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Original paper

Monitoring of clopidogrel treatment by multiple electrode platelet aggregometry[1),2)]

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Abstract

Low responsiveness to clopidogrel is an important cause of adverse events after coronary stenting. Multiple electrode platelet aggregometry (MEA) measured by the Multiplate® system seems to be suitable for monitoring clopidogrel treatment. We validated this method by analyzing hirudin blood samples from 150 healthy volunteers to establish reference ranges of the MEA tests, from 75 hematologic patients with anemia or thrombopenia to determine the dependence of MEA values on hematocrit (HCT) and platelet count, and from 1005 patients after percutaneous coronary intervention (PCI) and 600 mg clopidogrel loading dose to test the reproducibility of the results under clinical conditions. It was found that MEA results are not affected by the different methods of blood withdrawal and sample transport, if the blood is kept at rest for 30 min before measuring. Measuring must be performed within 3 h after blood withdrawal. It was found that MEA results are not valid in patients with HCT $\leq$0.30 L/L or platelets $\leq$100/nL. Because clopidogrel loading also causes a decrease of thrombin receptor-activating peptide (TRAP) values, clopidogrel responsiveness, defined by ADP values under the lower reference level (men: 32 U, women: 46 U), can only reliably be classified if the TRAP value is $>$20 U and the TRAP/ADP ratio $<$3. Clopidogrel monitoring should be performed within 24 h after PCI, despite the risk of unclear results in $\sim$12%. In summary, by concentrating on preanalytical conditions and blood count, MEA is suitable to detect clopidogrel response. The TRAP test should be performed simultaneously to allow a valid assessment.

Keywords: clopidogrel; impedance aggregometry; multiple electrode platelet aggregometry (MEA); Multiplate®; platelet aggregation; therapy monitoring.

Introduction

As a result of the continuing developments in stent technology, acute coronary syndrome (ACS) and chronic coronary heart disease (CHD), whose incidence in Germany is approximately 3–4%, can today be treated in many cases with percutaneous coronary intervention (PCI) [1, 2]. In Germany $\sim$250,000 coronary stents are implanted each year [2]. In spite of the dual platelet inhibition with acetylsalicylic acid and the ADP receptor antagonist clopidogrel prescribed in the guidelines of the Deutsche Gesellschaft für Kardiologie [2], 0.5–1% of patients experience a stent thrombosis following the implantation of a stent, which in 10–11% of patients leads to death [3, 4]. The main cause for this complication is the insufficient effectiveness of clopidogrel in one segment of the patients [5].

The gold standard for measuring platelet aggregation inhibition caused by clopidogrel or other thienopyridines is light transmission aggregometry (LTA) according to Born [6], although it is difficult to standardize, costly and can be performed in only a limited number of laboratories [7].

During the last years various methods or instruments for measuring platelet function have been developed, of which some are also suitable for point-of-care testing (POCT) [8, 9]. Among these procedures multiple electrode platelet aggregometry (MEA) with the ''Multiple Platelet Function Analyzer'' (Multiplate®, Dynabyte, Munich) has proven to be a particularly simple, quick and comparatively inexpensive method [10]. It is based on the whole blood impedance aggregometry developed by Cardinal and Flower [11], in which platelets, athrombogenic at rest, adhere to electrodes following activation and in this way effect an increase in resistance. In contrast to the Chrono-Log-Aggregometer (Havertown, PA, USA), established for the past 20 years primarily in the USA, with its reusable measurement cell that requires costly cleaning after each measurement, an analysis with the Multiplate®-test occurs in a disposable measurement cell, whereby a double determination is performed with each measurement and the verification of the result is software-driven. Since no centrifugation is required and the instrument

[1)]Original German online version at: http://www.reference-global.com/toc/labm/34/2.
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is equipped with a computer-controlled electronic pipette, the Multiplate®-System is suitable for POCT. Thanks to the software-supported user guidance performing a test is simple and the result is available after ~10 min. The price range per measurement is between €5 and €7.

