Case reports

Usefulness of glycoprotein IIb/IIIa inhibitors in unstable angina due to small vessel disease

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Key words:
Abciximab; Microvascular reperfusion; Thrombosis.

We describe the role of abciximab in unstable angina due to small vessel disease in a 58-year-old patient who was submitted to percutaneous transluminal coronary angioplasty and stenting of an occluded venous graft.

(Ital Heart J 2001; 2 (12): 927-931)

Received June 25, 2001; revision received October 4, 2001; accepted October 25, 2001.

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Introduction

The usefulness of glycoprotein IIb/IIIa antagonists has widely been recognized and the inclusion of these drugs in treatment regimens for acute coronary syndromes is now widespread[1-3]. Data collected in previous studies have been supporting the combined use of these drugs with antiplatelet agents and percutaneous interventions in patients with unstable angina. This therapeutic regimen has been shown to significantly decrease the rate of major events at short- and long-term follow-up with a stabilization of the patient's clinical status[4-8].

We describe the case of a patient with unstable angina who underwent reopening of an occluded venous graft and who, despite the fact that coronary angiography demonstrated TIMI grade 3 flow, stabilized only by the addition of intravenous abciximab to the therapeutic regimen. We suggest a possible role for glycoprotein IIb/IIIa inhibitors in small vessel disease.

Case report

A 58-year-old man suffering from unstable angina (Canadian class III) was admitted to our Department. He had a family history of cardiovascular disease, hyperlipidemia, and he had been a smoker. He had been operated for gastric ulcer in 1999. He had a non-Q wave myocardial infarction in 1986. At that time, his coronary angiography revealed significant disease involving the circumflex artery. He underwent coronary bypass grafting in March 1987 and on that occasion a venous conduit to the obtuse marginal system was employed. He was asymptomatic until April 1998, when he presented with unstable angina (Canadian class III). For this reason, he underwent a new coronary angiography which showed a patent venous graft and TIMI 3 flow. Since then, he has been suffering from episodes of ischemic chest pain for 2 years. During this period, he was started on calcium antagonist therapy and despite improvement in symptoms, he continued to complain of a mixed angina.

In September 2000, he was admitted to our ward because of recurrent short-lasting episodes of chest pain. The electrocardiogram showed ST changes on the following leads: ST segment depression in the V_1-V_3 leads and ST segment elevation in D2, D3 and aVF. There was no rise in the peak creatine phosphokinase values (Fig. 1). Subsequent coronary angiography indicated well preserved left ventricular function. The circumflex artery was totally occluded; the left anterior descending coronary artery was smaller than normal with non-significant stenosis (30%) in the initial course. Two small branches originated from its middle segment; the right coronary artery was a normal right main artery without significant stenosis. The venous graft to the obtuse marginal system was occluded and revealed only by the flow through a collateral system originating from the main right coronary artery.

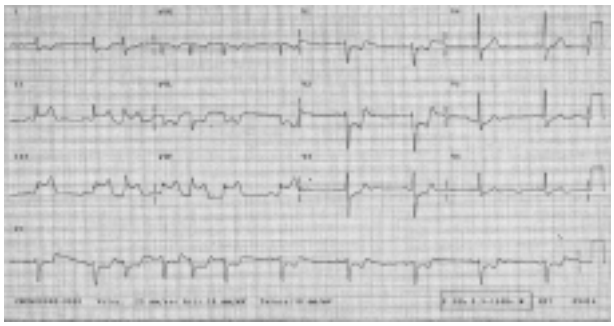

Figure 1. *Electrocardiogram during chest pain at the time of the first presentation with unstable angina. Note the ST segment depression in the V_1-V_3 leads and ST segment elevation in the D2, D3, and aVF leads.*

On this occasion, the patient underwent reopening of the venous graft to the obtuse marginal system with plain old balloon angioplasty (POBA). At the end of the procedure, a final angiographic view showed a TIMI 2 flow through the graft with a small thrombus in the distal part of the graft (Fig. 2). He was given heparin 25 000 IU (21 ml/hour i.v.) and ticlopidine 500 mg/die.

