CLINICAL RESEARCH

Resistance to platelet antiaggregants: an important cause of very late thrombosis of drug eluting stents? Observations from five cases

Résistance aux anti-agrégants plaquettaires : cause importante de thrombose très tardive de stent actif ? À propos de cinq observations

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Summary

\textbf{Background.} — Very late thrombosis of drug eluting stents is a rare complication that might be triggered by resistance to platelet antiaggregants (PAAs).

\textbf{Aim.} — Following an initial case where clinical data strongly suggested resistance to PAAs, we carried out a prospective systematic analysis of platelet aggregation in four subsequent cases of late thrombosis.

\textbf{Methods.} — Resistance to aspirin was investigated with the PFA-100 test employing a collagen-epinephrine cartridge (Platelet Function Analyzer; Dade Behring). Resistance to clopidogrel was determined by flow cytometry of intraplatelet vasodilator-stimulated phosphoprotein (VASP) phosphorylation.

\textbf{Results.} — All four cases showed resistance to either aspirin or clopidogrel, and two cases showed dual resistance to both of these PAAs.

\textbf{Conclusion.} — Analysis of platelet function in a patient with late stent thrombosis is useful and may allow adaptation of subsequent patient management. The value of monitoring platelet function after implantation of a drug eluting stent should be evaluated in prospective studies.

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Résumé

\textbf{Justification.} — La thrombose très tardive est une complication rare des stents actifs pour laquelle la résistance aux antiagrégants plaquettaires (AAP) pourrait être un facteur favorisant.

\textbf{Objectifs.} — Suite à un premier cas évoquant fortement une résistance aux AAP uniquement sur des données cliniques, nous avons réalisé de façon prospective pour les quatre thromboses très tardives suivantes une analyse systématique de l’agrégation plaquettaire.

Very late stent thrombosis and resistance to antiaggregants

Introduction

Late thrombosis of stents eluting active substances (active stents) is a rare complication, which is nevertheless devastating for patients. As with bare stents several groups of factors that can trigger thrombosis have been identified including those linked to the implantation procedure, those linked to the patient, and those linked to the stent itself [1]. However, where active stents in particular are concerned platelet antiaggregant (PAA) treatment appears to play an important role, especially premature discontinuation of PAAAs [2]. Resistance of a patient to the action of a PAA (aspirin or clopidogrel) has been described as another factor leading to thrombosis [3,4].

In this report, we describe five cases of very late thrombosis, occurring between 12 and 54 months after stent implantation, where resistance to PAAAs, suggested strongly in the first case from the patient’s medical history, was confirmed in the four subsequent cases by performing platelet function tests used for the evaluation of primary hemostasis.

Patients and methods

Following an initial case of very late thrombosis for which anamnesis strongly suggested resistance to PAAAs, we carried out a prospective systematic analysis of platelet aggregation in subsequent cases. Four patients were investigated over a period of 15 months. In order to verify good patient compliance before stent thrombosis, an interview was carried out according to the method of Girerd et al. [5]. Blood samples were also taken 6±1 days after the thrombosis, when the combination of aspirin (160 mg/day) and clopidogrel (75 mg/day) had been reintiated in these patients.

Resistance to aspirin was determined with the PFA-100 test using collagen and epinephrine (Platelet Function Analyzer, Dade Behring) and measurement of occlusion time (OT), where an OT of <190 sec indicates resistance to aspirin [6]. Resistance to clopidogrel was investigated by flow cytometry of intraplatelet vasodilator-stimulated phosphoprotein (VASP) phosphorylation, which enabled the determination of an index of platelet reactivity (IPR), an IPR of >50% indicating resistance to clopidogrel. Among the numerous platelet agonists, ADP plays a major role via intermediary P2Y12 receptors. Clopidogrel selectively and irreversibly inhibits the pathway of activation of the P2Y12 receptor by ADP and thus blocks ADP-dependant activation of platelets. VASP phosphorylation is one of the steps in P2Y12 receptor pathway.