First investigations demonstrated that the results of the MEA are a good match with those of the LTA [12] and that the method is obviously qualified to recognize clopidogrel low responders (CLR) [13]. Not yet sufficiently investigated has been which preanalytical preconditions for a valid measurement must be fulfilled, to which extent hematocrit and platelet count influence the measured values, at which cut-off value one could speak of insufficient clopidogrel effectiveness (=low response), the optimal point in time for a measurement following PCI and the reproducibility of the values in practical use.

Materials and methods

Conducting MEA measurements

A Sarstedt Monovette®, r-Hirudin/2.6 mL (Sarstedt, Nümbrecht, Germany) was used to collect blood from the arm vein and – unless otherwise described – was then stored at room temperature for 30 min. MEA measurements were performed within 120 min after blood collection in accordance with the manufacturer's instructions. The disposable measurement cell contains two pairs of highly conductive, silvered copper wires. Alternating current flows between each pair independent of each other. The adherence and aggregation of the platelets after activation increase the electric resistance between the sensor wires. This increase of the electrical resistance is measured continuously and recorded as a curve over time. The area under the aggregation curve (''Area under the curve''=AUC) is converted into freely selected ''aggregation units'' (=U). These ''aggregation units'' represent a measure for platelet aggregation following the addition of the activator and permit an estimate of the effectiveness of certain platelet aggregation inhibitors. The following two activators were used throughout:

1. ADP (0.2 mM) for the detection of the effect of thienopyridines.
2. Thrombin receptor-activating peptide (TRAP) (1 mM) for the recognition of an additional effect of GPIIb/IIIa receptor antagonists and for the evaluation of the global platelet aggregation ability.

Preanalytic influence factors

Since the blood collection skills of clinic personnel vary, we investigated whether a possible shear stress would influence the platelets of the MEA measurement. For this purpose we collected blood in two different ways from 20 donors: one arm was compressed with a blood pressure cuff, so that the dynamic pressure was clearly above the diastolic blood pressure. After this arm was compressed for at least 3 min, we used a 21G cannula to collect a blood specimen. The other arm was compressed only slightly and briefly, so that it was possible to use a 19G cannula to collect a specimen.

Since the manufacturer states that MEA measurements using ADP or TRAP activators should be performed after storage at room temperature of no less than 30 min, we tested what influence the type of storage has on the measurement values. We collected two tubules of hirudin blood each from 16 blood donors. Prior to measuring one tubule was stored vibration-free (resting storage) for 30 min, the other one was placed on a roll mixer or carried around and occasionally mixed upside down. This was intended to simulate the usual transport conditions of laboratory specimens.

In order to test to what extent pneumatic dispatch affects the measurement values, we collected two tubes of hirudin blood each from 20 people. One sample was immediately stored vibration-free, while the other sample was sent on a 30 s pneumatic ride. Following 30 min of resting storage of the second sample we took MEA measurements from both tubes.

Establishment of reference ranges

Reference ranges for the ADP and the TRAP test were established with the help of 92 platelet donors and 58 healthy laboratory employees of the Klinikum Augsburg (75 males and 75 females, ages 19–66 years; mean value (MV)=40). Interviews confirmed that the test persons had not taken any platelet-inhibiting drugs in the previous 10 days or that they suffered from any platelet function-impairing diseases.

MEA values following the administration of a clopidogrel loading dose

From January 2008 to July 2009 MEA measurements were performed in 1139 coronary stent recipients within 24 h after administration of the loading dose of 600 mg clopidogrel. In exceptional cases, e.g., the additional administration of GPIIb/IIIa antagonists, measurements were taken in subsequent days under a maintenance dose of 75 mg. One hundred and thirty-four patients, whose TRAP value or TRAP/ADP ratio was repeatedly too low or whose values were within a gray area or could not be evaluated safely because of anemia or thrombopenia, were excluded, so that ultimately 1005 patients became a part of the evaluation.