Sixteen hours following POBA, the patient was again symptomatic and presented with short-lasting episodes of chest pain during which his electrocardiogram showed the following ST changes: ST segment depression in the V_1-V_3 leads and ST segment elevation in the DII, DIII and aVF leads. There was no rise in peak creatine phosphokinase values. For this reason, whilst maintaining heparin and ticlopidine, an intravenous infusion of nitroglycerine was started and it was decided to perform another angiography. This second angiogram (24 hours following POBA) showed TIMI 0-1 flow through the graft with evidence of a subocclusive thrombus in the middle-proximal segment of the graft (Fig. 3). Thus he underwent coronary angioplasty again and a 23 mm long stent was implanted in the graft. The outcome of the procedure was excellent and repeat coronary angiography demonstrated complete resolution of the angiographically revealed thrombus and total restoration of TIMI grade 3 flow (Fig. 4). The symptoms ended. However, he was maintained on heparin 25 000 IU (21 ml/hour i.v.) according to the activated clotting time > 200 < 250 s and ticlopidine 500 mg/die.

Twenty-four hours later, short-lasting episodes of chest pain recurred with similar ST changes and without a rise in peak creatine phosphokinase values (Fig. 5). A third coronary angiogram performed during symptoms and ST changes did not reveal intraluminal patency reduction into the implanted stent or spasm of the graft and confirmed TIMI 3 flow (Fig. 6). Thus, in addition to previous therapy, he was started on intravenous diltiazem and oral felodipine (5 mg/die) and he was readmitted into the coronary care unit. Because of persistent chest pain and electrocardiographic segment changes, it was decided to start treatment with an intravenous abciximab bolus + intravenous injection (5 ml/hour), despite the fact that for this patient glycoprotein IIb/IIIa inhibitors were moderately contraindicated (Fig. 7). Only at this stage, within 1 hour of the beginning of the treatment, the patient became asymptomatic and the ST segment shifts returned to baseline (Fig. 8). There was no rise in peak creatine phosphokinase values. Four days later, the patient was discharged symptom-free from the hospital.

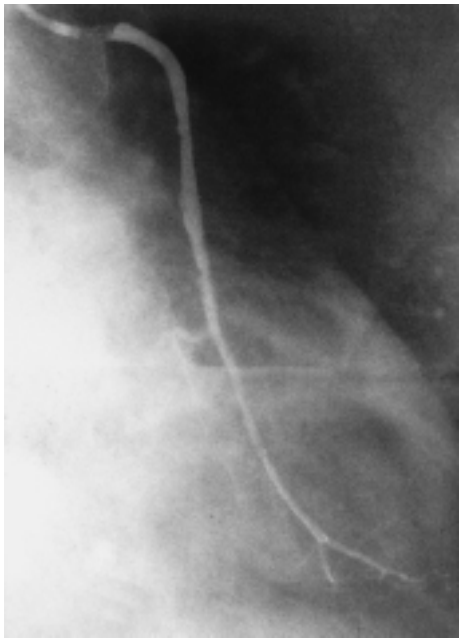

Figure 2. *The coronary artery bypass venous graft in the right anterior oblique projection (right anterior oblique 30, cranial 10) demonstrating patency of the graft at the end of the angioplasty procedure. Note the presence of a small thrombus in the distal segment of the graft.*

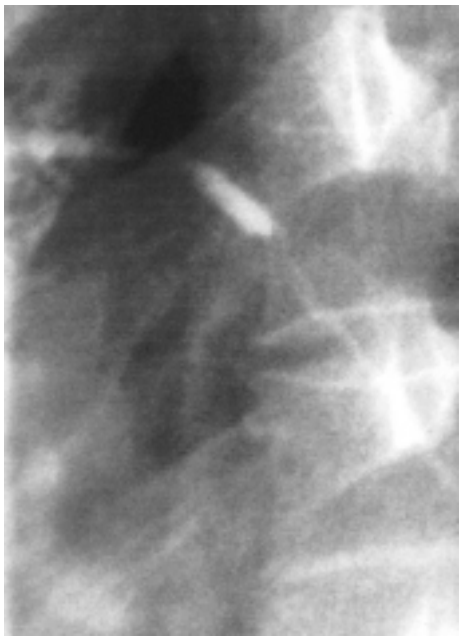

Figure 3. *The coronary artery bypass venous graft in the left anterior oblique projection (left anterior oblique 40) demonstrating subocclusion of the graft at control (24 hours following the plain old balloon angioplasty procedure).*

