The infusion of abciximab (ReoPro; Eli Lilly; Indianapolis, IN), a chimeric monoclonal antibody Fab fragment specific for platelet glycoprotein IIb/IIIa receptors, has been shown to improve the short-term outcome of patients who undergo coronary angioplasty and stent placement.1–4 Abciximab, in conjunction with heparin and other antiplatelet therapy such as aspirin, ticlopidine, or clopidogrel, is usually administered as a bolus 10 to 60 min before the procedure, followed by continuous infusion for 12 h. Major and minor bleeding complications are well recognized2,4 but can be reduced by less intense anticoagulation with heparin and early arterial access sheath removal.5,6 The majority of bleeding complications occur in the absence of thrombocytopenia,6 another well-documented adverse effect in 1 to 5% of patients.7 Thrombocytopenia varies from mild to profound and usually occurs within 24 h after initial exposure to the drug.7 Most bleeding events represent arterial access complications and as such are easily recognized, as are both GI and genitourinary hemorrhaging, which occur less frequently. Intracranial bleeding has been documented but is rare.1–4

Anecdotal instances of pulmonary hemorrhage, thought to be related to abciximab, in our practice prompted this study. Such bleeding is less easily diagnosed than hemorrhage in other sites and is possibly frequently misidentified. Bleeding into the lung parenchyma may present as new radiologic infiltrates or respiratory symptoms other than hemoptysis. Reports of the frequency and severity of alveolar hemorrhage after abciximab use are

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sparse,8,9 and it is quite likely that bleeding events are misdiagnosed, most frequently as pneumonia.

We undertook a review of the records of all patients who received abciximab during coronary intervention procedures at our institution between June 1995 and March 2000. The aim was to identify patients with either an established or possible diagnosis of alveolar hemorrhage to allow us to assess the frequency of this complication as well as to elucidate, if possible, any useful information that might enhance future diagnostic accuracy. We also reviewed the records of all patients during this period who underwent coronary interventions without receiving abciximab to identify similar bleeding events occurring independent of abciximab use.

**Materials and Methods**

The records of the cardiac catheterization laboratory at Mayo Clinic, Rochester were searched electronically to identify all patients who received abciximab during the study period. We identified 2,553 such patients whose records were then further examined for a diagnosis of either alveolar hemorrhage or occurrence of hemoptysis, and by cross-checking these with records of bronchoscopic procedures during this period. This was supplemented by an informal survey of staff and Fellows in the Division of Pulmonary and Critical Care Medicine for any patients they could recall with possible alveolar bleeding in the setting of a nonsurgical cardiac procedure. The records of 5,412 patients who underwent coronary procedures between January 1995 and March 2000 but did not receive abciximab were also examined for similar bleeding events.

Seven patients were identified with a diagnosis of pulmonary hemorrhage associated with abciximab use. Their records were reviewed for demographic and clinical information, including the timing and dose of abciximab, time to onset of the bleeding, symptoms, chest radiograph findings and pertinent laboratory data, details of confirmatory testing, treatment, and the ultimate outcome. The use of additional antiplatelet or anticoagulant medication was identified, as well as evidence of bleeding from other sites.

**Results**

Seven patients (six men; mean age, 75 years; range, 67 to 83 years) of the 2,553 patients (0.27%) who received abciximab were identified with proven or highly probable alveolar hemorrhage. Table 1 summarizes their demographic and clinical data. No episodes of pulmonary hemorrhage were identified in the 5,412 patients who had not received abciximab, a clinically and statistically significant difference (χ², 11.59; Fisher’s Exact Test, p = 0.0003).

The use of abciximab occurred in the setting of acute myocardial infarction in one patient, with the remainder of patients receiving the drug during elective angioplasty and stent placement. No patient had a prior history of bleeding, six patients were receiving aspirin, and one patient was receiving long-term warfarin treatment for chronic atrial fibrillation. All patients had received a standard dose of abciximab (bolus of 0.25 mg/kg followed immediately by an infusion at a rate of 1.25 μg/kg/min (maximum of 10 μg/kg for 12 h). Five patients were pretreated with ticlopidine (500 mg initial dose followed by 250 mg bid) and two patients were treated with clopidogrel (300 mg initial dose followed by 75 mg/d). All patients received a weight-adjusted dose of heparin administered during the procedure as a bolus (70 U/kg) aiming for an activated clotting time between 200 s and 300 s. Baseline coagulation measures were normal in all patients, and the mean peak activated clotting time was 323 s (range, 246 to 457 s). No patient received or had recently received thrombolytic therapy.