Dependence of MEA values on hematrocrit and platelet counts

In order to examine the dependence between platelet count or hematocrit (HCT) and the MEA values, we calculated the correlation coefficient for the corresponding data of 100 healthy test individuals. Since platelet function tests frequently do not provide usable results when platelet values, but also hematrocrit values, are low, MEA measurements were performed with 75 anemic and/or thrombopenic patients of the hematologic-oncologic outpatient clinic, who took no thienopyridines or GPIIb/IIIa antagonists.

Reproducibility of MEA-measurements

Since the Multiplate® device is equipped with five identical measuring channels, the hirudin blood of a test person was tested consecutively by one examiner in intervals of 15 min on all five channels for a total of five times, so that the differences between the individual measuring channels could be determined. In order to detect the range of imprecision within a period of 30–270 min following blood collection, hirudin blood from five donors was measured nine times each, whereby the same measuring channel was always used for each test person.

Since no control material is available for MEA measurements for reasons of stability, the interassay variability was determined with the blood of five test persons who made themselves available for blood collection ~30 times over a period of 18 months.

With 291 stent patients, who showed adequate platelet aggregation inhibition following the administration of the clopidogrel loading dose, the Multiplate® analyses were checked during subsequent days in part several times, in order to evaluate the reproducibility of the results in the clinical practice. In 17 patients a check of the responder status proved possible even several weeks later at their readmission to the hospital.

Statistical methods

Average value, median, standard deviation and variation coefficient were calculated according to the usual formulas. We used the two-tailed one-sample-t-test to check for significant differences between the various pre-analytical conditions. We used the two-sample-*t*-test to evaluate any significant difference in the TRAP values of reference persons and patients following a loading dose. When the χ^2-adjustment test to level 0.1 did not result in a normal distribution of data, we instead used the Wilcoxon-rank-sum test. The significance level was set at $p \leq 0.05$.

Results

Preanalytic influence factors

The results of the MEA measurements (Table 1) after venous compression of dissimilar strength and by means of cannulae with a different lumen showed no significant differences between the various blood collection procedures.

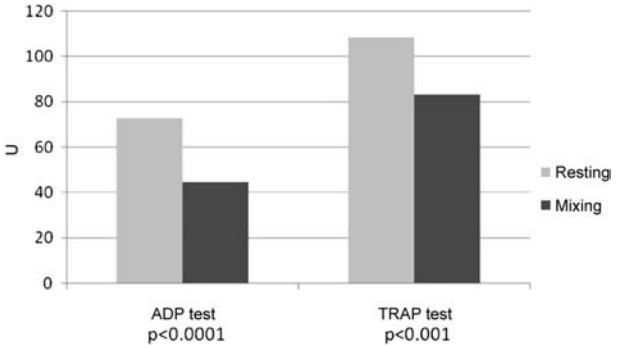

Figure 1 Results of MEA measurements in 16 healthy test persons following resting storage and storage with occasional or continuous mixing.

As demonstrated in Figure 1, the specimen tubules must be stored vibration-free during their waiting time of at least 30 min before a measurement is taken, since lower values were measured as a consequence of the occasional mixing that can happen during transport or when stored on a roll mixer.

The MEA values of the 20 hirudin blood specimens that were sent via pneumatic dispatch before being stored at rest did not differ from the values obtained from specimens collected at the same time and immediately stored vibration-free (average values of measurement with/without pneumatic dispatch: ADP test 70.5/70.3 U; TRAP test 104.8/105.6 U).

Establishment of reference ranges and determination of the cut-off value for responders

Reference values in males and females differed significantly in the ADP as well as the TRAP test, so that a gender-dependent evaluation was required (Figure 2).

While the distribution of measured values in the TRAP test is governed by a standard-normal distribution, the measured values for the ADP test follow a log-normal distribution. Since the lower limit of the ADP test is the deciding factor for establishing a cut-off value between low responders and responders, we calculated the 95% confidence interval for this value.

