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# Detection of clopidogrel resistance by MEA and LTA

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**Summary**
**Antiaggregation therapy is still the most frequently used approach to prevent thrombotic events in cardiovascular disease. It has a good clinical effect but there is increasing evidence of high residual platelet aggregation activity in a number of patients. Laboratory methods only allow us to detect clopidogrel "non-responders" or "low responders". Recent methods are based on monitoring residual platelet aggregation activity (aggregation methods) or detecting the number of free epitopes for binding a specific monoclonal antibody such as vasodilator-stimulated phosphoprotein phosphorylation (VASP). The aim of our study was the comparison of light transmission aggregometry (LTA) and multiple electrode platelet aggregometry (MEA) with induction by ADP at concentrations of 20 µmol/L with or without prostaglandin E1 ($PGE_1$). In the studied group of 84 patients with cardiovascular disease (CAD), an impaired individual response to clopidogrel therapy was detected by MEA and LTA in 11.9% and 10.7%, respectively. The LTA and MEA methods with induction by ADP with $PGE_1$ and without $PGE_1$ were statistically compared using Spearman's nonparametric correlation analysis. Both methods using $PGE_1$ have a positive significant correlation (P=0.003) in contrast to the results without $PGE_1$ with no significant correlation (P=0.732).**
**The sensitivity of clopidogrel resistance detection correlates well with other data in literature suggesting that there are 5% - 30% of clopidogrel low-responders depending on the type of platelet function assay used and the criteria for defining a low-responder. These results favour implementation of the ADP test with $PGE_1$ by MEA specifically for the identification of low-responders on clopidogrel.**
**Key words: antiplatelet therapy, clopidogrel, multiple electrode aggregometry, platelet aggregation**

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## Introduction

Antiaggregation therapy remains the most frequently used approach to prevent thrombotic events in cardiovascular disease. It has a good clinical effect but there is increasing evidence of high residual platelet aggregation activity in a number of patients.

In current literature, there are multiple definitions of resistance to antiplatelet drugs. The most common is resistance to a specific agent best indicated by persistent activity of the agent's target despite treatment. This definition also assumes sufficient dosage to provide optimal levels for target inhibition. However, thrombosis is a multifactorial process involving multiple pathways of platelet activation and factors other than platelets. For this reason, the occurrence of clinical events during treatment with a specific antiaggregation agent cannot be interpreted solely as "resistance" to the therapeutic agent (1).

On the basis of the above definition, laboratory methods only allow us to detect clopidogrel "non-responders" or "low responders". An optimal laboratory method is the key for good clinical correlation. Laboratory methods arise from knowledge of the metabolic conversion of thienopyridine pro-drugs. As a typical thienopyridine agent, clopidogrel is a pro-drug that requires hepatic conversion to an active metabolite in order to inhibit platelet function. Clopidogrel is absorbed in the intestine and extensively metabolized by hepatic cytochrome P450 (CYP3A4) to an active thiol metabolite (2, 3). This metabolite irreversibly binds to the P2Y12 receptor for the lifetime of the platelet. In addition to inhibiting adenosine diphosphate (ADP) - induced platelet aggregation, clopidogrel also inhibits ADP-stimulated P-selectin and CD40L expression (4–7).

Based on this explanation, a number of authors have optimized laboratory methods for monitoring clopidogrel therapy. These methods are based on monitoring residual platelet aggregation activity (aggregation methods) or detecting the number of free epitopes for binding a specific monoclonal antibody such as vasodilator-stimulated phosphoprotein phosphorylation (VASP). For many years, the gold standard for monitoring clopidogrel therapy action was the VASP method, while aggregation methods were considered less suitable. However, the costs of VASP and the need for experience with flow-cytometry substantially limit the use of this assay. These limitations formed the background of the present research on aggregation methods.

Numerous studies have examined the effects of antiaggregation therapy on ex-vivo assays of platelet function variability as the degree of inhibition of platelet function observed in individuals taking acetylsalicylic acid (ASA) or clopidogrel or both.

There are a number of modifications of the laboratory methods used for monitoring clopidogrel treatment on the basis of measuring residual platelet aggregation activity. Aggregation is induced by ADP in concentrations of 20 µmol /L with or without prostaglandin E1 (PGE1). A more detailed knowledge of the aetiopathology of platelet ac-

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tivation is needed for understanding these different results.

