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CLINICAL RESEARCH **Interventional Cardiology**

Stent Thrombosis Is Associated With an Impaired Response to Antiplatelet Therapy

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OBJECTIVES We sought to evaluate the response to antiplatelet therapy in patients with stent thrombosis (ST).

BACKGROUND Stent thrombosis is associated with considerable morbidity and mortality. An impaired response to antiplatelet therapy might be related to an increased risk for ST.

METHODS Eighty-two patients were included in the present study: 23 patients with previous ST, 50 matched controls (coronary stenting without ST), and 9 healthy volunteers. Platelet aggregation (PA) was studied (optical aggregometry) under monotherapy with acetylsalicylic acid (ASA) 100 mg daily for one month, followed by dual therapy with ASA 100 mg and clopidogrel 75 mg daily (loading dose 300 mg) for another month.

RESULTS Maximal (5 and 20 μmol) adenosine diphosphate-induced PA was significantly higher in patients with ST compared with controls (5 μmol, $p < 0.005$; 20 μmol, $p < 0.05$) and volunteers (5 μmol, $p < 0.005$; 20 μmol, $p < 0.05$). Resistance to ASA (>20% aggregation with 0.5 mg/ml arachidonic acid) was more prevalent in patients with ST (48%) compared with control patients (32%, p = ns) and volunteers (0%, p = 0.01). Clopidogrel significantly reduced PA in all three groups, but intergroup differences persisted. Clopidogrel resistance (<10% relative change) was similar in patients with ST, control patients, and volunteers (4%, 6%, and 11%, respectively, all p = NS). However, combined ASA and clopidogrel resistance was more prevalent in patients with ST (52%) compared with controls (38%, p = NS) and volunteers (11%, $p < 0.05$).

CONCLUSIONS Patients with previous ST show an impaired response to antiplatelet therapy with ASA compared with controls and volunteers. Additional treatment with clopidogrel is not able to overcome these differences in PA. Acetylsalicylic acid but not clopidogrel resistance appears to be associated with ST. (J Am Coll Cardiol 2005;45:1748–52) © 2005 by the American College of Cardiology Foundation

Stent thrombosis (ST) remains a serious complication of coronary artery stent implantation. Despite routine dual antiplatelet therapy with acetylsalicylic acid (ASA) and thienopyridines (1), the incidence of ST persists at a rate of 0.5% to 2 % (2,3). Several factors have been associated with

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an increased risk of ST: long and multiple stents (2,3), stent malapposition (4), residual dissection (2), and platelet polymorphism (5). Resistance to ASA and clopidogrel has been suggested as a possible cause of ST, but conclusive data are lacking (6–9). Thus, the purpose of the present study was to evaluate the response to antiplatelet therapy in patients with previous ST and to compare it with a control group of patients without ST and healthy volunteers.

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METHODS

Patient population. Between 1995 and 2003, 6,058 patients underwent bare-metal coronary stent implantation at our institution. Ninety-five patients suffered angiographically verified subacute (median seven days after implantation) ST during long-term follow-up. Of these patients, 12 (13%) died, 60 (63%) refused or had contraindications to study inclusion, and 23 (24%) agreed to participate. Fifty patients undergoing stent implantation followed by dual antiplatelet therapy for 1 to 12 months without ST during follow-up served as controls, and nine healthy volunteers served as a reference group. Control patients were matched with respect to age, gender, risk factors, and angiographic characteristics to exclude confounding factors (Table 1).

Exclusion criteria were acute coronary syndrome in the last six months, known allergy to ASA or clopidogrel, indication for long-term treatment with clopidogrel or other antiplatelet therapy except ASA, recent gastrointestinal bleeding, pregnancy, known platelet dysfunction, bleeding disorder, or abnormal platelet count (<100,000/mm^3). The mean time between stent implantation and study entry was

Abbreviations and Acronyms

ADP = adenosine diphosphate
ASA = acetylsalicylic acid
ARA = arachidonic acid
PA = platelet aggregation
ST = stent thrombosis

at least six months (64 ± 19 months for patients with ST; 41 ± 24 months for control patients, $p < 0.001$).