The resulting reference ranges are as follows (confidence intervals in parentheses):

	ADP test, U	TRAP test, U
Males:	35 (32–38)–114	68–134
Females:	50 (46–53)–132	79–151

Table 1 Influence of vein compression and cannula diameter on the results of MEA measurements.

n = 20	ADP test		TRAP test	
	Low compression 19G cannula	Strong compression 21G cannula	Low compression 19G cannula	Strong compression 21G cannula
Average value, U	83.3	81.2	117.2	114.5
Min/max value, U	44–117	34–113	78–134	90–141
Variation coefficient, %	19.8	22.0	12.8	14.4
	n.s.		n.s.	

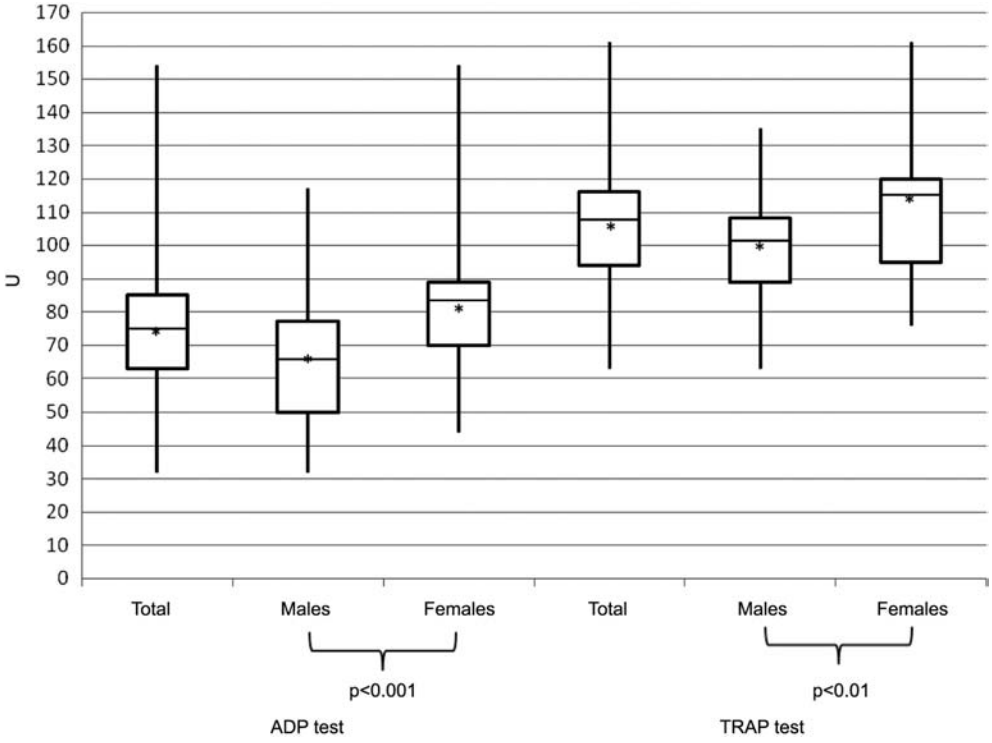

Figure 2 Results of MEA measurements in 150 healthy test persons (75 of each males and females). The horizontal line indicates the average value, the star indicates the median.

When monitoring the effect of thienopyridines the target range for the ADP value in males is <32 U, in females <46 U ($=$responder). With ADP values of >38 or >53 U patients are classified as ''low responders''. Patients with ADP values in the confidence interval ($=$gray area) should not be given a classification, but should be recommended for a control study.

Dependence of MEA values on hematrocrit and platelet counts

The measurement results of the ADP and TRAP tests were correlated with the platelet count and the hematocrit value in 100 blood donors. Platelet values were between 174 and 480/nL, HCT values were between 0.36 and 0.54 L/L. On the level of $p=0.01$ there was a linear, positive connection (correlation coefficient $r=0.462$ or 0.353) between the ADP or TRAP values and the platelet count, a weak negative linear connection ($r=-0.284$ or -0.264) between hematocrit and the ADP or TRAP values.

