

## Pulmonary Hemorrhage After Abciximab. Risk Factors and the Role of Protamine

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Large clinical trials have demonstrated the clinical effectiveness of therapy with inhibitors of the platelet surface-membrane glycoprotein IIb/IIIa receptor in a broad range of patients with ischemic heart disease. Abciximab, a platelet glycoprotein IIb/IIIa receptor blocker, is associated with improved long-term prognosis in patients who require angioplasty and stent placement. Severe bleeding from abciximab use is an uncommon event. We describe a patient with severe pulmonary hemorrhage after treatment with abciximab, and discuss predisposing factors and protamine infusion in this potentially fatal complication.

**Key words:** *Abciximab. Pulmonary hemorrhage. Coronary angioplasty.*

### Hemorragia pulmonar por abciximab. Factores de riesgo y papel de la protamina

Diversos ensayos clínicos han demostrado la eficacia de los inhibidores de la glucoproteína plaquetaria IIb/IIIa en un amplio espectro de pacientes con cardiopatía isquémica. El abciximab, un bloqueador de este receptor, mejora el pronóstico a largo plazo de los pacientes que requieren angioplastia e implante de *stent*. Los eventos hemorrágicos graves derivados del uso del abciximab son infrecuentes. Comunicamos el caso de una hemorragia pulmonar severa tras el tratamiento con abciximab. Discutimos los factores predisponentes y la administración de protamina en esta complicación potencialmente mortal.

**Palabras clave:** *Abciximab. Hemorragia pulmonar. Angioplastia coronaria.*

## INTRODUCTION

Abciximab has proven efficacy in reducing ischemic complications in patients who undergo angioplasty and stent implantation.<sup>1-4</sup> However, antiplatelet therapy with abciximab, aspirin, clopidogrel and, heparin can be associated with major bleeding complications.<sup>1-4,5</sup> We describe a patient with pulmonary hemorrhage following the use of abciximab. The clinical presentation of this entity can be confused with heart failure, infectious processes or pulmonary thromboembolism, and can go unnoticed or be managed improperly.<sup>5</sup>

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## CASE STUDY

This report describes the case of a 76-year-old woman with a history of hypertension, dyslipidemia and ischemic heart disease treated with complete percutaneous revascularization of the right coronary and left anterior descending arteries five years earlier. She was referred for coronary angiography by another hospital, where she had been admitted seven days before for acute coronary syndrome characterized by progressive angina that culminated in prolonged angina. The vital signs and physical examination were normal. The electrocardiogram (ECG) at admission disclosed sinus rhythm with no conduction disorders and a transient 2-mm ST segment depression in V4-V6. The hemogram, coagulation study, biochemistry with serial cardiac enzyme measurements, and chest x-ray were all normal. No troponin elevation was observed. Treatment was initiated with aspirin (300 mg/24 h), clopidogrel (75 mg/24 h), and enoxaparin (1 mg/kg/12 h). Clinical progress was favorable. A



**Figure.** Chest x-ray with diffuse alveolar infiltrate, predominantly in the upper lobes.

low-level stress test under therapy was clinically and electrically positive and the patient was referred to our hospital for a scheduled coronary angiography. On the morning of the test, the enoxaparin dose was omitted and the test was performed, revealing severe calcified stenosis in the proximal (non-dominant) circumflex artery and no significant lesions in the remaining vessels. A decision was made to perform angioplasty during the same procedure. A standard heparin dose of 100 U/kg was administered and after predilation, a coronary stent was implanted in the stenotic segment of the proximal circumflex artery. The patient presented chest pain with ECG changes and retrograde dissection, and slow flow was visualized at the proximal opening of the stent. A second proximal stent was implanted to cover the dissection from the ostium of the circumflex artery. However, this did not improve flow and the patient showed hemodynamic deterioration with severe bradycardia that required temporary pacemaker implantation and a brief period of cardiac massage. Abciximab was then administered by bolus (0.25 mg/kg) and continuous infusion (0.125 µg/kg/30 min). The patient's clinical condition finally stabilized, with TIMI-3 flow observed on angiography after balloon dilation. One hour later the patient presented dyspnea, hypotension, and hypoxemia that required intubation and mechanical ventilation. Subacute thrombotic occlusion of the proximal circumflex artery with acute ventricular failure was suspected, but ruled out by emergency coronary angiography. The left ventricular end-diastolic pressure was low and the ventriculography showed ventricular hyperkinesis. Based on severe hypoxemia and visible blood seen through the endotracheal tube, pulmonary hemorrhage was diagnosed. Abciximab perfusion was discontinued, and 50 mg of intravenous protamine was administered (previous activated clotting time, 350 s). The chest x-ray (Figure) showed bilateral pulmonary infiltrates of recent onset

and fibrobronchoscopy showed an absence of endobronchial lesions; hemoglobin had decreased by 5 g/dL. The patient received concentrated platelets, fresh plasma, packed red blood cells and fluids, and was discharged after a lengthy stay.

## DISCUSSION

The frequency of bleeding complications, particularly pulmonary artery hemorrhage, is higher in early clinical trials with abciximab and standard doses of heparin (EPIC, EPILOG group that received standard heparin doses, and CAPTURE),<sup>1-3</sup> versus low doses adjusted for weight (EPILOG group that received low heparin doses, EPISTENT)<sup>2,4</sup> (0.31 vs 0.04%).<sup>6</sup>

According to Aguirre et al,<sup>7</sup> in the EPIC study, female sex, history of acute myocardial infarction, low weight, higher age, and a prolonged or complicated angioplasty procedure implied a higher risk of hemorrhage among patients treated with abciximab. In the case of pulmonary hemorrhage, there is only limited data<sup>5,6</sup> on specific risk factors. Based on experience with 6 patients, Khanlou et al<sup>6</sup> suggested that chronic obstructive pulmonary disease, pulmonary hypertension, and high pulmonary capillary wedge pressure could be associated with an increased risk of alveolar bleeding.

Bleeding complications in patients treated with abciximab have been associated with elevated clotting times during the procedure.<sup>8</sup> Kereiakes et al<sup>8</sup> suggested that protamine administration immediately before the initial bolus of abciximab in patients with a clotting time >350 s reduces clotting times and the potential risk of hemorrhage. Pan et al<sup>9</sup> showed that neutralizing circulating heparin by protamine administration immediately after stent implantation is safe and does not involve a higher risk of stent thrombosis.

In our case, the transient increase in intrathoracic pressure from cardiac massage combined with the high heparin dose (100 U/kg), which did not consider the subsequent use of abciximab as indicated for an angioplasty complication, might have contributed to the development of this event. Early identification of this entity involves discontinuation of abciximab and other anticoagulants. Immediate reversal of the effect of heparin by protamine in our patient may have played a part in the favorable clinical outcome.

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