Study protocol. The local ethics committee approved the protocol, and all patients gave written informed consent. To minimize potential drug interactions, statins were discontinued during the study period. However, it was felt unethical to discontinue other cardiovascular medications, such as beta-blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists. First, platelet aggregation (PA) was assessed after an interval of four weeks under monotherapy with ASA 100 mg daily (any other antiplatelet medication was not permitted). Then, all patients received dual therapy with clopidogrel (300 mg loading dose, followed by 75 mg daily) in addition to ASA. A second PA was performed after a mean of 31 ± 4 days under combination therapy.

Table 1. Baseline Demographics and Angiographic Characteristics

	Patients With ST (n = 23)	Control Patients (n = 50)	p Value
Age, mean ± SD	64 ± 12	66 ± 4	NS
Female gender, %	30	17	NS
Hypertension, %	39	40	NS
Family history, %	26	34	NS
Current smoking, %	30	45	NS
Dyslipidemia, %	74	64	NS
Diabetes, %	14	14	NS
Previous CABG, %	5	9	NS
Multivessel disease, %	17	28	NS
LV ejection fraction, %			
Before ST	56 ± 15	65 ± 12	<0.05
After ST	49 ± 14		
Stent length, mm ± SD	15 ± 9	15 ± 7	NS
Stent diameter, mm ± SD	2.9 ± 0.2	3.1 ± 0.3	< 0.05
Inflation pressure, bar ± SD	13 ± 5	13 ± 3	NS
Residual dissection, %	5	0	NS
Treated vessel, %			NS
LAD	61	51	
LCX	17	15	
RCA	22	34	
Beta-blocker, %	65	51	NS
Calcium antagonist, %	0	13	NS
ACE inhibitor, %	52	21	< 0.05
AT-1 receptor antagonist, %	35	17	< 0.05
Nitrates, %	17	9	NS
Diuretics, %	55	15	< 0.05

Medication at time of PA assessment.

ACE = angiotensin-converting enzyme; AT-1 = angiotensin 1; CABG = coronary artery bypass grafting; LAD = left anterior descending; LCX = left circumflex artery; NS = not significant; PA = platelet aggregation; RCA = right coronary artery; ST = stent thrombosis.

Laboratory determinations. We determined PA using a four-channel light transmission aggregometer (APACT, Endotell AG, Allschwil, Switzerland). The technology has been described in detail previously (10). Platelet activation was achieved with low and high concentrations of adenosine diphosphate (ADP) (5 and 20 μmol). Activation by arachidonic acid (ARA) (0.5 mg/ml) was used to assess ASA resistance.

Drug resistance. According to previous publications, the following definitions were used.

Aspirin resistance:

1. ARA (0.5 mg/ml)-induced maximal PA: ≥20% (6,11), or
2. ADP (5 μmol/l)-induced maximal PA: ≥70% (11), or
3. ADP (20 μmol/l)-induced maximal PA: ≥70% (11).

Clopidogrel resistance (5 and 20 μmol/l ADP-induced PA) adapted from Gurbel et al. (12):

1. Normal response: relative change (δ) between aggregation under ASA and ASA plus clopidogrel ≥30%
2. Low response: δ = 10% to 29%
3. No response: δ <10%.

Statistical analysis. Continuous data were expressed as mean ± standard deviation. Wilcoxon rank sum test was used for intergroup comparison between patients with ST and control patients (Table 1). Comparison between categorical data was performed using the chi-square test. A paired *t* test served as method to compare intragroup continuous variables (Fig. 1). A one-way analysis of variance was used to assess differences of continuous values between the three different groups (Fig. 1). A two-sided p value of <0.05 was considered significant. All statistical analyses were performed with SPSS 10.0.5 software (SPSS Institute, Chicago, Illinois).

RESULTS

Baseline characteristics of patients with ST and control patients are shown in Table 1. Systolic left ventricular function was somewhat reduced in patients with ST as the result of ST-induced myocardial infarction. Therefore, more patients with ST were treated with angiotensin-converting enzyme inhibitors or angiotensin-1 receptor antagonists.