The 75 hematologic-oncologic patients who did not take thienopyridines were divided into four groups dependent on HCT and platelet values. The results of the MEA measurements can be seen in Table 2.

All MEA values in group 1 were markedly below the reference ranges. With 20/21patients the TRAP/ADP ratio was <3 (0–2.74; MV 1.46). One patient exhibited a responder constellation (TRAP/ADP$=$30/3). In group 2, 5/7 TRAP values were <20 U. One patient had a TRAP/ADP ratio of <3, one patient had unremarkable values. In group 3 only 10/26 patients had unremarkable values, three patients met the criteria for responder status. Nine patients had a TRAP/ADP ratio of <3 (1.46–2.88; MV 1.99) and the values of four others were in the gray area. The MEA values in group 4 were inconsistent: while 13/21 patients had values within the reference range, two patients exhibited the constellation typical for responder status. Six patients showed a TRAP/ADP ratio of <3.

The following conclusions were drawn from these results:

1. The Multiplate® test is not usable when the platelet count is ≤ 100/nL.
2. Since with platelet counts of >100/nL, but HCT values of ≤ 0.30, only 10/26 patients ($=38\%$) had values within the reference range and a responder constellation was found in 3/26 patients not taking thienopyridines, an HCT that is ≤ 0.30 should also be a exclusion criterion for the test.
3. At HCT values between 0.31 and 0.35 and platelet values >100/nL the results of 13/21 patients were within the reference range. 2/21 patients showed a responder constellation even without thienopyridines (TRAP/ADP: 79/25 and 38/12). MEA results in this HCT range must therefore be evaluated with reservation, most of all in the presence of lowered ADP values, and with a TRAP/ADP ratio of only just >3 they are in particular need of control.
4. When evaluating the effect of thienopyridines we must also take into consideration the result of the TRAP test. With TRAP values <20 U or with a TRAP/ADP ratio

Table 2 MEA values in patients with anemia and/or thrombopenia without use of thienopyridines.

Patient groups		ADP value MV Min/max, U	TRAP value MV Min/max, U
Group 1, n = 21			
HCT ≤0.30 L/L and platelets ≤100/nL		8.9	16.0
HCT: 0.21–0.30 L/L	MV 0.27	1/23	1/49
Plt: 8–99/nL	MV 45.6		
Group 2, n = 7			
HCT >0.30 L/L and platelets ≤100/nL		12.7	30.3
HCT: 0.31–0.41 L/L	MV 0.34	2/50	5/114
Plt: 20–80/nL	MV 44.0		
Group 3, n = 26			
HCT ≤0.30 L/L and platelets >100/nL		42.5	72.3
HCT: 0.22–0.30 L/L	MV 0.28	10/81	19/146
Plt: 104–506/nL	MV 213		
Group 4, n = 21			
HCT >0.30 L/L and platelets >100/nL		53.3	85.6
HCT: 0.31–0.35 L/L	MV 0.33	20/124	51/123
Plt: 110–608/nL	MV 259		

<3 no statements should be made on the effect of thienopyridines in spite of ADP values in the responder range, since there presumably are no regular measurement conditions.

MEA values following administration of the clopidogrel loading dose of 600 mg

Eight hundred and eighty-seven (88.3%) of the 1005 patients were classified as clopidogrel responders based on the above named criteria. Under standard clopidogrel therapy 118 patients (11.7%) exhibited ADP values in the reference range and accordingly were CLR. At the first measurement, 885 (88.1%) of the 1005 stent patients could be definitely evaluated in respect to their clopidogrel response. Of the remaining 121 patients, 99 were assigned with certainty to responder or low responder status at the second measurement, 16 at the third and 6 at the fourth measurement. Hence, measurement at an early point in time following stent implantation as a rule provides unambiguous findings.

The values contained in Table 3 demonstrate that, after stent implantation and use of the loading dose, TRAP values of patients also are significantly ($p < 0.001$) lower when compared to the reference collective.