Case observations

Case n°1

In August 2004, a 75-year-old patient with a history of chronic obstructive bronchitis and arteriopathy obstructing the lower limbs, and cardiovascular risk factors of smoking, excess weight and hereditary heart disease (Table 1), presented with anterior myocardial infarction complicated by sudden death and was resuscitated from inaugural ventricular fibrillation. The patient received intravenous thrombolysis following reperfusion criteria. Clinical evolution was uncomplicated: CPK peaked at 4800 IU/l (normal = 0-155IU/l) and transthoracic echography demonstrated a left ventricular ejection fraction (LVEF) of 45% with a large anteroseptal akinesia. Coronarography, carried out on the 8th day revealed a long and tight stenosis in the proximal left anterior descending artery (LAD) with TIMI 3 flow below. A short and dense stenosis was also present in the right coronary artery (RCA). A double angioplasty by direct stenting was carried out in the LAD (sirolimus stent; Cypher®, 3.0 x 18 mm, 11 atm) and RCA (bare stent; Driver®, 4.0 x 15 mm, 10 atm), with an excellent angiographic outcome. The patient then underwent cardiovascular reeducation with treatment combining clopidogrel (75 mg/day), aspirin (75 mg/day), perindopril (8 mg/day), simvastatin (40 mg/day), furosemide (40 mg/day), and then bisoprolol (2.5 mg/day). The combination of clopidogrel plus aspirin was continued for 15 months, and then monotherapy with clopidogrel was continued for 6 months. In the 19th month post-angioplasty, clopidogrel treatment was replaced by monotherapy with aspirin (75 mg/day). Eleven days later, the patient presented with signs of infarction including thoracic pain and ECG revealed ST-segment elevation in inferior leads with anterior mirroring, and first degree AV block. Thrombolysis with streptokinase was initiated but was ineffective; the patient deteriorated hemodynamically and was transferred to our center in a state of cardiogenic shock. Immediate coronaryography demonstrated thrombosis of the sirolimus stent in the LAD as well as a thrombosis of the bare stent in the RCA, with TIMI 0 flow in the two lesions. Despite initiation of mechanical dethrombosis by thrombo-aspiration with the Export® system, insertion of a bare stent in the RCA (Driver®, 4.0 x 30 mm, 12 atm) and dethrombosis of the stent in the LAD, orotracheal intubation, insertion of an intraaortic balloon pump and a probe for electrosystolic training, the patient died from electromechanical dissociation.

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Table 1  Clinical characteristics of the five cases of very late stent thrombosis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>CVRF</th>
<th>Localization and type of stents implanted</th>
<th>Stents with thrombosis</th>
<th>Time of very late thrombosis (months)</th>
<th>Treatment before the thrombosis</th>
<th>Immediate management of thrombosis</th>
<th>Treatment after the thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>Smoking Excess weight Hereditary</td>
<td>LAD - Cypher RCA - Driver</td>
<td>LAD - Cypher RCA - Driver</td>
<td>19</td>
<td>Aspirin 75 mg</td>
<td>Aspirin 250 mg IV + clopidogrel 300 mg trombosis + rescue angioplasty</td>
<td>Patient died</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>Dyslipidemia</td>
<td>LAD - Cypher RCA - Cypher</td>
<td>LAD - Cypher RCA - Cypher</td>
<td>33</td>
<td>Aspirin 75 mg</td>
<td>Aspirin 250 mg IV then 160 mg per os + clopidogrel 600 mg then 75 mg + abciximab primary angioplasty</td>
<td>Aspirin 75 mg + clopidogrel 150 mg</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>Dyslipidemia AHT Smoking</td>
<td>LAD - Titan LAD - Taxus</td>
<td>LAD - Cypher</td>
<td>29</td>
<td>Aspirin 75 mg + clopidogrel 75 mg</td>
<td>Aspirin 250 mg IV then 160 mg per os + clopidogrel 600 mg then 75 mg + abciximab primary angioplasty</td>
<td>Elective by pass + aspirin 160 mg</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>0</td>
<td>Proximal LAD - Cypher Distal LAD - Vision + Cypher</td>
<td>Proximal LAD - Cypher</td>
<td>12</td>
<td>Aspirin 75 mg</td>
<td>Aspirin 250 mg IV then 60 mg per os + clopidogrel 600 mg then 75 mg + abciximab primary angioplasty</td>
<td>Elective by pass + clopidogrel 75 mg</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>AHT</td>
<td>LAD - Driver LAD - Cypher</td>
<td>Proximal LAD - Cypher</td>
<td>48</td>
<td>0</td>
<td>Aspirin 250 mg IV then 160 mg per os + clopidogrel 600 mg then 75 mg + abciximab primary angioplasty</td>
<td>Aspirin 160 mg + clopidogrel 150 mg</td>
</tr>
</tbody>
</table>