ADP-induced PA. 5 μmol of ADP-induced aggregation under monotherapy with ASA was significantly blunted in patients with ST compared with control patients ($p < 0.005$) and volunteers ($p < 0.005$) (Fig. 1). There were no differences between control patients and volunteers. Clopidogrel significantly decreased maximal aggregation in each group (ST patients: from 63.9 ± 10% to 40.0 ± 10%; controls: from 53.4 ± 10% to 30.8 ± 10%; volunteers: from 44.8 ± 9% to 24.8 ± 8%; all $p < 0.005$) but was not able to overcome baseline differences under monotherapy with ASA. 20 μmol ADP-induced PA revealed comparable

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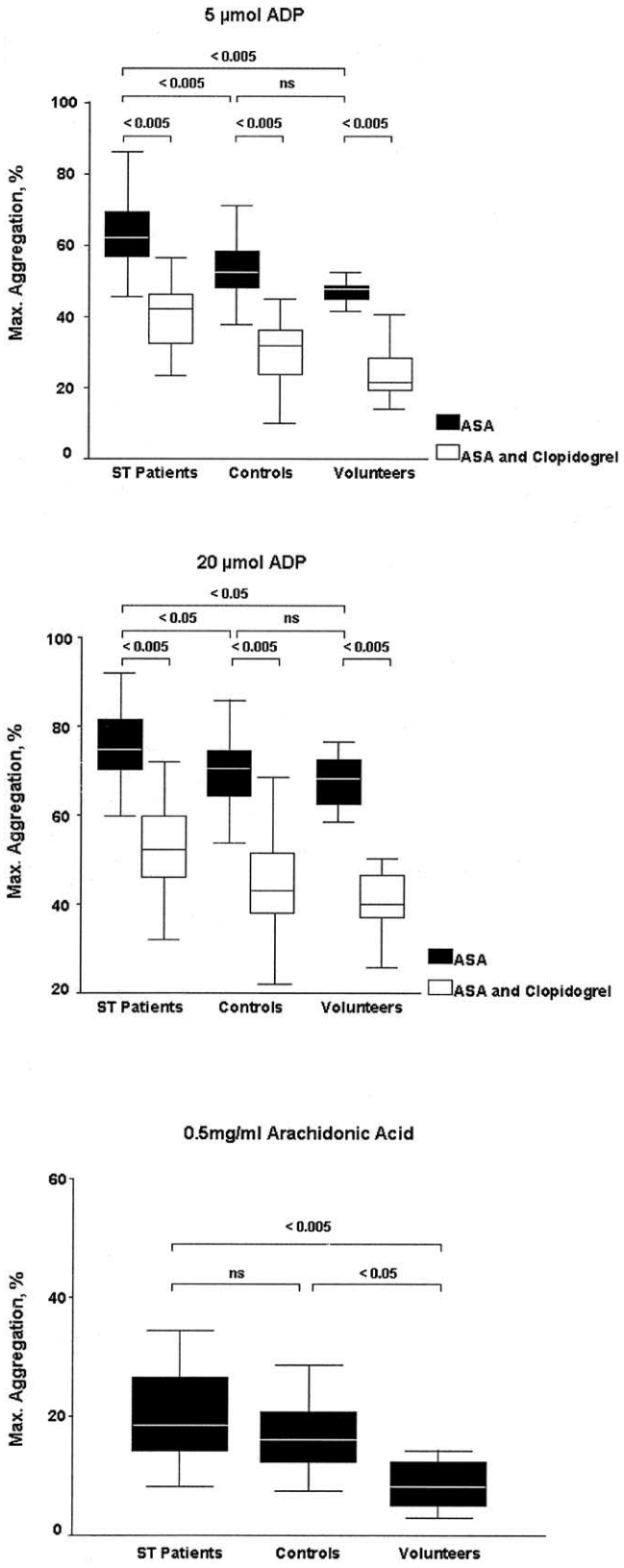