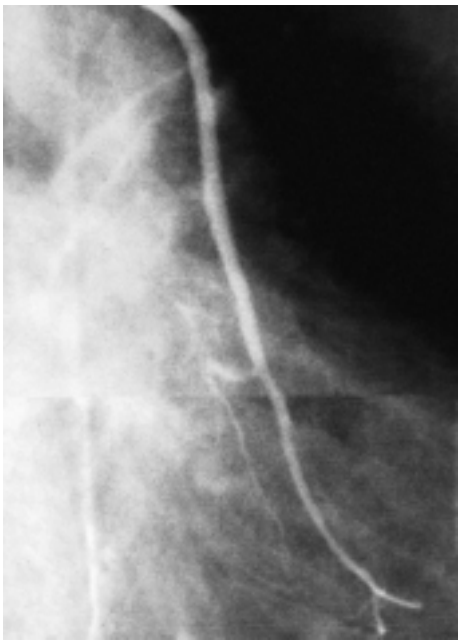

Figure 4. *The coronary artery bypass venous graft in the right anterior oblique projection (right anterior oblique 30, cranial 10) demonstrating complete resolution of the angiographically revealed thrombus and restoration of TIMI grade 3 flow throughout the graft.*

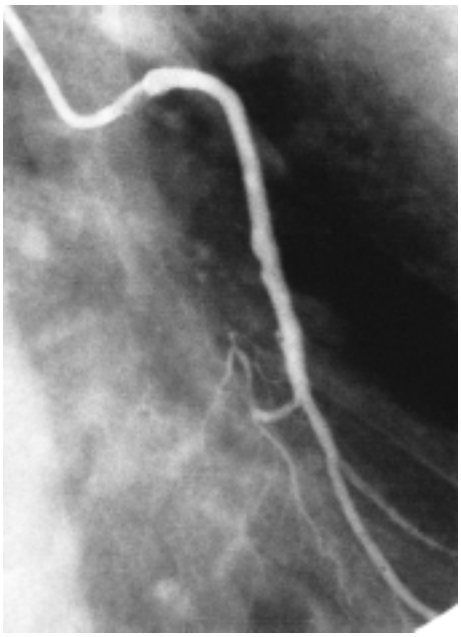

Figure 6. *The coronary artery bypass venous graft in the right anterior oblique projection (right anterior oblique 30, cranial 10) demonstrating patency of the graft at control (24 hours following the stenting procedure).*

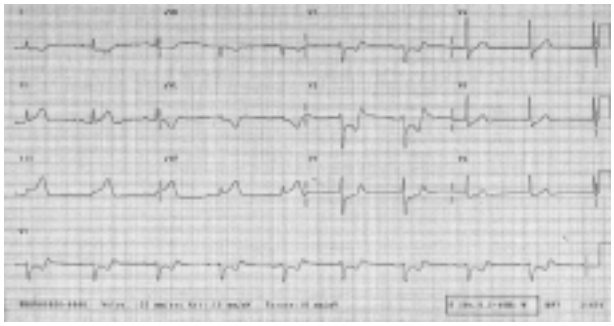

Figure 5. *Electrocardiogram during recurrence of chest pain. Note that this electrocardiogram was recorded at the time of the coronary angiogram which showed patency of the bypass venous graft.*

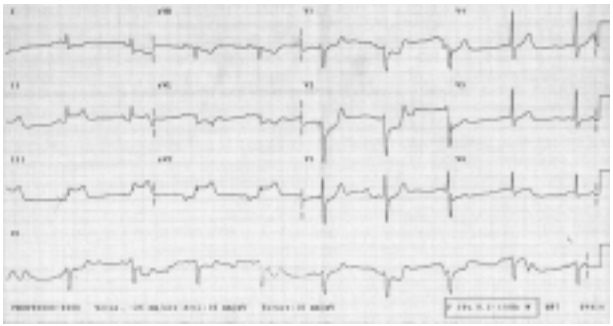

Figure 7. *Electrocardiogram recorded at the time of the last episode of chest pain before the administration of the glycoprotein IIb/IIIa inhibitor.*

Discussion

The occurrence of unstable angina in the absence of a ruptured plaque and of a coronary thrombus may be evoked by two different mechanisms. The first one might be represented by small vessel thromboembolism, caused by displacement of the atherosclerotic plaque, during balloon angioplasty and stent implantation, while the second one might be related to a vascular reperfusion injury due to a cardiac inflammatory response at the site of the small vessels.