CVRF: cardiovascular risk factors.  
AHT: Arterial hypertension.  
RCA: right coronary artery.  
LAD: left anterior descending artery.  
Cypher and Taxus: active stents.  
Driver, Titan and Vision: bare stents.

case no 2

In 2003, an 80-year-old man with dyslipidemia (LDL: 1.65 g/l) presented symptoms of effort angina, with positive exercise stress test (table 1). Coronarography demonstrated the existence of bitruncular lesions with tight stenosis of the LAD (figure 1A) and long stenosis of the second segment of the RCA. On the 25th November 2003 angiography was carried out and sirolimus stents were implanted in the LAD (Cypher® 3.0 x 23 mm, 12 atm) and RCA in C2 (Cypher® 3.0 x 23 mm, 12 atm) with an excellent angiographic result. Fifty minutes after angiography the patient presented with thoracic pain and ST-segment elevation from V1 to V3. An emergency coronaryography was carried out and demonstrated an acute LAD intrastent thrombosis with TIMI 2 flow below (figure 1C). Mechanical dethrombosis by balloon angioplasty (VIVA® 3.0 x 20 mm, 12 atm) under abciximab enabled restoration of normal coronary flow and disappearance of the thoracic pain and ST-elevation (figure 1D). Follow-up was uncomplicated with a CPK peak of 400 IU/l. The patient left hospital on clopidogrel (150 mg/ day for 5 days then 75 mg/day), aspirin (75 mg/day), bisoprolol (5 mg/day), perindopril (4 mg/day) and simvastatin (40 mg/day). On the 5th August 2005 (21 months later) the patient was seen by his cardiologist for his annual check up where it was decided to stop combined therapy with clopi-
with hyperkinesia of the other walls. No problem with compliance was found. The results of blood tests supported a good response to aspirin but biological resistance to clopidogrel, with TO > 300 sec and an IPR of 74% (table 2). After medico-surgical discussion it was decided to increase the dose of clopidogrel (150 mg/day). The patient left our service for a center of cardiovascular reeducation on clopidogrel (150 mg/day), aspirin (75 mg/day), bisoprolol (5 mg/day), perindopril (4 mg/day) and simvastatin (40 mg/day). A control IPR was carried out several months later: this new test revealed an IPR of 48%. Subsequent evolution was uncomplicated over a period of 9 months.

Case n° 3
A 78-year-old man with dyslipidemia (LDL: 1.55 g/l) and a history of smoking and hypertension was hospitalized on the 18th August 2003 for coronaryography in the context of effort angina with positive exercise stress test (table 1). This revealed a monotruncular lesion of the proximal LAD. Direct stenting was carried out with a bare stent (Titan®, 3.5 x 16 mm, 10 atm); an excellent angiographic result was obtained at the end of the procedure. At the beginning of 2004 effort angina recurred with positive proof of effort. Coronarography demonstrated a dense restenosis at the entrance to the stent. Direct stenting with insertion of an active stent (Taxus®, 12 x 3.5 mm, 10 atm) was carried out on 26th May 2004 with an excellent result. On the 11th October 2006, 29 months after insertion of the Taxus stent, the patient presented with signs of infarction including thoracic pain and antero-lateral ST-segment elevation on ECG. Immediate coronaryography demonstrated an acute thrombosis at the entrance of the proximal LAD stent with TIMI 0 flow and also significant stenosis at the level of the second and start of the third segment of the RCA. The insertion of a bare stent in the proximal LAD (Vision, 3.0 x 8 mm, 12 atm) followed by thrombo-aspiration using the Export® system under abciximab enabled restoration of TIMI 3 flow. An intraaortic balloon pump was inserted due to the appearance of signs of left ventricular insufficiency at the end of the procedure. Hemodynamic evolution was favorable despite a CPK peak of 8.135IU/l. Echography revealed a LVEF of 40% with large anteroseptal-apical hypokinesia. The patient was
questioned about his treatment before the acute event; this had consisted of clopidogrel (75 mg/day), aspirin (75 mg/day), felodipine (10 mg/day) and simvastatin (40 mg/day). There was no evidence of poor compliance by the patient. Tests for resistance to AAPs suggested biological resistance to both aspirin and clopidogrel, with a TO of 153 sec in the PFA-100 test with collagen-epinephrine and an IPR of 94% with the VASP test (Table 2). The patient was sent for myocardial revascularization by aorto-coronary bypass in view of the tritruncular lesions and particularly the three endoprotheses in the proximal LAD. Evolution at 7 months was uncomplicated.

