Role of platelet alpha-2_A adrenergic receptor in thienopyridine resistance of stable coronary heart disease patients – Clinical aspects and treatment options of antiplatelet drug resistance

PhD thesis

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1. Introduction

In Hungary atherothrombosis related diseases and their complications, such as acute coronary syndromes, myocardial infarction, stroke, peripheral arterial occlusions, and coronary stent thrombosis are leading causes of death. Pathological background of these diseases is atherothrombosis accompanying endothelial dysfunction, vascular inflammation and platelet hyperactivity. In both prevention and treatment of atherothrombosis antiplatelet drugs and modulators of vascular inflammation have central role.

Ineffectiveness of antiplatelet treatment is a risk factor of atherothrombosis therefore thorough understanding of factors related to treatment failure has enormous significance especially in patients undergoing percutaneous coronary intervention. According to current guidelines combination of aspirin and thienopyridines is the proper treatment of stable coronary heart disease patients undergoing percutaneous coronary intervention for preventing recurrent adverse cardiovascular events and reducing mortality. There are great interindividual differences in the effectiveness of both aspirin and thienopyridine treatment. High on-treatment platelet reactivity is often called antiplatelet drug resistance, however this latter is less precise. Antiplatelet drug resistance is not just a pharmacological resistance but also a pathological state that can change with time influenced by many inherited and acquired factors. Diagnosis of antiplatelet drug resistance is based on various non-standardized laboratory methods thus prevalence is greatly influenced by the selected method. High on-treatment platelet reactivity and major cardiovascular events such as coronary stent thrombosis are definitely related to each other. Stent thrombosis is a rare event in patients on dual antiplatelet regime but it has proved to be linked to ineffective antiplatelet therapy.

Present doctoral thesis discusses the biological background and measurement of antiplatelet drug resistance, identifies resistant patients at high risk of atherothrombosis, investigating a clinically useful algorhytm to breakthrough resistance and studying the role of platelet adrenergic receptor in thienopyridine resistance in patients on dual antiplatelet therapy.

2. Aims

1. To determine the prevalence of clopidogrel resistance in a group of patients with stable coronary heart disease on aspirin treatment. To determine parameters that separate resistants from responders. To study the relation of platelet aggregation and various markers of vascular inflammation.

2. To determine platelet aggregation and drug resistance of a patient group underwent coronary stent thrombosis and to compare their values to a stable coronary heart disease control group. Our aim was to establish a treatment algorithm to help clopidogrel resistant patients underwent stent thrombosis to become responders. In such cases even guidelines allow the modification of antiplatelet therapy.

3. In a case report of a very late drug eluting stent thrombosis our aim was to prove the role of acquired antiplatelet drug resistance related to a previous non-steroid anti-inflammatory treatment period.

4. To study the relations among circulating norepinephrine, alpha-2_A adrenergic receptor activity and thienopyridine resistance in stable coronary artery disease patients on dual antiplatelet therapy. Our aim was to measure the contribution of platelet adrenergic receptor activity to residual platelet aggregation of patients on dual antiplatelet therapy and to find relations between platelet adrenergic receptor activity and markers of platelet activation or vascular inflammation.

3. Methods

Patients

1. The first group of patients consisted of 65 individuals on aspirin monotherapy admitted for elective coronary angiography. Blood was drawn before angiography and 4 hours after intake of loading dose (300mg) clopidogrel.

2. The second group of patients consisted of 10 prospectively selected individuals whom within 1 month after coronary intervention suffered subacute stent thrombosis (n=8) or subtotal reocclusion (n=2) despite dual antiplatelet therapy. Blood was drawn 24 hours after stopping GPIIbIIIa treatment that had been given during the repeated coronary intervention.

3. We reported a case of very late (834 days old) drug eluting stent thrombosis patient who had been taken combined non-steroid anti-inflammatory treatment for 6 days prior to stent thrombosis. Blood was drawn 24 hours after stopping GPIIbIIIa treatment for repeated coronary intervention and one week after cessation of combined non-steroid anti-inflammatory medication.

