aspirin-induced platelet inhibition at T0 as assessed by MEA, the intraoperative blood loss was significantly higher than in patients with ex vivo

platelet aggregation within normal values (810 ± 370 ml vs. 450 ± 200 ml, p<0.001). With respect to the postoperative blood loss, there were no significant group differences (650 ± 440 ml vs. 600 ± 350 ml, p = 0.699). Surgical re-exploration due to an increased postoperative bleeding tendency had to be performed in 8 (7.8 %) patients. In this collective, MEA analyses detected persistent aspirin-induced platelet inhibition in 4 patients. Patients were treated in the ICU for 22.2 ± 6.7 hours before being transferred to intermediate care unit or peripheral ward.

The results of the conventional coagulation analyses at the measuring points T0, T1 and T2 are presented in Table 1. Compared to the baseline at T0, the aPTT and INR did not differ significantly at T1 or T2, while the fibrinogen concentration was significantly increased at T2, and both hematocrit and platelet count were significantly decreased at T1 and T2 (Table 1).

Platelet aggregation in the MEA at T0, T1 and T2 is shown in Figure 1. Compared to baseline at T0 (1074(875/1222) AU*min), platelet aggregation in the TRAPtest remained unchanged at T1 (995(773/1168) AU*min, p=0.552) and T2 (1028(854/1213) AU*min, p=0.075)). In the ASPItest, platelet aggregation was significantly reduced at T1 (420(285/792) AU*min, p=0.048) and T2 (377(256/635) AU*min, p=0.013) when compared to baseline (697(299/934) AU*min). There were no significant differ-

Table 1: Results of conventional coagulation analyses

	T0	T1		T2	
	n=102	n=102	p	n=102	p
aPTT [sec]	37±4	40±6	0.942	37±4	0.942
INR	1.3±0.1	1.3±0.1	0.508	1.4±0.2	0.535
Fibrinogen [mg/dl]	361±106	364±115	0.88	506±166	<0.001
Hematocrit [%]	40±5	33±4	<0.001	30±4	<0.001
Platelet count [/nl]	236±74	165±56	<0.001	181±69	<0.001

Parameters of conventional coagulation analyses one day before elective CABG (T0) and 4 hours (T1) and 5 days (T2) after restarting antiplatelet therapy with 100 mg/d aspirin. Data are presented as mean ± standard deviation; p values at T1 and T2 are describing differences in relation to T0.

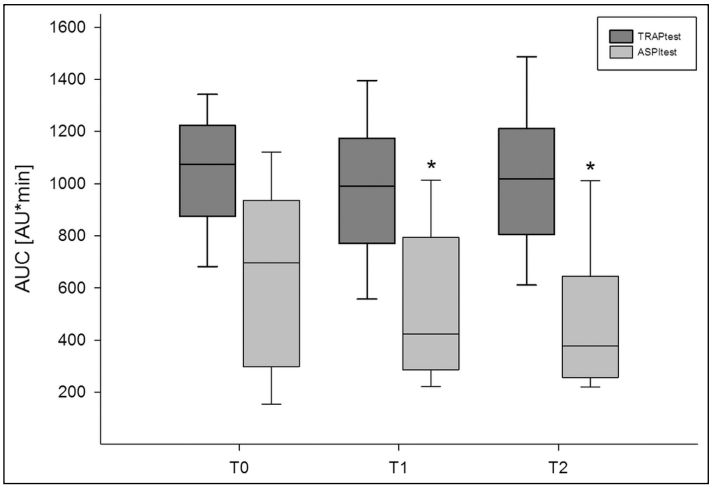

Figure 1: Pre- and postoperative platelet aggregation in MEA
*Platelet aggregation at T0, T1 and T2 in MEA following stimulation of platelet aggregation using thrombin receptor activating peptide (TRAPtest) or arachidonic acid (ASPItest). *indicates p < 0.05 compared to baseline measurements at T0; n=102.*

ences between platelet aggregation at T1 and T2.

Platelet aggregation in LTA is shown in Figure 2. Compared to baseline (84(57/89) %), platelet aggregation was significantly reduced at T1 (67(39/80) %, p<0.001) and T2 (54(36/79) %, p<0.001). There were no significant differences between platelet aggregation at T1 and T2 (p=0.191).