Results of control studies in patients with initially not clearly evaluable MEA values

At the first measurement, 121 of the 1005 patients (=12%) had a TRAP/ADP ratio of <3 and/or a TRAP value of <20 U or ADP values in the gray area. Control studies resulted in a responder status for 87, a low responder status for 34 (=28.1%) patients. In 30/34 CLRs the insufficient response to clopidogrel was discovered within seven days (MV 2.9), in the remaining four only after seven or more days.

Reproducibility of MEA measurements

The variation coefficients (CV) for measuring a specimen (ADP 76.7 U; TRAP 128.5 U) at all five channels were between 5.1 and 15.1% (MV 8.7) for the ADP test and between 4.4 and 8.0% (MV 6.8) for the TRAP test. For the CV of precision in series (ADP test: n = 5; TRAP test: n = 9; measurement at one single channel) the values obtained with

Table 3 ADP and TRAP values of clopidogrel responders and low-responders.

	Responder		Low responder	
	Males n = 635	Females n = 252	Males n = 94	Females n = 24
ADP test				
Average value, U	11.8	13.6	52.5	61.8
Min/max value, U	1–31	1–44	36–151	50–87
TRAP test				
Average value, U	62.9	71.7	97.7	104.8
Min/max value, U	21–128	22–138	48–154	82–138

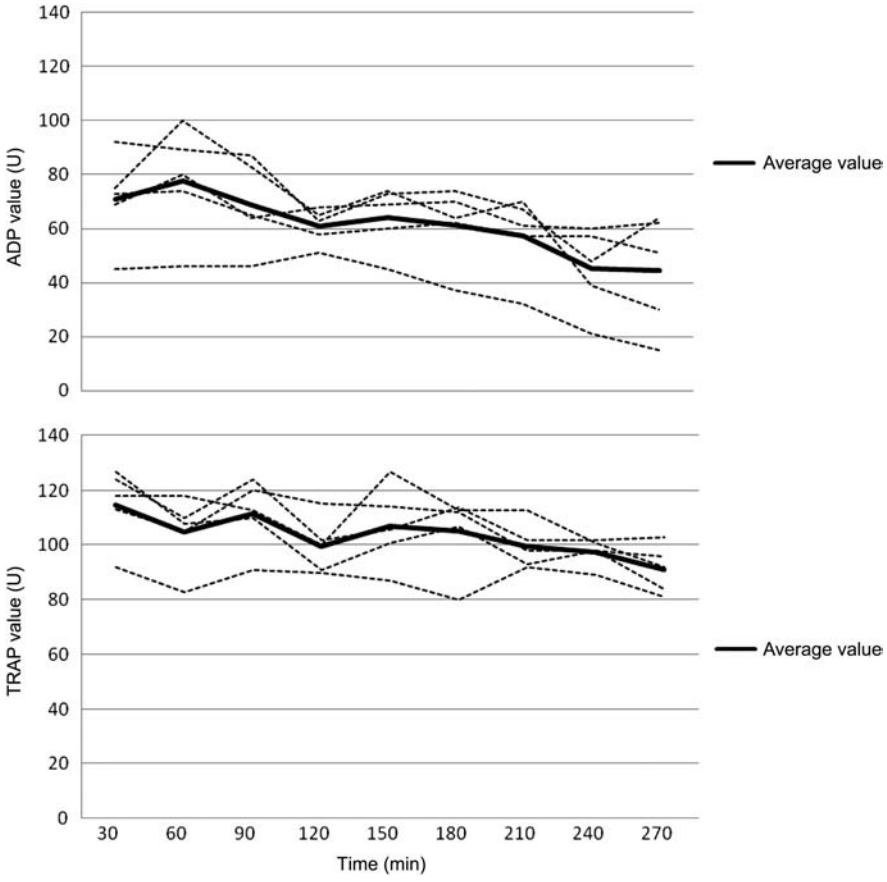

Figure 3 Dependence of ADP and TRAP values from time of measurement following blood collection.

the ADP test ranged from 5.4 to 16.6% (MV 11.4), with the TRAP test from 5.4 to 10.7% (MV 9.0). Since in the ADP test a marked lowering of values occurs after only 180 min following blood collection, only the first five measurements were evaluated in this test (Figure 3). For day-to-day imprecision CV values between 11.6 and 23.0% (MV 16.4) were measured in the ADP test, in the TRAP test measured values were between 9.3 and 14.0% (MV 11.1), whereby these results are additionally influenced by the intra-individual variability of the measurement values.