4. We enrolled 121 individuals on dual antiplatelet therapy proved to have coronary artery disease by at least one previous angiography to study the relations of circulating norepinephrine, platelet alpha-2_A receptor activity and thienopyridine resistance. Blood was drawn before repeated elective coronary angiography.

Platelet aggregation studies

In the first patient group (n=65) and in patients underwent coronary stent thrombosis (n=10) we performed ADP and collagen induced platelet aggregations with Born-aggregometry. ADP induced platelet aggregations were performed with different concentrations of ADP namely (0.32 - 0.64 - 1.25 - 2.5 – 5 - 10 μM), to be able to define ADP's EC_{50} value of each individual.

When studying the relation between adrenergic receptor activity and thienopyridine resistance on 121 stable angina patients on dual antiplatelet therapy, we performed ADP,

collagen and epinephrine induced aggregations, ADP induced shape change, defined mean platelet volume, and special aggregation studies detailed in three following sections:

1. We potentiated ADP and collagen induced aggregations with the simultaneous addition of very low – close to *in vivo* catecholamine levels – concentration (10ng/ml) epinephrine. We expressed the effect of very low concentration epinephrine on ADP induced platelet aggregation by the following formula:

$$\frac{AGGR_{ADP+ADRENALIN}}{AGGR_{ADP}} \text{ X } 100$$

The numerator shows the value of the ADP induced aggregation potentiated with the very low concentration epinephrine, the denominator shows the value of ADP induced aggregation. Thus the formula shows how much epinephrine potentiates ADP induced aggregation despite aspirin and clopidogrel treatment. Based on this formula we divided patients into quartiles.

2. After preincubation for 2 minutes of platelet rich plasma with alpha-2_A receptor antagonist atipamezole at 2μM concentration, we induced platelet aggregations with ADP, collagen and epinephrine. We expressed the inhibiting capacity of selective adrenergic receptor blocker on ADP induced aggregation by the following formula:

$$\frac{AGGR_{ADP} - AGGR_{ADP+ATIPAMEZOL}}{AGGR_{ADP}} \text{ X } 100$$

The numerator shows the difference of ADP induced aggregation and ADP induced aggregation after preincubation with atipamezole, the denominator shows the value of ADP induced aggregation. Thus the formula shows the inhibiting capacity of the selective adrenergic receptor antagonist on ADP induced platelet aggregation despite

aspirin and clopidogrel treatment. We divided our patients into quartiles based on this formula too.

3. After preincubation for 2 minutes of platelet rich plasma with $P2Y_{12}$ receptor antagonist cangrelor at 1μM concentration, we induced platelet aggregation with 5μM ADP. Difference between ADP induced aggregation and aggregation after cangrelor preincubation shows the value of clopidogrel resistance ($AGGR_{ADP}$-$AGGR_{ADP+CANGRELOR}$).

Flow cytometry

Within the study of adrenergic receptor activity we performed flow cytometric determination of the ratio of P-selectin positive activated platelets in 24 cases. We studied the relation of the ratio of P-selectin positive activated platelets, the activity of platelet adrenergic receptor and plasma circulating norepinephrine level.

ELISA studies

When determining the prevalence of clopidogrel resistance in 65 patients we measured markers of vascular inflammation such as hsCPR, soluble CD40L and von Willebrand factor. The question was that after clopidogrel loading, less than 10% change in the values of ADP induced aggregation or EC_{50} separate better non-responders from responders with significantly different levels of markers of vascular inflammation. When studying platelet adrenergic receptor activity we measured hsCRP, soluble CD40L and plasma norepinephrine levels as well.