The diagnostic accuracy of the ASPItest in indicating the therapeutic antiplatelet effect of aspirin, as assessed by LTA, was expressed by receiver operating characteristic (ROC) curves for each measuring point. The area under the ROC curve (AUC) was 0.95 (p<0.0001) at T0, 0.88 (p<0.0001) at T1 and 0.81 (p<0.0001) at T2. The corresponding cut-off values, sensitivities and specificities are given in Table 2.

The analyses of the association between platelet aggregation in LTA and MEA is shown in Figure 3 and revealed significant positive correlations for measurement point T0 (r = 0.744, p < 0.001), T1 (r = 0.583, p < 0.001) and T2 (r = 0.518, p < 0.001), respectively.

Despite cessation of aspirin therapy 6.4 ± 1.2 days prior to surgery, ex vivo platelet aggregation at T0 was below the lower reference value for arachidonic acid-induced platelet aggregation [745 AU*min] in 55 (54%) patients in MEA and 40 (39%) patients in LTA [78%]. Four hours after the ingestion of 100 mg aspirin (T1), ex vivo platelet aggregation following stimulation with arachidonic acid was below the lower reference values in 72 (71%) patients in MEA and 68 (67%) patients in LTA. At T2, ex vivo platelet aggregation was below the lower reference values for

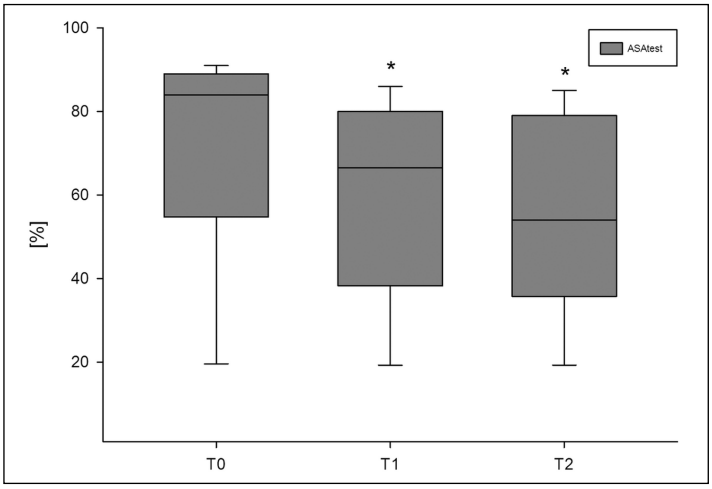

Figure 2: Pre- and postoperative platelet aggregation in LTA
*Platelet aggregation at T0, T1 and T2 in LTA following stimulation of platelet aggregation using arachidonic acid. *indicates p < 0.05 compared to baseline measurements at T0; n=102.*

Table 2: Receiver operating characteristic (ROC) curves analyses

Measuring point	AUC	95 % CI	p	Cut-off [AU*min]	Sensitivity [%]	Specificity [%]
T0	0.95	0.91-0.99	<0.0001	422	97	70
T1	0.88	0.81-0.95	<0.0001	410	91	69
T2	0.81	0.72-0.9	<0.0001	413	79	69

ROC: receiver operating characteristic, AUC: area under the curve, 95% CI: 95% confidence interval
AUC values of the ROC curves, the 95% CI, and p values. The cut-off values for the ASPItest [AU*min], indicating sufficient therapeutic antiplatelet therapy with the corresponding sensitivity and specificity (n=102).

