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Right Ventricular Dysfunction in Myocardial Infarction: A New Risk Factor for Clopidogrel Resistance?

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Abstract

Aims: Mortality in acute coronary syndroms (ACS) complicated by right ventricular dysfunction (RVD) still remains high. The aim of this study was to determine the association between RVD in ACS and the platelet inhibitory effect of clopidogrel.

Methods: In this single center observational study 50 patients with ACS were investigated, 38 with normal right ventricular function and 12 with RVD as determined by echocardiography and electrocardiography. The effect of clopidogrel was determined by the PRI/VASP-Index 24 hours after loading dose of 600 mg. PRI/VASP-Indices above 50% were claimed as clopidogrel non-responder.

Results: PRI/VASP-Index was significant higher in the RVD-group compared to control (Median: 74.5% ± 12.3 *vs.* 26.5% ± 23.3, p<0.01). The percentage of patients with unsatisfactory effect was significantly higher in the RVD group compared to control (83.3% *vs.* 23.7%, p<0.01). There were no increased rates of adverse cardiac events in both groups.

Conclusions: Patients with RVD complicating myocardial infarction show a significantly impaired response to clopidogrel. These patients suffer from congestive gastro- and enteropathy and liver dysfunction, in consequence resorption and metabolization of orally administered drugs including platelet-inhibitors like clopidogrel might be compromised.

Keywords: Clopidogrel non-responder; Platelets; Right ventricular infarction; ACS; Metabolization

Introduction

Right ventricular dysfunction (RVD) in acute coronary syndromes occur either primary in infarction of the right ventricle mainly caused by proximal occlusion of the right coronary artery or secondary in infarction of the left ventricle with consecutive increase of pulmonary pressure. The incidence of right myocardial infarction has ranged widely according to the diagnostic technique used and the patients profile. It is recognizable clinically in two thirds of hypotensive inferior infarction and most inferior infarctions with cardiogenic shock [1]. The recommended treatment in acute myocardial infarction is percutaneous coronary intervention (PCI) with stent deployment in order to restore myocardial perfusion [2-5]. Dual inhibition of platelet aggregation with a thienopyridine like clopidogrel and aspirin showed a dramatic reduction of major adverse cardiac events after PCI [6-8].

In the past years there have been several studies that showed the importance of sufficient response to clopidogrel to prevent thrombembolic complications [9,10]. Furthermore, different studies showed the importance of an early detection of clopidogrel resistance as it is associated with worse outcome after PCI [11,12].

Since clopidogrel is a prodrug, which has to be metabolized into the active metabolite by two Cytochrome P-450 dependent steps in the liver, the inter individual variability for the responsiveness to clopidogrel is high [13]. Especially in hemodynamically unstable patients with cardiogenic shock and multi organ dysfunction resorption and metabolization of clopidogrel may not be ensured [14].

The majority of patients with RVD usually show signs of liver congestion with consecutive liver dysfunction, increased liver enzymes (e.g. transaminases) and congestive gastro- and enteropathy with impaired resorption of nutrients and orally administered drugs like clopidogrel.

We therefore hypothesize that right ventricular dysfunction due to myocardial infarction leads to impaired clopidogrel response due to congestive gastro-and enteropathy and liver dysfunction and might increase adverse cardiovascular events.

Methods

The data from 50 patients with ACS, who were recruited through screening for participation in another prospective observational study comparing the efficacy of clopidogrel in patients after cardiac arrest, were used for a prospective, non-randomized analysis. The study protocol was approved by the local ethical committee (EK 164052010). A written informed consent was obtained of all eligible patients. All

data were collected, managed and analysed at the Heart Centre, University of Dresden. This analysis was carried out in accordance with the guidelines for good clinical practice and the Declaration of Helsinki.