Statistical analysis

We presented data with normal distribution as: mean ± standard deviation (SD), in cases of not normal distribution: median (M) and interquartile range (IQR). To compare data with normal distribution we used T-test; other data were compared with ANOVA, Mann-Whitney-U and Wilcoxon's Matched Pairs tests. Correlations were measured with the Spearman's Rank Order Correlation test. Prevalences of co-morbidities and anamnestic data were compared between quartiles with Fischer's exact test. We used Statistica® 7.1 software (Statsoft Inc., Tulsa, USA) for analyses. Border of significance was $p<0.05$.

4. Results

1. The prevalence of clopidogrel resistance

ADP induced aggregations of 65 stable coronary artery disease patients on aspirin were significantly decreased after taking 300mg loading dose clopidogrel: $M_{1.25\mu M\ ADP}$:49% (IQR:37–60%) versus $M_{1.25\mu M\ ADP}$:16% (IQR:9–26%); $M_{2.5\mu M\ ADP}$:61% (IQR:50–71%) versus $M_{2.5\mu M\ ADP}$:30% (IQR:20–42%); $M_{5\mu M\ ADP}$:64.5% (IQR:55–75%) versus $M_{5\mu M\ ADP}$:41% (IQR:31–52%); $M_{10\mu M\ ADP}$:79% (IQR:72–83%) versus $M_{10\mu M\ ADP}$:57.5% (IQR:46.5–69%) $p<0.001$. Measured with the above ADP concentrations Born aggregometry revealed median ADP's EC_{50} value of 1.375μM (IQR:0.998-1.68μM) before taking loading dose clopidogrel. 4 hours after taking 300mg clopidogrel median ADP's EC_{50} value became 2.22μM (IQR:1.8-2.55). This difference was strongly significant ($p<0.001$). If we separated non-responders by less than 10% change in 10 μM ADP induced aggregation value after clopidogrel loading, ratio of non-responder was the highest (15%) and decreased significantly in cases of lower ADP inductor concentrations (5μM: 13.56%, 2.5μM: 12.12%, 1.25μM: 6.15%; $p<0.05$ Fisher's exact test). If we separated non-responders by less than 10% change in ADP's EC_{50} value after clopidogrel loading, ratio of non-responders was 7.94%.

Plasma markers of vascular inflammation were not significantly different between responders and non-responders based on any of the above criteria. When non-responders were separated by the ADP's EC_{50} value plasma markers of vascular inflammation were non-significantly higher than in responders (hsCRP:3.74 g/l (IQR:3.49-4.6) versus 2.36 g/l (IQR:1.26-4.2); sCD40L:230.1 pg/ml (IQR:175-317.8) versus 179.83 pg/ml (IQR:148.75-249.55); von Willebrand factor:212.28% (IQR:145.24-237.99) versus 150.4% (IQR:111.78-198.24; $p>0.05$).

2. Treatment algorithm for clopidogrel resistant patients underwent coronary stent thrombosis

Mean ADP's EC_{50} value of the 10 patients underwent coronary stent thrombosis was 1.045±0.27μM, mean 5μM ADP induced aggregation was 69±11%. Comparing ADP's EC_{50} values of the 65 stable angina patients after clopidogrel loading and the 10 patients