Platelet aggregation induced by ADP is preceded by rapid increase in the concentration of $Ca^{2+}$ ions in the cell cytoplasm (8). The increasing $Ca^{2+}$ concentration is caused by ADP acting at the $P2Y_1$ receptor. This receptor is a Gq-coupled receptor linked to phospholipase C and the generation of inositol 1,4,5-triphosphate. Rapid increase in intracellular $Ca^{2+}$ occurs mainly through release of $Ca^{2+}$ into the cytoplasm from intracellular stores and additionally by extracellular $Ca^{2+}$ influx (9). The released $Ca^{2+}$ leads to cell activation followed by initiation of aggregation. It is already known that mobilization of $Ca^{2+}$ from intracellular stores is inhibited by raised levels of cAMP via inhibition of phospholipase C activation. Agents that raise the level of cAMP in platelets thus reduce $[Ca^{2+}]i$ and this leads to inhibition of platelet aggregation. One such agent is PGE1 which increases cAMP by stimulating adenylate cyclase. Based on this knowledge, an optimal laboratory method can be proposed with good clinical correlation for measuring the effect of a specific antiaggregation agent such as clopidogrel on receptors like the $P2Y_1$ receptor.

Platelet aggregation can also be regulated by endothelial functions. The endothelium is involved in a multitude of physiological processes including the control of cellular trafficking, the regulation of vasomotor tone and the maintenance of blood fluidity. Endothelial cells (ECs) possess surface receptors for a variety of physiological substances, for example thrombin and angiotensin II, which may influence vascular tone directly or indirectly through various haemostasis-related events. Once activated, ECs express on their surface, and in some cases release into the plasma, a variety of intracellular adhesion molecules (e.g. vascular cell adhesion molecule, E-selectin, P-selectin, and von Willebrand factor, vWf), which modulate leukocyte and platelet adhesion, inflammation, phagocytosis and vascular permeability. Intact ECs exert a powerful inhibitory effect on haemostasis by virtue of the factors that they synthesize and release or express on their surface. The endothelium can affect the methods for detecting the effect of antiplatelet therapy by potentiating residual platelet activity.

Dual antiaggregation therapy (ASA and clopidogrel) is the treatment of choice for preventing thrombotic complications in patients undergoing percutaneous coronary intervention (PCI). Clopidogrel with a single loading dose as thrombotic prevention has been shown to be optimal, but recent studies have demonstrated that the response to clopidogrel varies widely. This highlights the need to incorporate a method for monitoring the effects of clopidogrel therapy in clinical practice.

## Design and Methods

### Patients

Clopidogrel-mediated platelet inhibition was evaluated after obtaining signed, written informed consent from 84 patients (67 males, 17 females) with cardiovascular disease (coronary, peripheral, or carotid artery disease) after coronary stent implantation. The median age of this cohort of patients was 60.5 years and a family history of cardiovascular disease was present in 56% of the patients. The associated diseases in this group were hypertension in 68%, diabetes mellitus in 26.5% and dyslipidemia in 80.9%.

The control group consisted of 40 healthy blood donors with a comparable sex ratio and a median age of 32.5 years in order to establish cut-off values for both tests.

All patients received a loading dose of 300 mg clopidogrel 24 hours (h) prior to intervention followed by a once-daily dose of 75 mg clopidogrel. The exclusion criteria were known ASA or thienopyridine intolerance (allergic reaction, gastrointestinal bleeding), treatment with vitamin K antagonists (warfarin, phenprocoumon, acenocoumarol), treatment with dipyridamol or non-steroidal anti-inflammatory drugs, a family or personal history of bleeding disorders, malignant paraproteinemias, myeloproliferative disorders or heparin-induced thrombocytopenia, severe hepatic failure, known qualitative defects in thrombocyte function, a major surgical procedure within one week before inclusion, a platelet count < 100,000 or > 400,000/µl and a haematocrit < 0.30.

The samples for laboratory testing were taken at least 72 hours after receiving a loading dose of clopidogrel treatment for the maximum antiaggregation effect.