The onset of the first abnormality—hemoptysis, abnormal chest radiographic finding, or hypoxemia—ranged from 2 h to 2.6 days from the first administration of abciximab. In four of the seven patients, the presenting feature was hemoptysis; two patients presented with alveolar infiltrates, hypoxemia, and a significant (2.4 g/dL and 3.1 g/dL) decrease in hemoglobin followed by hemoptyisis; and the seventh patient developed acute respiratory failure and cardiorespiratory arrest. In this patient, there was blood in the endotracheal tube and autopsy confirmed alveolar bleeding. The diagnosis was confirmed in two of the remaining six patients at bronchoscopy, with diffuse bleeding in one patient and persistent bleeding from the right upper lobe in the other patient. The first patient required ventilatory support followed by the development of acute renal failure requiring dialysis. She ultimately died 14 days after receiving abciximab when she elected to be extubated. Four diagnoses were based on major hemoptyisis accompanied by a significant (> 2 g/dL) decrease in hemoglobin concentration, abnormal chest radiographic findings, and hypoxemia. One of these patients died 5 months later. An autopsy done elsewhere was reported to show bronchopneumonia but without mention of any signs of hemorrhage.

All patients showed new infiltrates on chest radiograph. These were diffusely distributed in all but one patient, who had only a right upper lobe abnormality (Fig 1, 2). All had significantly abnormal PaO₂ levels at the time of diagnosis, and only one patient had evidence of bleeding elsewhere with hematuria and hematochezia. The latter was likely predisposed to previous radiation proctitis following treatment for prostatic carcinoma 4 years earlier. The patient declined sigmoidoscopy, and the bleeding stopped spontaneously only to recur 4 months later. All seven patients were ex-smokers, and four of the seven patients had a previous diagnosis of COPD.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Time to Diagnosis, h</th>
<th>Hemoglobin Before/After Abciximab Treatment, g/dL</th>
<th>Platelets, 10^9/L</th>
<th>ACT, s</th>
<th>INR</th>
<th>PaO₂ at Diagnosis, mm Hg</th>
<th>Chest Radiograph</th>
<th>Blood Products, U</th>
<th>Basis for Diagnosis of Alveolar Hemorrhage</th>
<th>Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>4</td>
<td>13.8/12.8</td>
<td>197</td>
<td>383</td>
<td>1.4 (receiving warfarin)</td>
<td>52</td>
<td>Bilateral diffuse</td>
<td>Acute respiratory failure/massive hemoptysis</td>
<td>PTCA</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>7</td>
<td>12.8/9.7</td>
<td>238</td>
<td>294</td>
<td>1.3</td>
<td>72</td>
<td>Bilateral R &gt; L</td>
<td>Bronchoscopy</td>
<td>PTCA</td>
<td>Controlled with balloon tamponade/thrombin</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>32</td>
<td>11.7/9.3</td>
<td>309</td>
<td>266</td>
<td>0.9</td>
<td>60</td>
<td>Bilateral lower lobe</td>
<td>Hemoptysis</td>
<td>PTCA and stent</td>
<td>Died 5 mo later (pneumonia)</td>
<td>Resolved</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>8</td>
<td>14.6/10.0</td>
<td>132</td>
<td>246</td>
<td>0.98</td>
<td>64</td>
<td>Bilateral upper lobe</td>
<td>Hemoptysis</td>
<td>PTCA and stent</td>
<td>New hematochezia 4 mo later</td>
<td>Resolved</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>2</td>
<td>12.7/8.4</td>
<td>181</td>
<td>457</td>
<td>1.06</td>
<td>48</td>
<td>Bilateral upper lobe</td>
<td>Hemoptysis, hematochezia, and hematuria</td>
<td>PTCA and stent</td>
<td>Resolved</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>62</td>
<td>16.2/9.9</td>
<td>148</td>
<td>300</td>
<td>1.17</td>
<td>65</td>
<td>RUL infiltrate</td>
<td>Hemoptysis</td>
<td>PTCA and stent</td>
<td>Resolved</td>
<td></td>
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<tr>
<td>7</td>
<td>83</td>
<td>62</td>
<td>13.5/10.4</td>
<td>240</td>
<td>315</td>
<td>1.1</td>
<td>46</td>
<td>Bilateral infiltrate</td>
<td>Bronchoscopy</td>
<td>PTCA and stent</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

*ACT = activated clotting time; PRBC = packed RBCs; INR = international normalized ratio; FFP = fresh frozen plasma; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; IABP = intra-aortic balloon pulsation; R = right; L = left; RUL = right upper lobe.
All patients had bleeding considered significant enough to require blood product administration, and all received packed RBC transfusions (1 to 4 U), two patients required platelet transfusions, and one of these patients was given fresh frozen plasma in addition. One patient died following a cardiorespiratory arrest within 2 h of his cardiac procedure and was found to have a significant quantity of blood in his airways at endotracheal intubation during attempted resuscitation. A second patient died after 2 weeks of mechanical ventilatory support, and another patient died of pneumonia 5 months later. One patient required intubation to protect the nonbleeding lung and was then treated with topical epinephrine and iced-water lavage but finally required balloon tamponade and endobronchial beef thrombin application to control the hemorrhage, a process that took nearly 4 h. No patient appeared to have a recurrence of pulmonary bleeding. There was no record of later bleeding from another site. A follow-up chest radiograph in one patient showed complete clearing 4 months later, but only short-term follow-up was available in the remaining four patients who left the hospital alive. They were, however, already improving within 2 to 4 days before being dismissed from hospital.