on continuous clopidogrel treatment underwent coronary stent thrombosis, this latter group had significantly decreased EC_{50} value (1.045μM versus 2.22μM $p<0.001$). There were no baseline EC_{50} values of patients underwent stent thrombosis, as these patients had been taken clopidogrel continuously. However median EC_{50} value of the 65 stable angina patients on aspirin monotherapy was even significantly higher - 1.375μM (IQR:0.998-1.68μM) - than those with stent thrombosis on dual antiplatelet regime and their median 5μM ADP induced platelet aggregation was 64.5% (IQR:55–75%). In cases of patients underwent coronary stent thrombosis proven to be clopidogrel resistant by decreased ADP EC_{50} value we modified antiplatelet therapy. Every modification of antiplatelet treatment was followed by repeated aggregometry. We considered the therapy effective when 5μM ADP induced aggregation decreased below 55%. This was an artificial threshold based on that 65 stable angina patients' upper quartile of 5μM ADP induced aggregation after 300mg clopidogrel was above 52%. Increasing the daily dose of clopidogrel to 150mg at 10 resistant patients made 5 patients to be responder (ADP 5μM: 45±6%), 2 patients to be partial responder (ADP 5μM:55.5±6.5%). At these 7 patients we did not modify their therapy further. In cases of the 3 resistant patients to daily 150mg clopidogrel we changed clopidogrel to ticlopidine 250mg twice a day, as metabolism of ticlopidine is different. At 2 patients therapy was effective (ADP 5μM:39±3%), one patient remained resistant to both clopidogrel and ticlopidine (ADP 5μM:64%). In his case we modified therapy to 200 mg dipyridamole+25 mg aspirin and 250 mg ticlopidine twice a day reaching effective platelet inhibition (ADP 5μM: 32%).

3. Case report: acquired thienopyridine resistance and very late DES-thrombosis with related to drug-drug interaction

Aggregation studies of a patient suffered very late drug-eluting stent thrombosis on combined non-steroidal anti-inflammatory treatment showed increased ADP-, collagen-, and epinephrine induced aggregations related to a patient group on dual antiplatelet therapy. Thus platelet hyperactivity was present beside combined non-steroidal anti-inflammatory treatment. Aggregation curves showed lack of disaggregation as well. 7 days after stopping non-steroidal anti-inflammatory drugs but maintaining dual

antiplatelet therapy we performed repeated aggregometry that showed effective platelet inhibition and pronounced disaggregation. 5μM ADP induced aggregation decreased from 60% to 38%, 2μg/ml epinephrine induced aggregation decreased from 37% to 16%. Peak value of 1μg/ml collagen induced aggregation remained the same (54%), but observing the curve disaggregation that lacked at the first measurement has been recovered.

4. Role of platelet adrenergic receptor in thienopyridine resistance

Aggregometry of 121 stable angina patients showed that very low concentration of epinephrine significantly potentiates ADP- and collagen induced platelet aggregations *in vitro* despite dual antiplatelet therapy ($M_{1.25\mu M\ ADP}$:26.5% [IQR:15–42.5%] versus $M_{1.25\mu M\ ADP+epinephrine}$: 43%[IQR:27–61%] p<0.001; $M_{5\mu M\ ADP}$: 53% [IQR:38–65%] versus $M_{5\mu M\ ADP+epinephrine}$: 64.5% [IQR:50–75%] p<0.001; $M_{collagen}$: 17% [IQR:6–32%] versus $M_{collagen+epinephrine}$: 42% [IQR:23–57%] p<0.001).

Selective alpha-2_A adrenergic receptor antagonist atipamezole inhibited epinephrine induced platelet aggregation significantly: $M_{epinephrine}$:27.5% (IQR:17–37%) versus $M_{epinephrine+atipamezole}$: 7% (IQR:3–13%) p<0.0001.

Furthermore, atipamezole has significant inhibitory potency on ADP- and collagen induced platelet aggregation despite dual antiplatelet therapy ($M_{1.25\mu M\ ADP}$: 26.5% [IQR:15–42.5%] versus $M_{1.25\mu M\ ADP+atipamezole}$: 23% [IQR:12–35%] p<0.001; $M_{5\mu M\ ADP}$: 53% [IQR:38–65%] versus $M_{5\mu M\ ADP+atipamezole}$: 47% [IQR:34–58%] p<0.001; $M_{collagen}$: 17% [IQR:6–32%] versus $M_{collagen+atipamezole}$: 11% [IQR:3–20%] p<0.001). These results suggest contribution of alpha-2_A adrenergic receptor activity to aggregations induced by other agonists such as ADP and collagen.