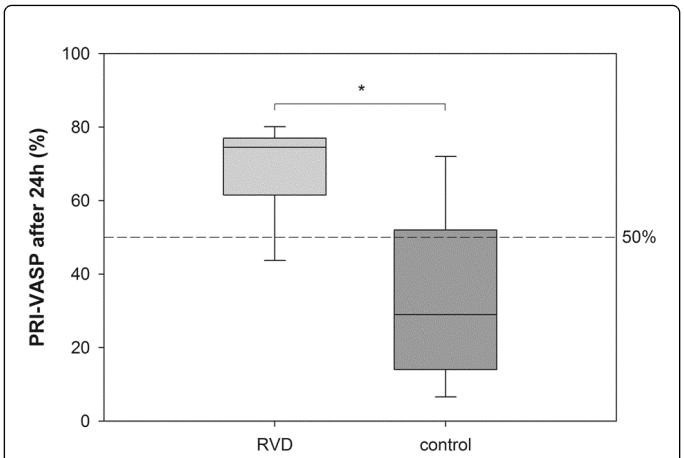

Figure 1: PRI/VASP-Index 24 hours after initial loading with 600 mg Clopidogrel in RVD-group compared to control (Boxplots, Bold line indicates median-values, dashed line has been drawn at PRI/VASP 50% to indicate threshold between responder/nonresponder, p<0.01).

The primary objective of the study was to determine the effect of clopidogrel on platelet inhibition in patients with ACS and consecutive RVD compared to matched controls with ACS with preserved right ventricular function.

The secondary objective was the occurrence of major adverse cardiac events and bleedings.

Eligible subjects were male or female patients 18-80 years of age with ACS caused by coronary heart disease requiring stent.

Patients who met all of the following criteria were enrolled in the RVD group: (1) ACS with stenosis or occlusion of either right coronary artery (RCA) or ramus circumflexus (RCX), (2) presence of ST-segment elevation of at least 0.1 mV in the V3R or V4R lead, (3) echocardiographic signs of acute right ventricular dysfunction (increase of RV-Diameter>30 mm or right ventricular pressure, decrease of tricuspid annular plane systolic excursion (TAPSE)<20 mm, RV-free wall motion abnormalities). Patients with ACS who did not meet the criteria mentioned above for acute RVD were matched as controls.

Exclusion criteria were (1) history of cancer, (2) history of hemorrhagia or idiopathic thrombosis, (3) known hyper-reactivity against thienopyridienes, (4) history of severe liver dysfunction (e.g. cirrhosis Child B/C), (5) pre-existing pulmonary hypertension as determined by a transthoracic echocardiograaohy not older than 1 year, (6) severe thrombocytopenia (<100/nl), cardiac arrest and cardiogenic shock.

Thirty eight patients showed normal right ventricular function (control), 12 patients showed right ventricular dysfunction as defined above (RVD-group).

At admission to the intensive care unit all patients received an electrocardiogram and echocardiography. With diagnosis of ACS a loading dose of clopidogrel (600 mg p.o.) was administered and coronary angiography was performed. Further medical treatment was at the physician´s discretion.

Characteristic	Overall (N=50)	RVD (N=12)	Control (N=38)	p-value
Age (Years)	67 ± 11.9	73 ± 8.4	62.6 ± 13.3	p<0.01
Male sex-no. (%)	38 (76)	9 (75)	29 (76)	0.92
ACS no (%)	50 (100)	12 (100)	38 (100)	0.13
History of CIHD-no. (%)	21 (42)	6 (50)	15 (40)	0.14
Hypertension-no. (%)	45 (90)	11 (92)	34 (89)	0.83
Diabetes mellitus-no (%)	19 (38)	7 (58)	12 (32)	0.96
Active Smokers-no. (%)	7 (14)	0 (0)	7 (18)	p<0.05
Hypercholesterolemia-no. (%)	28 (56)	5 (42)	23 (61)	0.25
Adipositas per magna-no. (%)	15 (30)	4 (33)	11 (29)	0.81
Bare metal stents (%)	29 (58)	10 (83)	19 (50)	0.2
Drug eluting stents (%)	17 (34)	2 (17)	15 (40)	0.31
Right coronary artery as culprit lesion (%)	23 (46)	9 (75)	14 (37)	p<0.05
Medications in use				
Aspirin-no. (%)	50 (100)	12 (100)	38 (100)	0.18
Clopidogrel-no. (%)	50 (100)	12 (100)	38 (100)	-
GpIIbIIIa-Inhibitor-no. (%)	6 (12)	2 (17)	4 (11)	0.57
ACE-Inhibitors no. (%)	38 (72)	9 (75)	29 (76)	0.92
CSE-Inhibitoren no. (%)	44 (88)	11 (92)	33 (86)	0.16
Beta-Blockers no. (%)	43 (86)	10 (83)	33 (86)	0.76
Heparin (%)	50 (100)	12 (100)	38 (100)	p<0.04

Table 1: Baseline characteristics.