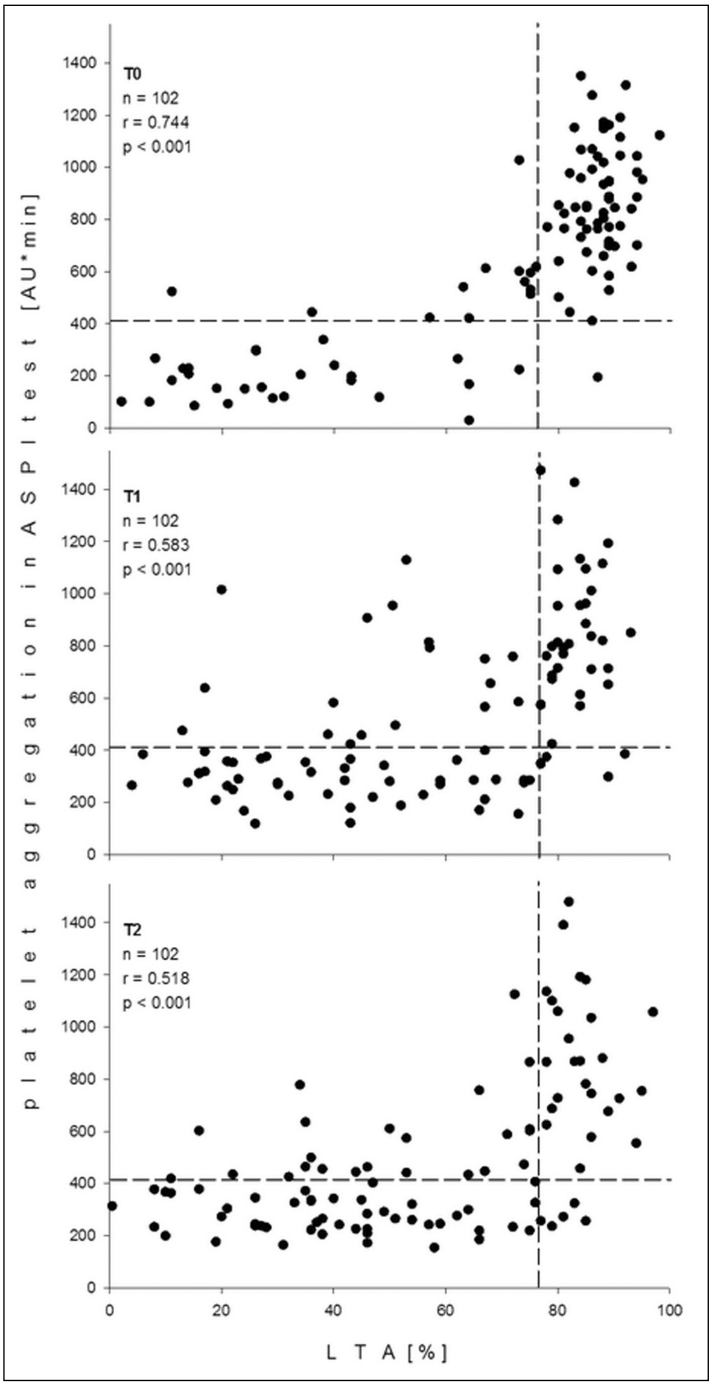

Figure 3: Correlation between MEA and LTA
*Correlations between platelet aggregation following stimulation with arachidonic acid in MEA (ASPItest) and LTA (ASAtest) at T0, T1 and T2. The horizontal dashed lines show the recommended cut-off value (420 AU*min) for therapeutic platelet inhibition in the ASPItest. The vertical dashed lines are showing the lower cut-off value for platelet aggregation in the ASAtest; n=102.*

arachidonic acid-induced platelet aggregation in 79 (78%) patients in MEA and 68 (67%) patients in LTA.

Despite the postoperative restarting of daily antiplatelet therapy with 100 mg of aspirin, arachidonic acid-induced platelet aggregation was within normal reference values at T1 in 30 (29%) patients in MEA and 34 (33%) patients in LTA and at T2 in 27 (26 %) patients in MEA and 34 (33%) patients in LTA (Fig. 3). Each of the patients identified as aspirin-nonresponder in MEA was also detected by LTA analyses both at T1 and T2. Overall, LTA and MEA showed equivalent classifications in 78 (76%) patients at T1 and 73 (72%) patients at T2.

Discussion

In the current investigation, convincing evidence is presented, that MEA is a reliable and quick method for detection of aspirin non-responsiveness in the perioperative period of patients undergoing cardiac surgery. Arachidonic acid-induced platelet aggregation is reported to be the most appropriate method for the assessment of the aspirin-induced inhibition of platelet aggregation [20]. LTA, using arachidonic acid as the in vitro activator for platelet aggregation, represents the gold standard for platelet function testing [14]. However, LTA is limited to specialized laboratories and is not feasible for monitoring platelet function at the bedside. Hence, reliable methods other than LTA for the point-of-care assessment of aspirin therapy would be attractive. In this context, the Platelet Function Analyzer (PFA-100®, Dade-Behring GmbH, Marburg, platelet stimulation by epinephrine/collagen), the "Rapid Platelet Function Assay" (RPFA, VerifyNow®-ASA, Accumetrics, San Diego, USA, platelet stimulation by arachidonic acid) and the new "Multiple Electrode Aggregometry" (MEA®, IL, Munich, Germany, platelet stimulation by arachidonic acid) are considered to be alternatives to LTA. However, there are only few data on whether the different tests produce consistent results. In previous investigations, PFA-100® as well as VerifyNow-ASA® did not seem to agree with LTA in the assessment of aspirin responsiveness [21-22], and the authors consequently concluded that these two methods were not recommendable for the identification of aspirin non-responsiveness. Pedersen et al. found a good repeatability of MEA results in a study comparing arachidonic acid induced platelet aggregation using MEA and LTA in 21 healthy individuals and 43 patients suffering from coronary artery disease treated with daily 75 mg aspirin. However, since the included participants did not undergo surgical intervention, study results cannot uncritically be transferred to a perioperative patient's collective [23].

