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Aspirin Therapy Resistance in Coronary Artery Bypass Grafting

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1. Introduction

The success of coronary artery bypass grafting (CABG) surgery mainly depends on the patency of graft vessels. The predominant mechanism of early graft failure after coronary surgery is associated with antiplatelet treatment using drugs such as acetylsalicylic acid (ASA). Prevention using oral ASA in the early postoperative phase in patients with vascular disease is associated with a 25% to 44% reduction in adverse cardiovascular events (1; 2). Daily ASA doses ranging between 75-1200mg can similarly reduce fatal and nonfatal events (2; 3), although studies directly comparing lower and higher doses with regard to clinical outcomes in the CABG setting have been lacking [4].

2. Clinical ASA resistance

The antithrombotic effect of ASA has been primarily attributed to the irreversible blockade of the cyclooxygenase-1 (COX-1) enzyme in platelets that leads to attenuation in the production of an important platelet agonist, thromboxane A₂ TXA₂ (1; 2). ASA irreversibly inhibits cyclooxygenase-1 by acetylating a serine residue at position 529, thereby preventing the conversion of arachidonic acid to unstable prostaglandine intermediate PGH₂, which is converted to thromboxane TxA₂, a potent vasoconstrictor and platelet agonist [22]. The finding that a considerable number of patients show an impaired antiplatelet effect of ASA in CAD patients, eminently after CABG threw new light into the discussion concerning poor patency rates of bypass grafts: the early period after CABG shows a coincidence of an increased risk for bypass thrombosis (amongst others, due to platelet activation and endothelial cell disruption of the graft) and an increased prevalence of ASA resistance [5]. In recent years,

an increasing number of reports about ASA resistance have led to a growing concern among clinicians and patients about the efficacy of ASA treatment (6; 7; 8; 9), although one study group could not reveal any ASA resistance after CABG [10]. ASA resistance can be defined clinically as an ischemic event while on ASA therapy. Various studies have evaluated the antiplatelet effect of ASA therapy and have reported the prevalence of ASA resistance 0.4% - 35% of cardiovascular [11, 18] and 5 - 65% of stroke patients [19, 20].

ASA failure has been attributed to many causes, including insufficient dosage, reduced absorption or increased metabolism, diabetes mellitus, genes polymorphisms, cell-cell and drug-drug interactions and poor compliance [12]. Recent findings have suggested that the pyrazolinone analgesic metamizol, ibuprofen and other nonsteroidal analgesic anti-inflammatory drugs, but not diclofenac, may prevent the irreversible inhibition of platelet thromboxane formation by ASA [15]. The variation suggests about many more treatment failures with ASA therapy (including incompliance of patients) can be explained by a reduced anti-platelet effect for pharmacological reasons Table 1.

Drug-related ASA / Clopidogrel resistance

- Incompliance (23)
 - Pharmacokinetics / Pharmacodynamics
 - Insufficient bioavailability (low dose-effect relationship)
 - Prevention of binding to the Ser529 by other NSAID (Ibuprofen, Indomethacin, Naproxen)
 - Exogenous toxins (diabetes mellitus, smoking)
 - Impaired sensitivity of platelet COX-1 (CABG)
 - Gene polymorphism(s) (COX-1, COX-2, Thromboxan-A2-synthase, Glycoprotein Ia / IIb-, -Ib / V / IX and IIb / IIIa receptor, Collagen, v.-Willebrand factor and factor VIII)
 - Alternative metabolism of thromboxan-A2-biosynthesis (ASA resistance)
 - Changing of enteral resorption and biotransformation (Clopidogrel resistance)
-

Disease-related ASA / Clopidogrel resistance

- Platelet hyperreactivity due to ASA-insensitive mechanisms
 - Changes in the collagen receptor
 - Platelet "sensitizing" by Isoprostanes
-

Table 1. Mechanisms of ASA / Clopidogrel resistance

3. ASA response tests

The common using tests platelet function analyzer (PFA-100_{TM}) closure times (CT); turbidimetric platelet aggregation (TPA) and impedance platelet aggregation (IPA) depending of platelet and leukocyte counts, Hb, fibrinogen and von Willebrand factor collagen binding assay (VWF:CBA), the best valid laboratory procedure was not been determinate to screen for ASA or clopidogrel resistance. One of the studies on on-pump CABG patients agrees with previous findings suggesting that different platelet function assays that are suitable for

detecting ASA resistance can not be used interchangeably. Simple linear regression analysis revealed significant association among CEPI-CT, AA TPA and AA IPA and collagen IPA Table 2 [14]. In the majority of cases AA IPA (impedance platelet aggregation induced by arachidonic acid) [16, 17] and ADP-induced platelet aggregation [4] were utilized.