Recent studies have demonstrated the efficacy of glycoprotein IIb/IIIa receptor inhibition in preventing major complications such as myocardial infarction, distal embolization and the no-reflow phenomenon after angioplasty in patients with unstable coronary syndromes[9,10]. It has been noted that patients undergoing balloon angioplasty are likely to present angiographic evidence of the presence of a thrombus within the target vessel at the end of the procedure[11] and that during these

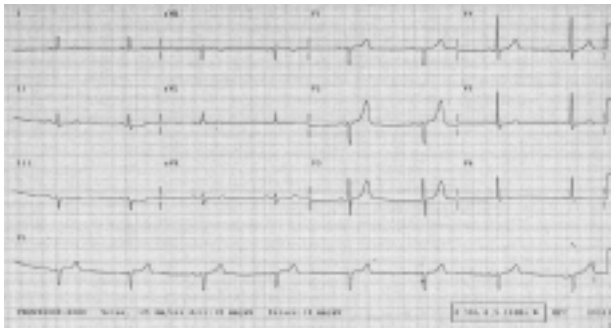

Figure 8. *Electrocardiogram recorded during resolution of symptoms 1 hour following the initiation of treatment with abciximab.*

interventions, retrograde embolism of thrombotic material can occlude other branches[12]. Moreover, the use of stenting predisposes to deeper arterial trauma because of high pressure inflation[7,13-15] leading to platelet activation and increased thrombin generation[16]. Abciximab reduces platelet thrombus formation and fibrin deposition by decreasing the total platelet aggregate mass[17], inhibits clot retraction through interaction with the cytoskeletal components of the platelets[18] and also remodels thrombus architecture by increasing the porosity and decreasing the elasticity of the fibrin platelet mesh[19,20]. Even after binding to the glycoprotein IIb/IIIa receptor, fibrinogen has an affinity constant that is lower than that of abciximab and can be displaced by this drug. Furthermore, dissolution of an already formed thrombus may result from the inhibitory effect of abciximab on plasminogen activator inhibitor-1[20,21]. Indeed, a possible mechanism of thrombus resolution may involve a combination of pharmacological and mechanical effects. In this setting, it is possible that abciximab prevents further distal thrombosis and allows the endogenous fibrinolytic system to clear the large burden of thrombus, which would otherwise be easily embolized. However, it is interesting to note that in our case unstable angina recurred only 24 hours following the stenting procedure. If the mechanism of dislodgment of the thrombus is advocated, it is conceivable that chest pain and ST changes would have persisted after the procedure and that, in contrast to what was observed immediately after stenting, these symptoms would not have completely resolved. Moreover, the transmural extension of these ischemic episodes as shown by ST segment elevation, their short duration, and the absence of enzyme release could also exclude an embolic origin of ischemia.

Coronary spasm of the graft which is another possible mechanism of ischemic chest pain could also be excluded, as during coronary angiography performed at the time of chest pain no evidence of coronary spasm was observed in any segment of the graft; thus, it was not considered useful to perform a provocative test.

A vascular reperfusion injury due to cardiac inflammatory responses may represent another mechanism which could explain the recurrence of unstable angina observed in the present case. Indeed, by various angioscopic findings it has been demonstrated that after balloon angioplasty or acute coronary syndromes, a stimulatory status for various inflammatory pathogenetic mechanisms persists in the plaque for at least 1 month and could later lead to vessel occlusion. Thereby, stimulation of thrombogenic and inflammatory mechanisms caused by damage of the small vessel endothelium can favorably promote thrombosis and thrombolysis in small vessels and affect biochemical mechanisms which could cause an unbalance between beta and alpha receptors and small vessel vasoconstriction[22]. Indeed, an altered microvascular vasomotor tone occurring during percutaneous coronary procedures could justify transient, transmural, short-lasting ischemic episodes of chest pain, which may quickly and spontaneously remit. Finally, those substances released by the inflammatory cells could further increase microvascular vasoconstriction.

In this setting, glycoprotein IIb/IIIa inhibitors may maintain not only the patency of recanalized vessels, but also improve myocardial perfusion by preventing interaction of platelets and release of vasoconstrictive mediators into the microvasculature[3,8,23]. It is interesting to note that abciximab is the only glycoprotein IIb/IIIa inhibitor which, differently from other antagonists such as eptifibatide and tirofiban, binds also the vitronectinic receptor and the leukocyte MAC-1 receptor[17,18,24]. As recently shown, both receptors promote platelet-mediated thrombin generation, while the former regulates the arteriolar vasomotor tone[25]. Finally, recent studies have suggested a possible relation between embolization and inflammation, revealing that levels of inflammatory markers such as the C-reactive protein are greatly reduced by glycoprotein IIb/IIIa inhibitors[1,18,22,24].

One potential limitation of our study was the conflicting effect resulting from the administration of calcium antagonists just before that of glycoprotein IIb/IIIa inhibitors. Because of their action on the small coronary vessel muscle, calcium antagonists might have potentiated the therapeutic effect of glycoprotein IIb/IIIa inhibitors at the site of the small vessels. However, enough time was given to test the efficacy of calcium antagonists before abciximab administration.

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