### Blood sampling

Blood was withdrawn from the antecubital vein using a 21-gauge butterfly needle (0.8 x 19 mm; Greiner Bio-One, Kremsmünster, Austria) 72 h after percutaneous intervention. After the initial 3 ml of blood had been discarded to reduce procedurally induced platelet activation, blood was drawn into a 3.8% sodium citrate Vacuette tube (Greiner Bio-One; 9 parts of whole blood, 1 part of sodium citrate 0.129 M/L) for evaluation by light transmission aggregometry, into a 3.2% sodium citrate Vacuette tube (Greiner Bio-One; 9 parts whole blood, 1 part sodium citrate 0.109 M/L) and into a Vacuette tube containing hirudin (15 IU/mL) for determination by multiple electrode platelet aggregometry.

To avoid procedural deviations, all blood samples were taken by the same team using the same method. The blood samples were mixed adequately by gently inverting the tubes. To avoid investigator-related variation of results, each of the different tests was performed by just one single blind operator. The results of all assays were available to all patients (10).

### Light transmission aggregometry (LTA)

LTA was performed on the APACT 4004 aggregometer (LABiTec, Ahrensburg, Germany). Citrate-anticoagulated whole blood was centrifuged at 150 x g for 10 minutes (min) at room temperature to obtain platelet-rich plasma (PRP). Platelet-poor plasma (PPP) was obtained from the remaining specimen by re-centrifugation at 2,000 x g for 10 min. Platelet counts were not adjusted

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with a median platelet count of 250 x $10^{12}$/L (range 225–278 x $10^{12}$/L). The baseline optical density was set with PPP. Aggregation was performed using ADP (Helena Biosciences, United Kingdom) at a final concentration of 10 μM with/without $PGE_1$ and a final concentration of 30 μmol/L and optical density changes were recorded photoelectrically for 6 min as platelets began to aggregate. The maximal aggregation response was registered and used to differentiate between patients with and without residual ADP-inducible platelet aggregation (11 – 13).

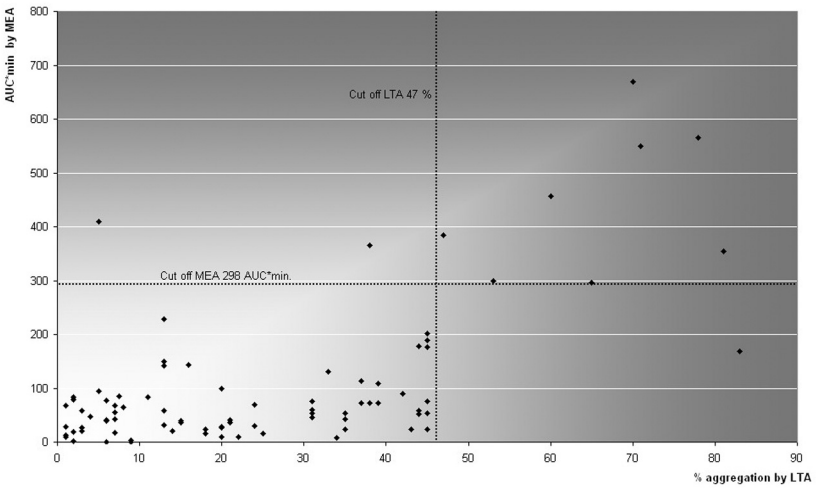
**Multiple electrode platelet aggregometry (MEA)**

Whole blood impedance aggregometry was performed with the Multiplate analyzer (10-15) (Dynabyte, Munich, Germany). One Multiplate test cell contains two independent sensor units and one unit consists of two silver-coated highly conductive copper wires 3.2 mm long. After dilution (1:2 with 0.9% NaCl solution) of hirudin-anticoagulated whole blood and stirring in the test cuvettes for 3 min at 37 °C, ADP (Dynabyte, Munich, Germany, final concentration of 6.4 μM) was added and the aggregation was continuously recorded for 6 min. The adhesion of activated platelets to the electrodes was initiated using ADP (Dynabyte, Germany) to a final concentration of 10 μM with/without $PGE_1$ and a final concentration of 30 μmol/L and the adhesion was monitored as an increase in impedance detected for each sensor unit separately and transformed to aggregation units (AU)*min that were plotted against time (14, 15).