Figure 1. Platelet aggregation (**top**: 5 µmol adenosine diphosphate [ADP]; **middle**: 20 µmol ADP) in patients with stent thrombosis (ST), control patients, and volunteers. **Black boxes** = acetylsalicyclic acid (ASA) (100 mg daily) alone; **white boxes** = ASA plus clopidogrel (75 mg daily). Platelet aggregation (**bottom**: 0.5 mg/ml arachionic acid) on ASA (100 mg daily) in patients with ST, control patients, and volunteers.

results as with 5 µmol ADP but on a higher aggregation level (Pearson correlation coefficient r = 0.7). Differences between groups remained similar (Fig. 1).

Arachidonic acid-induced PA. Aggregation with ARA was highest in patients with ST (23.7 ± 18%) followed by control patients (18.0 ± 12%, p = ns) and volunteers (8.7 ± 4%, p < 0.005 vs. patients with ST). Values remained unchanged under dual therapy with ASA and clopidogrel (ST patients: 19.5 ± 11%; controls 17.1 ± 13%; volunteers 11.1 ± 4%).

Resistance to ASA or clopidogrel. The ASA resistance was highest in ST patients using one of the following definitions:

1. ARA: see the upper panel of Figure 2
2. 5 µmol ADP: ST patients 26%, controls 6%, volunteers 0% (p = 0.06 for ST patients vs. volunteers)
3. 20 µmol ADP: ST patients 78%, controls 53%, volunteers 44% (p < 0.05 for ST patients vs. controls or volunteers).

Clopidogrel resistance occurred with similar frequency in all groups (Fig. 2, middle panel). Low response was more frequent in patients with ST, but there were no significant differences among groups:

1. 5 µmol ADP: ST patients 30%, controls 19%, volunteers 11% (all p = NS)
2. 20 µmol ADP: ST patients 39%, controls 28%, volunteers 33% (all p = NS).

Combined ASA and clopidogrel resistance was most frequent in patients with ST, reflecting the high incidence of abnormal response to either ASA or clopidogrel:

1. ARA (for ASA resistance) and 5 µmol ADP (for clopidogrel resistance or low response): ST patients 70%, controls 53%, volunteers 22% (p < 0.05 for patients with ST vs. volunteers)
2. ARA (for ASA resistance) and 5 µmol ADP (for clopidogrel resistance) (Fig. 2, bottom panel).

DISCUSSION

The present study evaluated the relation between ST and PA. The principal finding was a significantly higher aggregation level in patients with ST compared with control patients and volunteers. The addition of clopidogrel to ASA did not overcome this difference but reduced the aggregation level in all groups to a similar extent (Fig. 1). Similarly, the incidence of ASA resistance was consistently higher in patients with ST compared with control patients and volunteers. Previous studies identified ASA resistance as a strong predictor for cardiovascular events during follow-up (6). Failure of ASA to protect against cardiovascular events has been attributed to poor compliance, drug interactions, alternative pathways of platelet activation (13,14), and genetic polymorphisms (15). Poor compliance to drug intake does not apply to our study because patients were