Selective $P2Y_{12}$ receptor antagonist cangrelor was used to *in vitro* determine functional $P2Y_{12}$ receptor pool despite dual antiplatelet therapy. Cangrelor strongly and significantly inhibited ADP- and collagen induced platelet aggregations ($M_{1.25\mu M\ ADP}$: 26.5% [IQR:15–42.5%] versus $M_{1.25\mu M\ ADP+cangrelor}$: 4% [IQR:1–9%] p<0.001; $M_{5\mu M\ ADP}$: 53% [IQR:38–65%] versus $M_{5\mu M\ ADP+cangrelor}$: 15.5% [IQR:9.5–22%] p<0.001; $M_{collagen}$: 17% [IQR:6–32%] versus $M_{collagen+cangrelor}$: 6.5% [IQR:1–14%] p<0.001).

Patients were divided into quartiles based on the aforementioned formulas detailed in „Methods" section. Formulas show potentiating efficacy of very low concentration epinephrine and inhibiting capacity of atipamezole on 5μM ADP induced platelet aggregation. We compared baseline aggregation values, functional $P2Y_{12}$ receptor pool beside clopidogrel therapy, plasma norepinephrine, serum C-reactive protein, plasma soluble CD40L levels and mean platelet volume between patient quartiles. Baseline demographic data were not differing significantly between patient quartiles. When comparing quartiles based on potentiating efficacy of very low concentration epinephrine, patients in the lowest quartile (n=24) had significantly higher baseline ADP- and collagen induced platelet aggregations compared to patients in the highest quartile (n=29) ($M_{1.25\mu M\ ADP\ lowest}$: 28% [IQR:20–40.5%] versus $M_{1.25\mu M\ ADP\ highest}$: 20% [IQR:13–28%] p=0.01; $M_{5\mu M\ ADP\ lowest}$: 65% [IQR:51–73%] versus $M_{5\mu M\ ADP\ highest}$: 38% [IQR:30–47%] p<0.001; $M_{collagen\ lowest}$: 23% [IQR:12–32%] versus $M_{collagen\ highest}$: 6% [IQR:2–16%] p=0.003). Epinephrine induced aggregation and ADP induced shape change were also higher in the lowest quartile but non-significantly. More important result that inhibition of cangrelor was significantly higher in the lowest quartile therefore functional $P2Y_{12}$ receptor pool is greater here (M_{lowest}: 43.5% [IQR:33.5–53%] versus $M_{highest}$: 26% [IQR:19–34%] p<0.001). Thus in those patients where epinephrine has the less potentiating efficacy on ADP induced platelet aggregation more functional $P2Y_{12}$ receptor exist despite dual platelet inhibition indicating resistance. When comparing patient quartiles based on the inhibiting capacity of atipamezole on 5μM ADP induced platelet aggregation, we found an inverse correlation. In patients with less potentiating efficacy of epinephrine on ADP induced aggregation inhibiting capacity of atipamezole was significantly greater (M_{lowest}: 22.9% [IQR:11.6–36.35%] versus $M_{highest}$: –6.45% [IQR:-29.5–11.3%] p<0.001). Our results show that in patients where lower potentiating efficacy of very low concentration epinephrine exists, platelet hyperactivity, reduced efficacy of clopidogrel and increased activity of platelet adrenergic receptor can be observed. Serum C-reactive protein, plasma soluble CD40L, plasma norepinephrine levels and mean platelet volume did not differ significantly between quartiles.