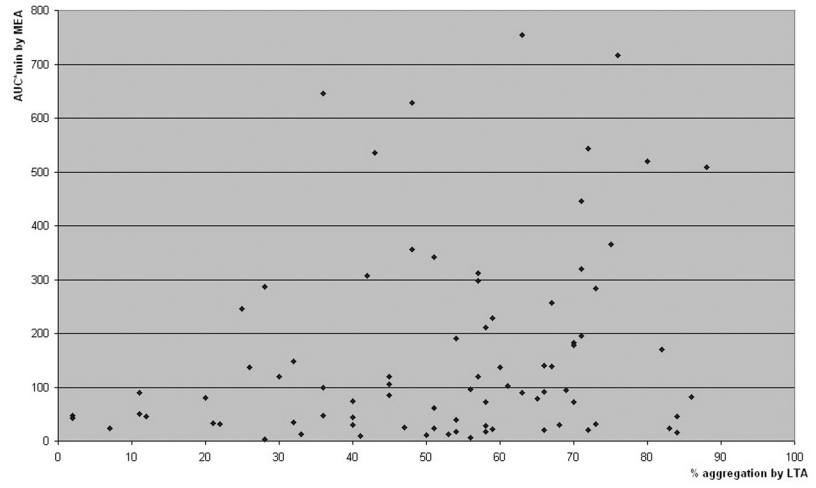
## Results

In the studied group of 84 patients with cardiovascular disease (CVD), an impaired individual response to clopidogrel therapy was detected by MEA and LTA in 11.9% and 10.7%, respectively.

In our opinion, the crux of the problem lies in the definition of cut-off values and the implementation of these methods. Our locally determined reference ranges in a population of 40 healthy blood donors were 298 – 711 AUC/min. for ADP HS with $PGE_1$ using MEA and 47 – 99% for ADP with $PGE_1$ using LTA. The cut-off values for failure of clopidogrel therapy for methods with $PGE_1$ were determined as 298 AUC/min. for MEA and 47 % for LTA. The cut-off values for methods without $PGE_1$ could not be determined, because the statistical distribution of results was without any relationship. $PGE_1$ reduce the activation contribution from ADP binding to $P2Y_1$ receptors, thus making the assay using $PGE_1$ specific for the effects of ADP mediated by $P2Y_{12}$. The test using $PGE_1$ as activator is designed to measure the platelet $P2Y_{12}$ receptor blockade – specific effect of clopidogrel treatment.




**Graph. 1.**




**Graph. 2.**

The difference between detecting systems minimally influenced the result for resistance to antiaggregation therapy. Both methods offer comparable results of 11.9% and 10.7%, respectively in resistant patients, although LTA has more marginal results (11%). The statistical comparison of MEA and LTA methods with a specific blocker of the $P2Y_1$ receptor by Spearman non-parametric analysis showed a positive significant correlation (p=0.01) in the group of non-resistant patients. The statistical comparison methods without a specific blocker of the $P2Y_1$ receptor failed to provide any significant correlation by Spearman non-parametric analysis.

## Discussion

The two methods used here offer comparable results but the different de-

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tection methods increase the variability of these results. However, the increase in variability is only a few percent and this is minimal in comparison with published results (resistance detected ranges from 0 to 45% in the literature).

The general problem of laboratory detection of resistance to thienopyridine drugs lies in the variability of blood sampling, test implementation and result interpretation.

Blood was collected into sodium citrate 0.129 M/L as an anticoagulant for LTA. Multiple electrode aggregometry yields better results with samples where 15 IU/L hirudin is used as an anticoagulant. The sensitivity is slightly higher using hirudin than sodium citrate. A larger difference in reproducibility occurs in measurement using MEA. The reproducibility using blood samples with hirudin as an anticoagulant was under 5% in comparison with 12% when sodium citrate was used.

The main problem in laboratory result interpretation is the use of a specific blocker of the $P2Y_1$ receptor. One specific agent is $PGE_1$. The use of this specific blocker of the $P2Y_1$ stimulating reaction decreased aggregation by ADP from 1 – 49% and 6 – 608 AUC*min, respectively in a group of patients treated with clopidogrel. When we look at the results without using this specific blocker (graph 2), we cannot define the cut-off value for either LTA or MEA. The use of this specific blocker has unique possibilities for defining the cut-off values for both methods.