**Case n°4**

A 52-year-old patient, without any known risk factor, presented in September 2005 with infarction in the anterior myocardium and received pre-hospitalization fibrinolysis at

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Results of platelet aggregation tests.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PFA-100</td>
</tr>
<tr>
<td>Case 1</td>
<td>Not performed</td>
</tr>
<tr>
<td>Case 2</td>
<td>&gt;300 sec</td>
</tr>
<tr>
<td>Case 3</td>
<td>153 sec</td>
</tr>
<tr>
<td>Case 4</td>
<td>88 sec</td>
</tr>
<tr>
<td>Case 5</td>
<td>133 sec</td>
</tr>
</tbody>
</table>

PFA: platelet-function analyzer.
VASP: vasodilator-stimulated phosphoprotein phosphorylation
Biological resistance to aspirin: TO < 190 sec with aspirin (PFA-100).
Biological resistance to clopidogrel: IRP > 50% with clopidogrel (VASP).

Figure 2.  **A.** The same patient as figure 1 with very late thrombosis (33 months) of a sirolimus stent implanted in the left anterior descending artery. **B.** Very late thrombosis associated with a sirolimus stent implanted in the right coronary artery. **C.** After balloon angioplasty of the left anterior descending artery. **D.** After balloon angioplasty of the right coronary artery.
h +4 (table 1). Emergency coronaryography demonstrated an old occlusion of the RCA at the end of the second segment and two dense stenoses in the proximal and distal LAD, with TIMI 1 flow below. The rest of the reservoir was atheromatous without significant stenosis. Angioplasty of the proximal LAD was carried out with an active stent (Cypher®, 2.75 x 13 mm, 16 atm) associated with dethrombosis and complementary double angioplasty in the distal LAD (bare stent; Vision®, 2.5 x 12 mm, 16 atm, and active stent (Cypher®, 2.5 x 8 mm, 15 atm). TIMI 3 flow was obtained at the end of the procedure without residual stenosis. Follow-up was straightforward with a CPK peak of 1.200U/l and a LVEF of 51% with anterior hypokinesia and apical akinesia on echography. Treatment on discharge comprised aspirin (75 mg/day), clopidogrel (75 mg/day), ramipril (10 mg/day), fluvastatin (20 mg/day) and acebutolol (200 mg/day). In September 2006, 12 months later, it was decided to stop clopidogrel. Thirty days later, the patient presented with signs of infarction with thoracic pain and ST-segment elevation from C1 to C3 on ECG. Coronarography revealed thrombosis of the active stent in the proximal LAD, associated with tritruncular lesions. Dethrombosis under abiciprimab was carried out by thrombo-aspiration with the Export® system, restoring TIMI 3 flow at the end of the procedure. Follow-up was normal, echography revealed a LVEF of 45% with anteroseptal-apical hypokinesia and a CPK peak of 6.000IU/l. Tests for resistance to AAPs were carried out after establishing good compliance by the patient, and demonstrated biological resistance to aspirin with a TO of 88 sec and the absence of clopidogrel resistance with an IPR of 41% (table 2). A decision was made to perform an aorto-coronary bypass within a period of 3 weeks in view of the tritruncular lesions. Subsequent evolution was uncomplicated over a period of 7 months.