Control studies were performed with 291 hospitalized coronary stent patients with adequate inhibition of platelet function receiving 75 mg of clopidogrel/d, so that the reproducibility of measurements could be evaluated in the clinical practice. We also pursued the question of whether the result in patients, who were judged to be clopidogrel responders in the first measurement, would have been more definite in a later measurement. As stated earlier, the evaluation of the responder status is the more certain, the higher the TRAP value and the ratio TRAP/ADP.

When monitoring MEA measurements only 75 patients (25.8%) showed more unambiguous results. In follow-up measurements, 198 patients (68.0%) had measurement results that, although also pointing clearly to a responder status, did not permit a more unequivocal evaluation. On the other hand, in follow-up measurements no unambiguous statements as to responder status could be made concerning 17 of the patients (5.8%). Initially one patient was a clopidogrel responder, but exhibited low responder status in a follow-up measurement. In those 17 patients whose control study occurred 29–475 days (MV 213) later, responder status could be confirmed in all cases while the values were a good match with the correlation coefficients of 0.790 for ADP and 0.734 for TRAP.

Discussion

The Multiplate® system was developed primarily as a POCT method and at present is used mostly for the quick bed-side evaluation of platelet function in patients with perioperative coagulation defects [14]. The use of this instrument in the central laboratory of a clinic is rather an exception, but it does allow the utilization of the measuring system by various clinical specialties and ensures constant quality, since the measurements are performed by qualified personnel. When MEA tests occur at a central location, it is necessary to clarify to what extent preanalytic factors, e.g., varying collection and transport conditions, delays in performing the measurements, etc., can influence the results. As yet there are almost no studies on this subject [15].

To avoid any platelet-activating shear stress when measuring platelet function, the vein used to collect the blood should not or should only be compressed for a short period and a cannula with the widest possible lumen should be used, all of which is difficult to ensure in the day-to-day work of the clinic. Our investigations demonstrated that the method of blood collection does not influence the MEA measurements. The pneumatic dispatch of hirudin tubule also seems to present no problem. The precondition in all cases is that the blood specimen must not be subject to any vibration for at least 30 min before measurements are taken. Permanent or even occasional mixing during storage leads to significantly lower MEA values, which has also been established by other investigators [15]. At least during the first 30 min platelets are obviously refractory and during this period they will only recover if placed at rest [7].

As demonstrated by our results, AUC values in the ADP test as well as the TRAP test decrease continuously at the latest 90 min after blood collection, whereby ADP values drop noticeably faster than TRAP values. This stability difference of the measured quantities means that a false-low ADP value with a still relatively high TRAP value, caused by measurement that was performed too late, can mimic responder status. Hence, reliable monitoring of thienopyridine is possible only if a MEA measurement is performed without delay after 30 min of resting storage and – as stated in the manufacturer's instructions – no later than 180 min after blood collection.