Clopidogrel is a pro-drug that needs to be metabolized to the active thiol metabolite by the cytochrome P450 (CYP) system. This activation is a source of significant inter-individual variability in clopidogrel responsiveness (16, 17). The presence of CYP3A4, CYP3A5 and CYP2C19 polymorphisms can reduce the formation of the active metabolite of clopidogrel, resulting in less platelet inhibition (18). The polymorphisms in the genes encoding P-glycoprotein (an efflux transporter) and purinergic receptor P2Y(12) (the active site for clopidogrel) have been studied for their role in clopidogrel responsiveness (19). Polymorphisms of platelet receptors, GP Ia (807C>T, rs1126643), GP VI (13254T>C, rs1613662), GP IIIa (HPA-1, rs5918), PAR-1 (IVS-14A>T, rs168753), P2Y(12) (34C>T, rs6785930 and H1/H2 haplotype, rs2046934), and genetic variations of the gene coding for cyclooxygenase-1 (COX-1) (-842A>G, rs10306114 and 50C>T, rs3842787) were studied, but only for their role in the risk of bleeding associated with clopidogrel therapy (20).

## Conclusion

The sensitivity of detection of clopidogrel resistance correlates well with other data in literature suggesting that there are 5% – 30% of clopidogrel low-responders depending on the type of platelet function assay used and the criteria for defining a low-responder (21 – 23). These results favour implementation of the ADP test with $PGE_1$ by MEA specifically for the identification of low-responders on clopidogrel (confirmed by a significant statistical correlation). We also determined aggregation using LTA, APACT 4004 (LABiTec, Ahrensburg, Germany) on citrated platelet-rich plasma, which demonstrates very similar results to MEA. However this method produces more results very near the cut-off limit, representing 11% of detected samples and misrepresenting the true resistance to antiplatelet therapy.

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# Výběr z tisku a zpráv o knihách

**Does microgranular variant morphology of acute promyelocytic leukemia independently predict a less favorable outcome compared with classical M3 APL? A joint study of the North American Intergroup and the PETHEMA Group**

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Mikrogranulární varianta (M3V) akutní promyelocytární leukemie (APL) přichází asi u 15 % - 25 % dospělých pacientů s APL a u dětských leukemií je poněkud častější. Morfologii charakterizuje zpravidla chybění nebo jen řídká granulace a nečetné Auerovy tyčinky. Vedle odlišných morfologických znaků má také odlišné biologické vlastnosti, včetně vysokého počtu bílých krvinek (WBC) při diagnóze, častou expresi CD2, CD34 a mutace *FLT3 ITD*. Některé soubory uvádějí spojení S-isoformy promyelocytů s M3V. Při konvenční chemoterapii byla tato varianta spojována s vyšší incidencí časného úmrtí, ale nikoliv nutně i s horším výsledkem ve srovnání s klasickou APL. Jen málo studií se zabývalo celkovým výsledkem léčby M3V v období po zavedení all-trans retinové kyseliny (ATRA). Proto se autoři v této studii zaměřili na analýzu celkového výsledku léčby u pacientů s M3V při léčbě založené na strategii: ATRA plus antracyklin.

Analýza byla provedena na 3 velkých souborech pacientů, léčených podle protokolů severoamerické skupiny Intergroup a protokolů skupiny PETHEMA celkem u 155 pacientů s M3V (medián věku 39 roků, rozmezí 3-79). V souboru 748 pacientů s klasickou M3 APL byl medián věku 40 roků (rozmezí 1-83). Podrobné členění základní charakteristiky pacientů je uvedeno v tabulce. Významný rozdíl byl v celkovém počtu bílých krvinek (WBC) mezi pacienty s M3V a klasickou M3. Kompletní remise byla dosažena u souboru 155 pacientů s M3V v 82 %, u souboru 748 pacientů s klasickou chorobou M3 v 79. Incidence diferenciačního syndromu APL byla 26 % ve srovnání s 25 % u klasické M3. Podíl časného úmrtí u M3V byl 13,6 % ve srovnání s 8,4 % u pacientů s klasickou M3 APL. Pětileté celkové přežití OS bylo 70 % u pacientů s M3V variantou APL a 80 % u pacientů s klasickou M3 APL Jestliže se výsledky léčby upravily podle počtu bílých krvinek a skóre rizika pro relapsy nebyly zjištěny signifikantní rozdíly mezi pacienty s M3V a klasickou M3 APL.

Autoři hodnotí v závěru výsledky své analýzy: ATRA zůstává hlavní částí léčby pro všechny podtypy APL, včetně M3V. Přes vyšší riziko komplikací popisované u pacientů s M3V, přidání ATRY významně přispělo k výsledkům léčby, které byly zde referovány na velkém souboru nemocných. M3V nepredikuje sama o sobě nezávisle méně příznivý výsledek léčby ve srovnání s klasickou M3 APL.

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