Case n°5

A 50-year-old female with treated hypertension had an inert stent inserted into the proximal LAD following an acute coronary syndrome. Six-months later, an active sirolimus stent was implanted due to intrastent restenosis (Cypher®, 3.0 x 23mm, 12 atm) (table 1). In April 2007, 4 years after implantation of the active stent, and after carrying out myocardial perfusion scintigraphy, which was normal, it was decided to stop clopidogrel 5 days before breast surgery. Immediately after surgery, the patient presented with thoracic pain and ST-segment elevation and required transfer to our unit for emergency coronaryography. This revealed an intra-stent thrombosis in the LAD with TIMI 0 flow below. Dethrombosis was carried out at the same time, first by thrombo-aspiration with the Export® system and then by balloon dilation (Viva®, 3 x 20 mm, 6 atm) with restoration of TIMI 3 flow at the end of the procedure. Follow-up was straightforward, echography revealed a LVEF of 55% with anterior akinesia and a CPK peak of 4800 IU/l. The results of AAP resistance tests supported biological resistance to aspirin, with a TO of 133 sec, as well as to clopidogrel, with an IPR of 58% (table 2). The patient left our unit on treatment with aspirin (160 mg/day), clopidogrel (150 mg/day), atorvastatin (80 mg/day), pantoprazole (40 mg/day), celeriprol (200 mg/day), trandolapril (2 mg/day), and trinitrine on demand. The immediate evolution was marked by multiple episodes of ventricular tachycardia requiring implantation of an implanteable defibrillator. The 6 months follow up was uncomplicated.

Discussion

The availability of active stents has drastically reduced the incidence of restenosis by neointimal hyperplasia without increasing the risk of thrombosis (early) in pivotal randomized trials [7,8]. Thrombosis of active stents is a rare complication with an incidence of 0.4-1% [9,10,11], but is nevertheless a devastating event leading to myocardial infarction in three out of four cases and death in 25-45% of patients [12,13]. The frequency of late thrombosis (reported up to 4 years) is estimated to be between 0.52% and 1.2% depending on the more or less restrictive definition of thrombosis and the population studied (in randomized trials) [14,15] or registered [12,16]. After 12 months, the term very late stent thrombosis is used [17]. However, while the rate of acute and subacute thrombosis (≤30 days) is identical after insertion of an active stent or a bare stent [18], controversy exists about the higher risk of late thrombosis (>30 days), or very late thrombosis. The randomized BASKET-LATE study compared the evolution of patients who had received bare stents (Vision®) or active stents (Cypher® or Taxus®). The patients were treated for 6 months with clopidogrel plus aspirin, and then followed for 12 months after discontinuation of dual therapy. This study demonstrated a significantly higher number of cases of non-fatal infarction or cardiovascular death in the group implanted with active stents (4.9% versus 1.3%, p < 0.01) [19]. Nevertheless, this was a limited series of patients and recent meta-analyses of randomized trials, comparing either sirolimus stents with bare stents [14,15,20,21], or paclitaxel stents with bare stents [20], did not find any increase in overall risk of thrombosis in the 4 years, but suggested a moderate but significant increase in very late thrombosis. This increased risk can be explained by the delay in endothelialization of active stents compared to bare stents [22]. Discontinuation of AAP treatment or the premature discontinuation of the clopidogrel-aspirin combination are the most important factors favoring stent thrombosis [9], before reendothelialization of the stent is achieved. This is the principal mechanism proposed by McFadden et al. [2].

While the recommendations concerning the duration of dual AAP treatment are clear after insertion of an inert stent (at least 1 month after implantation), those concerning implantation of an active stent remain unclear. Whereas the value of continuing the combination well beyond the 3 or 6 months in current recommendations in patients with active stents is clear, prolongation of treatment beyond 1 year remains controversial.