As studying the role of platelet adrenergic receptor in platelet hyperactivity we divided our patients into quartiles again, now based on the inhibiting capacity of atipamezole on

5μM ADP induced platelet aggregation. See „Methods" section for the formula. Patients in the highest quartile (n=29) had significantly greater 5μM ADP- and collagen induced baseline platelet aggregations compared to patients in the lowest quartile (n=30) ($M_{5\mu M\ ADP\ highest}$: 57% [IQR:41.5–67%] versus $M_{5\mu M\ ADP\ lowest}$: 43% [IQR:33–55%] p=0.01; $M_{collagen\ highest}$: 18.5% [IQR:10.5–32.5%] versus $M_{collagen\ lowest}$: 7% [IQR:0–20%] p=0.03). Similarly, cangrelor inhibition was significantly greater in the highest quartile compared to the lowest ($M_{highest}$: 41% [IQR:33–45%] versus M_{lowest}: 30% [IQR:20–41%] p=0.004). Based on these results we found platelet hyperactivity and greater functional $P2Y_{12}$ pool in those patients where inhibiting capacity of atipamezole on 5μM ADP induced aggregation was the highest. In case of high inhibiting capacity of atipamezole potentiating efficacy of epinephrine is low indicating a previously activated platelet adrenergic system.

Plasma norepinephrine level and ADP induce shape change were non-significantly higher in the highest patient quartile based on inhibitory capacity of atipamezole. Serum C-reactive protein, plasma soluble CD40L levels, mean platelet volume and baseline demographic data were not differ significantly between patient quartiles.

Median plasma norepinephrine level of all patients was 515.7 pg/ml (IQR: 424.3–857.2 pg/ml).

Although we performed platelet flow cytometry on a minority of our patients (n=24) we found interesting results. Weak but significant positive correlation was found between plasma norepinephrine level and the ratio of P-selectin positive activated platelets (r=0.53; Spearman's Rank Order Correlation Test). Median P-selectin positivity was 1.82% (IQR:1.18–2.88%). Comparing ratio of P-selectin positivity those patients in the lowest quartile of plasma norepinephrine level had significantly lower level than in the highest quartile of plasma norepinephrine level (M:0.7% [IQR:0.37–1.22%] versus M:2.08% [IQR:2.03–4.77%] p=0.01).

Interesting result that patients with diseased internal carotid artery had significantly higher norepinephrine level compared to others (M:790.33pg/ml [IQR:515.67-1417.5] versus M:594.165pg/ml [IQR:419.28-875.58] p=0.047).

5. Conclusions and theses

1. When studying thienopyridine resistance by platelet aggregometry it is useful to determine ADP EC_{50} value to eliminate the effect of the used ADP concentration on the prevalence of resistance.

2. Patients underwent coronary stent thrombosis have significantly lower EC_{50} value related to a stable angina patient population indicating thienopyridine resistance. By modification of antiplatelet therapy it was possible to eliminate antiplatelet drug resistance in all patients with high risk of atherothrombosis.

3. Based on platelet aggregation studies we showed high on-treatment platelet reactivity related to combined non-steroidal anti-inflammatory drug treatment in a case of very late drug-eluting stent thrombosis. Furthermore cessation of non-steroidal drugs resulted in effective platelet inhibition.

4. In Hungary we introduced a simple method for measurement of clopidogrel resistance by using the selective $P2Y_{12}$ receptor inhibitor cangrelor during platelet aggregation.

5. For the first time we showed that despite dual platelet inhibition very low concentration epinephrine potentiates significantly ADP- and collagen induced platelet aggregations of stable coronary disease patients *in vitro*.

6. For the first time we showed that despite dual platelet inhibition selective alpha-2_A adrenergic receptor antagonist atipamezole significantly inhibits ADP- and collagen induced platelet aggregations of stable coronary disease patients *in vitro*. Thus we proved the contribution of platelet adrenergic receptor to residual platelet activity despite dual antiplatelet therapy.

7. For the first time we described the correlation between activity of platelet alpha-2_A adrenergic receptor and thienopyridine resistance of stable coronary disease patients on dual antiplatelet therapy.

8. We found weak positive correlation between plasma norepinephrine level and the ratio of activated P-selectin positive platelets in stable coronary disease patients on dual antiplatelet therapy.

6. List of publications

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