Whole blood samples were collected to citrate-tubes 24 hours after the first loading dose of clopidogrel. The effect of clopidogrel on platelets in blinded samples was analyzed using a commercially available flow cytometer assay (PLT VASP/P2Y12, BioCytex, France) in an independent analytic laboratory and the PRI/VASP-Index was determined. All patients with a PRI/VASP-Index above 50% were defined as clopidogrel nonresponder [15]. Patients exhibiting very early clopidogrel resistance were treated with an extra loading of clopidogrel and further check of clopidogrel resistance. Monitoring of hemodynamic parameters was routinely performed. Transthoracic echocardiography was performed on all patients at the day of admission including left ventricular ejection fraction (LV-EF), wall motion abnormalities, tricuspid annular plain systolic excursion (TAPSE), right ventricular systolic pressure (RVSP), enddiastolic diameter of right ventricle and right atrium, grade of tricuspidal insufficiency (TI) and diameter of Vena cava inferior (VCI).

Furthermore blood samples were drawn on admission and in sequence within clinical routine.

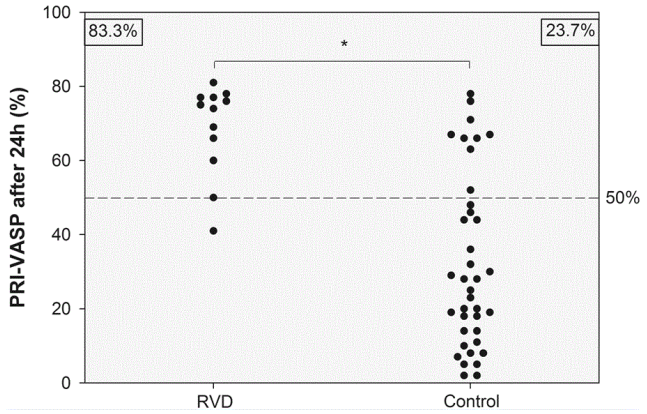

Figure 2: PRI/VASP-Index 24 hours after initial loading with 600 mg Clopidogrel in RVD-group compared to control (2D-Plot, percentage value indicating clopidogrel nonresponder in each group. Dashed line has been drawn at PRI/VASP 50% to indicate threshold between responder/nonresponder, p<0.01).

A statistician using SPSS v.19 performed statistical analysis. The distribution of continuous data was examined using the Kolmogorow-Smirnov-test. Data with a normal Gaussian distribution were analysed using the Student´s t-test, data with a non-Gaussian distribution were analysed using the Mann-Whitney U test. Categorical Data were compared using the chi-square test, except when the absolute number of events in each group was<5, in which case Fisher's exact test was used. P values ≤ 0.05 were considered as statistically significant.

Results

Baseline Characteristics are shown in Table 1. Twenty four percent of the patients had RVD. Mean age in the RVD group compared to control was 73.0 ± 8.4 and 62.6 ± 13.3 (p<0.01). There were no significant differences in concomitant diseases or administration of drugs between the two groups. Surprisingly there were no active smokers in the RVD group.

Echocardiographic and laboratory data are shown in Table 2. There was no significant difference in LV-EF between the two groups. RVSP, TAPSE, grade of TI differed significantly (p<0.01 for each), indicating a worse right ventricular function in the RVD group. Laboratory data showed no differences between the two groups except for significantly higher creatinine levels and a lower GFR in the RVD group compared to control group (162.9 ± 137 µmol/L *vs.* 107.8 ± 29.2 µmol/L and 41.9 ± 25.9 ml/min/m^2 *vs.* 65.0 ± 18.4 ml/min/m^2, p<0.05).

PRI/VASP-Index 24 hours after initial LD of clopidogrel is shown in Figure 1. There was a significant higher PRI/VASP-Index in the RVD group compared to control group (Median: 74.5% ± 12.3 *vs.* 26.5% ± 23.3, p<0.01).

The percentage of patients with unsatisfactory effect (PRI-VASP-Index>50%) was significantly higher in the RVD group compared to control group (10 (83.3%) *vs.* 9 (23.7%), p<0.01, Figure 2).