	AATPA	Collagen TPA	AAIPA	Collagen IPA
CEPI-CT	$r=0,49^*$ $p<0,0001$	NS	$r=0,35$ $p<0,0001$	$r=0,31$ $p=0001$
AATPA		$r=0,38^*$ $p<0,0001$	$r=0,43^*$ $p<0,0001$	$r=0,28$ $p=0,0006$
Collagen TPA			NS	$r=0,22$ $p=0,006$
AAIPA				$r=0,52$ $p<0,0001$

*confirmed by multiple regression analysis

CEPI-CT, collagen/epinephrine closure times; TPA, turbidimetric platelet aggregation; AATPA, turbidimetric platelet aggregation induced by arachidonic acid; collagen TPA, turbidimetric platelet aggregation induced by collagen; IPA, impedance platelet aggregation; AAIPA, impedance platelet aggregation induced by arachidonic acid; collagen IPA, impedance platelet aggregation induced by collagen.

Table 2. Linear regression analysis (Spearman rank correlation coefficients, levels of significance ($P<0.01$)) determined in 42 CABG patients before, 1h and 24 h after 300 mg of aspirin intravenously (n=126)

The clean comparison between both different procedures of CABG: on- and off-pump surgery is unperformed, the role of using extracorporeal circulation as potential destroyer of cell components for ASA Response uncertain. ASA resistance is a transient phenomenon during the early postoperatively period in approximately 30% of OPCAB patients, whereby the ASA response was reversed by 6 months [16, 17].

The new age antiplatelet therapy with clopidogrel, prasugrel or ticagrelor seems be effective in most cardiology diseases (Platelet Inhibition and Patient Outcomes = PLATO Study) like acute coronary syndrome (ACS), unstable angina pectoris, myocardial infarction (non-STEMI or STEMI) with non- and invasive procedures [13], however is not standard medication for patients after CABG procedure like ASA. Clopidogrel (75mg/day) is a prodrug, which needs to be metabolized in the liver to active metabolites catalysed by Cytochrom-P450-Oxygenase CYP 3A4 and 3A5, which irreversibly inactivate the platelet ADP receptor P2Y₁₂. Different to ASA clopidogrel does to influent the thienopyridins not cyclooxygenase and thromboxan formation. Platelet inhibition in patients group with response to clopidogrel was enhanced by switching to ticagrelol therapy and all clopidogrel. A few studies have revealed important individual heterogeneity in platelet response to clopidogrel in patients

with stable coronary disease, but the clinical significance of this phenomenon has not yet been investigated. Matetzky showed in his study that in 15 out of 60 consecutive patients STEMI (25%) were resistant to clopidogrel and subsequently were at increased risk of recurrent cardiovascular events in a 6-month follow-up [24].

Non-Responders and Responders treated with ticagrelor will have platelet reactivity below the cut points associated with ischemic risk in the RESPOND Study [4]. Their resistance in cardiac surgery after using of extracorporeal circulation (on-pump) or without (off pump) is unidentified.

Regarding the PLATO trials (Platelet Inhibition and Patient Outcome by ticagrelor) underwent CABG endpoints were a non-significant reduction of the primary endpoint like total major bleeding [HR: 0.84 (95% CI = 0.60–1.16), $p = 0.29$], significant reduction of CV death [HR: 0.52 (95% CI = 0.32–0.85)] and all-cause death [HR: 0.49 (95%CI = 0.32– 0.77)] [13]. CABG-related major bleedings according to PLATO or TIMI bleeding definitions were observed very commonly during CABG.

4. Conclusion

Antiplatelet therapy with ASA is the cornerstone of treatment in coronary artery disease patients especially after CABG surgery. The question of ASA resistance can be defined clinically as an ischaemic event while on ASA treatment daily. Laboratory assays of ASA response are surrogate measures as platelet aggregation inhibitor in *vitro* does not coincidentally translate into prevention of thrombosis in *vivo*, however the tests are not comparable among themselves. Clinical studies are needed to discover the optimal dosing and the clinical significance of laboratory aspirin resistance for sufficiency of graft function.

Abbreviations

CABG=coronary artery bypass grafting, **ASA**=acetylsalicylic acid, **CAD** = coronary artery disease, **mg**=milligram, **COX-1**=cyclooxygenase-1, **OPCAB**=off-pump coronary artery bypass, **TXA₂** = thromboxane A₂, **STEMI**=ST segment elevation myocardial infarction

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