Because the type of cell being investigated is easily activated and unstable, in comparison to other laboratory examination measurements of platelet function are susceptible to faults, difficult to standardize and characterized by high imprecision [7, 8, 16–18]. For intra-assay variability the Multiplate® system quotes CV values between 3.9% and 19.9% [10, 12, 16]. Depending on the measuring channel we found coefficients of variation between 9.2% and 16.4% in the ADP test and between 3.3% and 7.8% in the TRAP test. When taking into account all measurement channels, the coefficient of variation for the ADP test was 12.1% and for the TRAP test it was 7.2%. The relatively high CV of the ADP test in our series of measurements is conditioned on the fact that on average the values measured 60 min after blood collection were markedly higher than the 30 or 90 min values (see Figure 3). Obviously at that time the reconstitution of the intracellular reservoir is again mostly completed [7], so that the platelets exhibit a maximum ability to aggregate before – this time because of platelet aging – there again occurs an initially slow and later stronger decrease of the ability to aggregate. No such phenomenon is recognizable in the TRAP test. Therefore, the ideal time of an ADP measurement for monitoring the effect of thienopyridine would be 60 min after blood collection, which is also recommended for optical aggregometry [7]. Since such timing of measurements is not possible in the clinical practice, we investigated the reproducibility of the method under these conditions. With ~94% of patients classified as clopidogrel responders in the first measurement the result was confirmed in the control examination within the following days. With ~6% the second measurement did not provide an unambiguous result. The control found a deviating result from the initial diagnosis of low responder status in only one of 291 patients, although this might be due to a lack of compliance.

As also determined by other work groups [19–21], thienopyridine therapy causes a lowering of TRAP values. Obviously it is not only the GPIIb/IIIa receptor antagonists, but also the thienopyridines that inhibit the TRAP induced platelet aggregation to a certain extent, and our results demonstrate that the main effect is detectable following the administration of the loading dose. This phenomenon can complicate the evaluation of the effectiveness of ADP receptor antagonists. In analogy to other platelet function tests MEA measurements are influenced by anemia and thrombopenia [18, 22, 23]. In our studies, patients with an HCT of $\leq$0.30 L/L and/or a thrombopenia of $\leq$100/nL had increasingly lowered MEA values or responder-typical constellations even without the use of platelet aggregation inhibitors. Therefore, the co-evaluation of the TRAP test and the TRAP/ADP ratio in patients with borderline HCT and platelet values is of great importance, since otherwise a low ADP value can be misinterpreted as responder status. According to our results a reliable evaluation of the effectiveness of thienopyridine therapy is not possible in patients with TRAP values of $\leq$20 U or a TRAP/ADP ratio of $\leq$3. 34/118 (=29%) of all CLRs would have been wrongly classified as responders without the co-evaluation of the TRAP-value.

When conducting intervention studies, in which a low responder status would occasion a corresponding change of therapy, it is necessary to define a cut-off value that separates responders from low responders. For this purpose we determined reference ranges for ADP and TRAP values in healthy test persons and in both tests found clearly higher values for females, which also manifested itself in different cut-off values. Gender-dependent reference values were also found by means of MEA testing and with LTA testing [16, 24]. It is known from various studies that females possess an increased basic platelet reactivity, and our results therefore do not surprise [25]. Besides a low hematocrit the cause for these gender-dependent differences appears mostly hormone-related [24, 25].

Since the risk of a stent thrombosis exists primarily in the first five days following PCI [3, 4], an examination of clopidogrel effectiveness should be performed within the first 24 h after the administration of the loading dose and therapy should be adjusted accordingly as soon as possible. Besides compliance with preanalytic conditions it is necessary to heed the following, if reliable results are to be obtained: Since a manifest anemia and thrombopenia makes a measurement meaningless, a current blood count should be available. If the named criteria in respect to the level of the TRAP value and the TRAP/ADP ratio are not met or if the results are borderline, a control examination is indicated.

Our studies demonstrated that to obtain definite results multiple controls are required with ~12% of patients. This appears reasonable in spite of the associated stress for the patient and the additional cost, since almost 30% of patients with initial findings in need of control were shown to be

CLR in a repeat measurement. Hence the portion of CLRs in this group is nearly three times as high as in the total collective.

As these data show, the effectiveness of clopidogrel following a stent implantation can be monitored in the routine clinical practice through MEA measurement by means of the Multiplate® system as long as the preconditions described above are observed. A prospective intervention study was able to prove that a MEA-driven optimization of therapy following PCI markedly reduced the rate of low responders and the number of cardiovascular events like death from cardiac cause, non-fatal myocardial infarction and non-fatal stroke [26].

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Conflict of interest

All authors declare that there are no conflicts of interest.

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