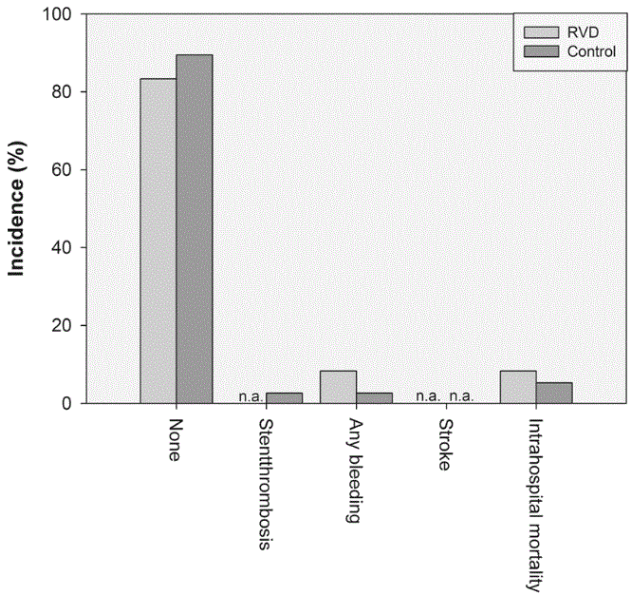

Figure 3: Percentage of major adverse cardiac events (MACE) and bleedings (TIMI-classification), p:ns.

Echocardiographic data	Overall (N=50)	RVD (N=12)	Control (N=38)	p-value
LV-EF (%)	43.65 ± 11.7	43.18 ± 12.5	43.78 ± 11.7	0.86
RVSP (mmHg)	38.0 ± 14.5	48.2 ± 9.0	33.36 ± 14.3	P<0.01
TAPSE (mm)	22.09 ± 5.5	14.86 ± 3.5	23.96 ± 4.2	P<0.01
Grade of TI	1.03 ± 0.7	1.77 ± 0.6	0.83 ± 0.6	P<0.01
Laboratory data				
Creatinekinase-MB (µkat/L)	2.95 ± 3.0	3.32 ± 3.4	2.84 ± 2.8	0.34
pH at admission	7.39 ± 0.09	7.37 ± 0.08	7.39 ± 0.09	0.41
Lactat mmol/L	2.37 ± 2.2	2.81± 2.9	2.23 ± 2.0	0.45
Blood glucose mmol/L	8.5 ± 3.9	10.31± 4.7	7.84 ± 3.4	0.076
Creatinin µmol/L	121.3 ± 74.4	162.9 ± 137	107.8 ± 29.2	P<0.05
GFR (ml/min/m^2)	59.2 ± 22.6	41.9 ± 25.9	65.0 ± 18.4	P<0.05
ASAT (µkat/L)	5.57 ± 13.1	10.29 ± 22.9	3.84 ± 6.7	0.17
ALAT (µkat/L)	2.46 ± 7.1	5.23 ± 12.8	1.44 ± 2.5	0.13
Platelets (10^9/L)	216.3 ± 72.2	179.5 ± 89.4	228.0 ± 63.6	0.45
Hemoglobin (mmol/L)	7.79 ± 1.5	7.4 ± 1.0	7.9 ± 1.6	0.31
Cholesterol (mmol/L)	4.18 ± 1.45	3.75 ± 1.85	4.29 ± 1.37	0.47

Table 2: Clinical characteristics at admission.

Major adverse cardiac events are shown in Figure 3. There were no strokes in both groups. One stent thrombosis occurred in the control group due to coronary dissection. Mortality was 8.3% in the RVD

group and 5.2% in the control group (ns.). No TIMI-Major bleedings occurred; minor bleedings were 8.3% and 2.6% for RVD *vs.* control (ns.).

Discussion

The present prospective observational study including 50 patients with ACS showed an insufficient response to clopidogrel as determined by PRI/VASP-Index in patients with acute right ventricular dysfunction following myocardial infarction. There were no significantly increased rates of major adverse cardiac events in this group.

Right ventricular dysfunction complicating myocardial infarction is of utmost clinical importance since it denotes a limited prognosis of these patients. In a meta-analysis of 22 studies involving a total of 7136 patients with acute myocardial infarction, 27.5% had right ventricular involvement, which was associated with a 2.59-times increased mortality [16].

In the present study the ADP-dependent response to clopidogrel determined by the PRI/VASP-Index was significantly reduced in patients with acute right ventricular dysfunction after myocardial infarction.