In the present study, we demonstrated that arachidonic acid-induced platelet aggregation in MEA significantly correlated with platelet aggregation in LTA in a perioperative study collective. This applied to both pre- and postoperative assessments of arachidonic acid-induced platelet aggregation (Fig. 3). Furthermore, ROC analyses demonstrated the ability of MEA to predict therapeutic platelet aggregation as assessed by LTA (Table 2).

MEA results seemed to be independent from the observed postoperative variation of conventional coagulation parameters. Platelet aggregation in the TRAPtest remained unchanged, while hematocrit and platelet count were significantly reduced at T1 and T2 and fibrinogen concentration was significantly increased at T2 compared to baseline (Fig. 1, Table 1). Furthermore, ex vivo platelet aggregation in the ASPItest was probably not influenced by potential perioperatively acquired platelet dysfunctions since the thrombin-induced platelet aggregation in the TRAPtest remained unchanged during the study period (Figure 1)."

There is increasing evidence that aspirin non-responsiveness is clinically important since two meta-analyses, including a total of 33 studies and 4743 patients, showed that patients suffering from laboratory aspirin resistance had a higher incidence of major cardio- and cerebrovascular events as well as

mortality [11, 13]. Poston et al. identified laboratory aspirin resistance in elective CABG patients on the first postoperative day as a significant, independent predictor of graft thrombosis with an odds ratio of 2.59 [24]. The available data on the prevalence of aspirin non-responsiveness vary depending on the study population, aspirin dosage and performed platelet function assay between 0.4 and 83.3 % [10, 12]. Three recently published meta-analyses found that the average prevalence of laboratory aspirin resistance ranged from 25 to 27 % [11-13].

Platelet aggregation in MEA highly significantly correlated with LTA (Fig. 3). Each patient who showed normal platelet aggregation in MEA despite restarted aspirin therapy also showed values within normal reference values in LTA analyses at T1 and T2. LTA analyses showed that the prevalence of aspirin non-responsiveness (ASAtest ≥ 78 %) was 33 % (34 of 102 patients) at T1 and T2. 29 of these patients were determined to be aspirin-non-responders in MEA at both T1 and T2, which supported the thesis, that MEA would be a reliable method for the point-of-care detection of platelet reactivity despite aspirin therapy, the so-called aspirin resistance.

Thus far, no controlled studies have been performed to define a cut-off value to identify the therapeutic inhibition of platelet aggregation in the ASPItest. In their observational study in patients receiving long-term aspirin treatment, von Pape et al. recommended a cut-off value of 300 AU*min, since arachidonic acid-induced platelet aggregation was below 300 AU*min in 96 % of the patients [25]. In the present study, ROC analyses (Table 2) showed that the highest sensitivity (97%) and specificity (70%) of the ASPItest to indicate the therapeutic inhibition of platelet aggregation were achieved with a cut-off value of 422 AU*min. Thus, a cut-off value of 422 AU*min in the ASPItest may be recommended as the upper reference value for indicating sufficient aspirin-induced platelet inhibition.

There were some limitations to this study. Besides not referring to clinical outcome parameters, all patients postoperatively received the same daily dosage of aspirin (100 mg). Considering that daily postoperative aspirin dosages may vary based on local institutional standards between 75 and 325 mg [20], it would have been interesting to evaluate MEA for the assessment of different, potentially weight-adapted aspirin dosages.

Despite these limitations, this study has clinical impact. For the first time, MEA was studied to be feasible for the pre- and postoperative assessment of arachidonic acid-induced platelet aggregation at the bedside in elective CABG patients. Taking into consideration aspirin-nonresponsiveness, MEA could be useful to control and, if necessary, to adapt the postoperative aspirin dosage in order to achieve an adequate inhibition of platelet aggregation.

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