**Discussion**

The use of abciximab during and after coronary angioplasty and elective stent placement has been associated with significantly improved patient outcomes, particularly a reduction in periprocedural myocardial infarction and less need for urgent reintervention. The most significant and frequent complication has been bleeding, most frequently at the vascular access site, but also from the GI tract and only rarely intracranially. The frequency and severity of these bleeding complications appear to correlate with body weight and the concomitant use of additional anticoagulant therapy, especially heparin but other antiplatelet drugs as well. Severe thrombocytopenia (<20 × 10^9/L) has been observed but has usually been transient.

Alveolar hemorrhage occurred infrequently during the study period (incidence, 0.27%) with seven documented episodes among 2,553 patients. The number of patients in whom intrapulmonary bleeding might have been mild and unrecognized, or incorrectly diagnosed, is unknown. The bleeding in the seven identified patients was dramatic and likely to have been associated with the use of abciximab. The temporal association and the absence of similar episodes in patients not receiving abciximab suggest that the bleeding was likely related to the use of abciximab. Significant pulmonary hemorrhage in patients undergoing coronary procedures before abciximab became available was reported by Brown et al in patients seen up to 1994; 4 of 88 patients were identified with pulmonary hemorrhage following intracoronary stent placement, and 1 of these patients died. Anticoagulation measures in these patients...
included warfarin, heparin, aspirin, dipyridamole, and dextran infusions with activated clotting time targets of >300 s during the procedure. Three patients, including the one who died, had activated partial thromboplastin times >180 s at the time of bleeding. We did not identify any similar events in 5,412 patients who did not receive abciximab, and it is likely that this reflects changes in practice that have led to less intensive anticoagulation. It would therefore appear that aggressive anticoagulation can be rarely associated with pulmonary hemorrhage; but alternatively, very potent antiplatelet therapy with abciximab combined with aspirin, ticlopidine or clopidogrel, and heparin, a combination in almost routine practice currently, can also be associated with this serious complication.

In the seven patients described, there were major clinical and radiologic manifestations necessitating significant therapeutic interventions, but the small number of events does not lend itself to the identification of specific risk factors. The fact that these were mainly older patients (all men except one) with a background of cigarette smoking and at least some COPD does not necessarily define a subpopulation that may be at particular risk for this complication. However, it is reasonable to expect that the gas-exchange consequences of alveolar bleeding would be of greater severity in the setting of underlying additional lung disease.

The potential causes of hemoptysis, new radiographic infiltrates, and hypoxemia in this group of patients with severe, often unstable, coronary artery disease are numerous and include infection, heart failure, aspiration, and pulmonary thromboembolism. However, the close temporal relationship between abciximab administration and the onset of pulmonary abnormalities argues compellingly in favor of bleeding. Alveolar hemorrhage with the use of abciximab has been reported infrequently and may well be an underrecognized complication. The frequency of severe hemorrhage is clearly low, but the true extent of the complication remains unknown.

Transient hypoxemia, new radiologic infiltrates, and mild hemoptysis may be misattributed to pulmonary edema or pneumonia and all but the most obvious bleeding misdiagnosed. This would potentially expose patients to inappropriate treatment for heart failure or the unnecessary use of antibiotics for presumed pneumonia. In addition, the recognition of the complication could lead to an early discontinuation of the postprocedure abciximab infusion as well as prevent the inappropriate use of heparin and additional antiplatelet drugs. One of the patients in our group was initially suspected to have a pulmonary embolism, a not-uncommon scenario in the hospitalized patient with new respiratory symptoms, but with the potential for completely inappropriate anticoagulant use. A second patient was believed to have pulmonary edema until blood was seen in the endotracheal tube placed for acute respiratory failure requiring ventilatory support.

Figure 2. Patient 5 developed a dense right upper lobe consolidation and faint left upper lobe infiltrates 2 h after receiving abciximab. The hospital admission radiograph is shown on the left.
We identified seven proven or highly probable episodes of significant alveolar bleeding occurring within 3 days of the use of abciximab that resulted in one immediate death and one death after 2 weeks, during which acute renal and respiratory failure developed. All patients required blood product transfusions and developed varying degrees of respiratory failure. This report should draw renewed attention to this potentially underrecognized complication and alert those using this drug to consider the possibility of pulmonary/alveolar bleeding as the explanation for new respiratory symptoms or radiographic abnormalities. In patients with all but the most trivial changes, bronchoscopy may be diagnostic and may even have therapeutic value, using either balloon tamponade of the affected area, if localized, or through the use of locally applied hemostatic substances, as was done in one of the patients described herein. Diagnostic flexible bronchoscopy should be considered early in all patients receiving abciximab who develop new respiratory symptoms or chest radiographic abnormalities, because treatment is likely to be significantly modified if bleeding is identified.

References