Hence, the reasons might be manifold. First, as clopidogrel is a prodrug, a lower rate of metabolization to its active metabolite due to hepatic congestion and impaired liver function is possible. Second, intestinal congestion could lead to a reduced intestinal resorption of the drug. In hemodynamic instable patients after myocardial infarction a reduced clopidogrel effect was identified [17] without clearly distinguishing the reason that is responsible. Finally, a combination of both reduced resorption and metabolization is likely. But the reduced resorption seems to contribute to the main share of the failing clopidogrel effect.

Another reason for inadequate response to clopidogrel might be increased platelet activation in myocardial infarction as measured by flow cytometry [12]. Patients with high pre-treatment platelet reactivity showed an impaired response to clopidogrel, which may contribute to reduced antiplatelet effect of the drug [15].

Concomitant administration of drugs (e.g. PPIs), genetic alterations (CYP2C19) and concomitant diseases (e.g. diabetes mellitus) are further claimed to reduce response to clopidogrel. Even in combination with these variables it just explains only about 11.5% of the impaired response to clopidogrel [16].

Standardized definitions to define low responders to clopidogrel are still lacking. This is caused both by a numerous assays currently available and methodological differences within each technique. Here, the PRI/VASP- Index was used to identify clopidogrel non responders. Advantages of this flow cytometric method are a low inter-laboratory variability of results due to standardized kits and the stability of blood specimen, which can be stored up to 48 hours [18]. The cutoff for nonresponsiveness to clopidogrel was defined as a PRI/VASP-Index >50%, as this value has illustrated an increased rate of major adverse cardiovascular events MACE [19].

Several studies showed an association of a high residual platelet reactivity after clopidogrel administration with higher rates of thrombembolic events like stent thrombosis [9,10,20].

Therefore, all patients with impaired response to clopidogrel should be mentioned as high risk patients for developing stent thrombosis. Adjusting the clopidogrel loading dose has been shown to enhance the respond to clopidogrel and reduce thrombembolic complications [9].

With the admission of the third generation thienopyridine prasugrel the clopidogrel non responders were treated with prasugrel. Two patients with non-responsiveness to clopidogrel due to acute right ventricular dysfunction were switched to prasugrel. These patients were demonstrating a noticeably enhanced platelet inhibition as indicated by a decreased PRI/VASP-Index 24 hours after administration of prasugrel (mean PRI/VASP-Index 14%). This might be due to faster and more consistent resorption and metabolization of prasugrel into its active metabolite, hence prasugrel seems to be an adequate alternative for clopidogrel nonresponders. If there are higher rates of bleedings or other adverse events in patients with right ventricular dysfunction it has to be investigated in further studies. Nevertheless, the recently published guidelines for patients with ST-elevation myocardial infarction recommend the administration of prasugrel or ticagrelor as ADP receptor antagonists over clopidogrel [21].

The study has some limitations. First, this was a single centre study with only a small number of patients with right ventricular dysfunction being investigated, so that the number of patients of each group differs substantially. Second, by measuring only the PRI/VASP-Index the patho mechanism for inadequate response to clopidogrel stays unclear. So both reduced resorption and metabolization of clopidogrel has to be considered. This could only be distinguished by determining plasma levels of active and inactive metabolites of clopidogrel, which was not performed. Thus it seems likely, that a combination of both effects is responsible for the reduced platelet inhibition, which however cannot not be proven. Besides, there was no determination of any genetic alterations like CYP2C19 polymorphism, although the clinical effect of this polymorphism is small [22-24].

In the present study no increased rates of early stent thrombosis or reinfarction were recorded. This might be due to the small number of patients with acute right ventricular dysfunction. Furthermore the study was not designed as outcome trial. Especially the number of major adverse cardiac events is small, so that the clinical relevance remains unclear. At last, with the publication of the recent guidelines for ST-elevation myocardial infarction the use of newer ADP receptor antagonist like prasugrel and ticagrelor are recommended over clopidogrel, so that an increased platelet inhibition in patients with right ventricular dysfunction is assumed.

Conclusion

Patients with RVD complicating myocardial infarction show a significantly impaired response to clopidogrel. The combination of congestive enteropathy and hepatic congestion might lead to a reduced resorption and metabolization of the orally administered prodrug clopidogrel. As nonresponsiveness to clopidogrel could lead to increased thrombembolic events, these patients should be considered as high risk patients. In the present study no increase in major adverse cardiac events were observed.

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