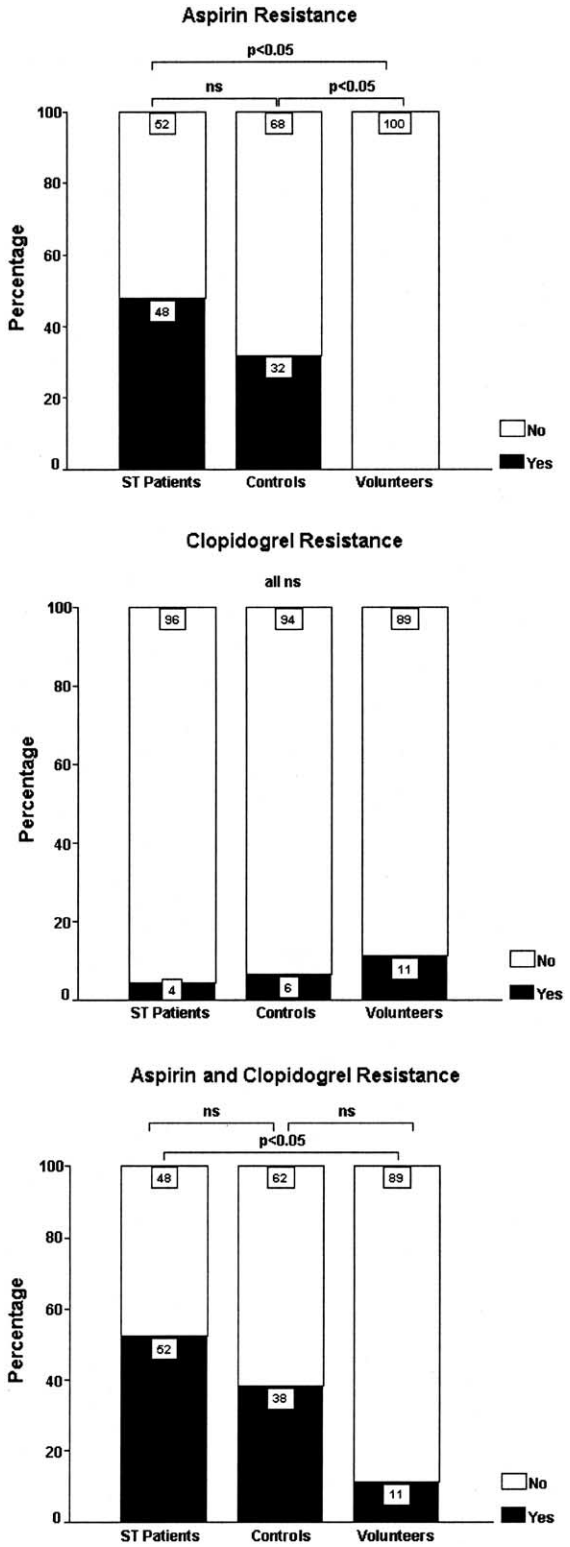

Figure 2. Resistance to acetylsalicyclic acid (ASA) (**top**: 0.5 mg/ml arachionic acid, defined as ≥20% maximal platelet aggregation). Clopidogrel resistance (**middle**: 5 μmol/l adenosine diphosphate, defined as relative change between aggregation under ASA and ASA plus clopidogrel <10%). Acetylsalicyclic acid and/or clopidogrel resistance (**bottom**: combined results of the **top and middle panels**). ns = not significant; ST = stent thrombosis.

monitored for drug intake and because aggregation values under ARA remained constant over time. Drug interactions have been minimized by excluding drugs other than prescribed by the protocol. Thus, alternative pathways of platelet activation and genetic polymorphisms appear responsible for the phenomenon of ASA resistance, and screening tests could be envisioned in patients undergoing coronary stent implantation to identify those at risk for ST. Clopidogrel showed a comparable inhibitory effect in all three groups. The incidence of clopidogrel resistance (i.e., the inability to further reduce PA by >29% beyond ASA alone) was generally low, but as many as 39% of patients showed a low response to this drug. These data are in line with previous reports (12), although the definition of clopidogrel resistance may vary among different studies.

Another important finding of the present study was the inability of clopidogrel to overcome the impaired response to ASA in ST patients because the level of ADP-induced aggregation remained higher in this group. Higher clopidogrel doses (e.g., loading 600 mg, 150 mg daily) may have improved the low response to this drug (8). Notwithstanding, the causes for ST are multifaceted, but ASA resistance may play a key role among other factors.

Study limitations. This is a retrospective case-control study, with its inherent shortcomings. The number of patients studied limits the power to detect clinically important differences in prevalence of resistance between groups. In addition, only a limited number of patients with ST were studied. Many of them refused to participate because of fear of ST recurrence. Finally, urine metabolites of thromboxane were not measured.

Conclusions. The phenomenon of resistance to ASA and the combination of ASA and clopidogrel may play an important role in the pathophysiology of ST. In the future, simple and reliable tests to assess for these resistances are warranted to prevent atherothrombotic events and their sequelae.

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