Resistance of a patient to the action of AAPs is another major risk factor for thrombosis. Some studies have demonstrated an increase in number of cardiovascular events associated with resistance to aspirin in patients treated for stable or unstable angina [23-25]. Matetzky et al. [26] and Baragan et al. [3] reported an identical phenomenon in the case of resistance to clopidogrel. The prevalence of resistance to AAPs varies according to different studies. It is estimated that the desired antiaggregant effect is not obtained in 5-45% of patients taking aspirin and in 4-30% of those taking clopidogrel. This large variation in prevalence can be explained by the use of different methods for the analysis of platelet function and by a lack of standardization of techniques between laboratories [27]. Aggregometry is the most widely used technique for the analysis of platelet reactivity. However, this technique is...
not widely available, is long and difficult to standardize, suffers from poor reproducibility and is difficult to interpret [28]. Progress in our knowledge of the mode of action of antiaggregants has enabled the development of new tests. The analysis of intraplatelet VASP phosphorylation by flow cytometry has been standardized and is reproducible [29], making it a valuable test in cardiology for the detection of resistance to clopidogrel. Barragan et al. noted that 63% of patients presenting with stent thrombosis were resistant to clopidogrel versus 40% in the group without stent thrombosis (p < 0.0001). The variability in biological response over time in the same patient may be a limitation to the predictive value of this test for clinical events.

The PFA-100 system (Dade-Behring) is used to measure adhesion and platelet aggregation under conditions of high shear-stress conditions in a manner close to in vivo measurement of bleeding time [30]. The time necessary to obtain a stop in flow is called the occlusion time (OT) and depends on platelet function. This is a rapid test that is easy to carry out [31]. Resistance to aspirin can be demonstrated by the PFA-100 test with collagen-epinephrine [32]. Few prospective studies have been carried out on the prognostic value of the PFA-100 test post-angioplasty. Gianetti et al. [33] evaluated platelet function using the PAF-100 test, 30 ± 8 h after angioplasty in 175 patients hospitalized either for stable angina (n = 94), or for acute coronary syndrome (n = 81). After follow-up for 6 months, the risk of relapse of coronary events determined by multivariate analysis was greatly increased in the group with an OT of < 190 sec in the PFA-100 collagen-epinephrine test.

No prospective study to date, however, has demonstrated the relevance of these tests to predict stent thrombosis and learned Societies do not recommend the prospective studies demonstrating a correlation between the diagnosis of biological resistance and the subsequent appearance of new restenosis because it has been shown to be effective against the diagnosis of resistance to antiaggregants when changing from bi- to monotherapy. The final case demonstrates thrombosis of an active stent 4 years after its implantation, but 6 days after stopping clopidogrel for surgery. This patient also presented dual resistance to aspirin and clopidogrel. It should be noted that this patient, like patient 3, had been treated by implantation of an active stent for restenosis of a bare stent. Although this indication is currently approved because it has been shown to be effective against the appearance of new restenosis [36], we cannot formerly rule out the possibility that it increases the risk of stent thrombosis.

In our cases, the first emergency procedure was mechanical deobstruction with a loading dose of AAP + anti-GPIIb/IIIa (type: abciximab). During dethrombosis the following steps in patient management should be followed: first, patient compliance must be established. If this is not in question, platelet aggregation tests should be carried out. In the case of resistance, management is not clear and depends on the area at risk, the result of emergency interventional procedure carried out, and the presence of other known risk factors for thrombosis. Heart surgery may be proposed in a patient with a high risk of rethrombosis or with a large area at risk. If this is not the case, combined AAP treatment should be continued, doubling the dose of clopidogrel, and rechecking the platelet function tests under the modified doses.

In conclusion, the cases presented here show that analysis of platelet function is of value in patients suffering from stent thrombosis, but may also be useful clinically when applied prospectively, in particular in patients with a high risk of thrombosis. These tests may provide vital information about the management of AAP treatment in these patients. However, there is currently no consensus on the nature of the tests or which tests to carry out. Randomized, prospective studies demonstrating a correlation between the diagnosis of biological resistance and the subsequent appearance of thrombosis are necessary.
Very late stent thrombosis and resistance to antiaggregants


