Bronchial Artery Embolization for the Management of Nonmassive Hemoptysis in Cystic Fibrosis*

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**Study objectives:** Hemoptysis is a common complication in patients with cystic fibrosis (CF). Current approaches to patients with hemoptysis include conservative medical therapy, bronchial artery embolization (BAE), and surgery. We investigated the effectiveness of early BAE on the outcome in patients with minor bleeding.

**Design, patients, and interventions:** We reviewed the clinical records from the Cystic Fibrosis Service for eight consecutive patients treated with medical therapy who had undergone early BAE and eight matched patients treated with conservative medical therapy alone.

**Measurements:** We assessed the mean number of bleeding episodes, pulmonary exacerbations, lung function (FEV₁), Shwachman score, and Nottingham Health Profile (NHP) scores, the year before BAE and for the 3 ensuing years.

**Results:** During a 3-year follow-up, patients who underwent embolization had significantly fewer bleeding episodes (p < 0.001) and pulmonary exacerbations (p < 0.006). Lung function declined significantly in both groups (p < 0.001). The modified Shwachman score declined significantly during the follow-up only in patients who did not undergo embolization (p < 0.001). Patients treated by early embolization had significantly better NHP scores, indicating a better quality of life (p < 0.05). None of the patients who underwent BAE had adverse reactions.

**Conclusions:** Early BAE in patients with CF who have nonmassive hemoptysis is an effective, safe therapeutic approach offering better long-term control of recurrent bleeding and quality of life than medical therapy alone.

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**Key words:** bronchial artery embolization; cystic fibrosis; hemoptysis

**Abbreviations:** BAE = bronchial artery embolization; CF = cystic fibrosis; NHP = Nottingham Health Profile; NS = not significant

Cystic fibrosis (CF) is the most frequent genetic disease among white persons.¹⁻⁴ The incidence in Italy is approximately 1 in 2,500 live births. Because of advances in diagnostic techniques, management of complications, and lung transplantation, the overall survival and the quality of life in patients with CF have remarkably improved during the past decade. Nevertheless, the major cause of death among patients with CF is end-stage respiratory failure.⁴⁻⁵

The long-term outcome depends crucially on the various complications that inevitably develop, predominantly involving the respiratory tract. Among the most dangerous is hemoptysis,⁴ often a life-threatening event. Its incidence ranges from 5 to 61%.⁶⁻⁷ In most patients, bleeding originates from enlarged and tortuous bronchial arteries. In others, it arises from systemic nonbronchial arteries through a collateral circulation.⁸⁻¹⁰ The cause of bronchial artery hypertrophy and angiogenesis in patients with CF is the chronic inflammation in the lung parenchyma. Chronic inflammation may also increase pulmonary artery pressure, thus causing arteriovenous fistulas. In most cases, hemoptysis is triggered by a pulmonary exacerbation. Other factors, including malabsorption of vitamin K and repeated use of penicillins, may help to increase the risk of bleeding by causing coagulation abnormalities.¹¹ The severity of bleeding varies from blood-streaking of

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sputum to massive hemoptysis. Approximately 5 to 7% of patients with CF have massive hemoptysis. Most patients have less severe blood loss.\textsuperscript{12,13}

The currently available approaches to patients with hemoptysis are conservative medical treatment, bronchial artery embolization (BAE), and surgery.\textsuperscript{12} The treatment of choice depends mostly on the severity and urgency of the circumstances. Whereas BAE is the preferred treatment for massive or chronic recurrent hemoptysis, with an overall control in up to 90% of the cases,\textsuperscript{14,15} in patients with nonmassive bleeding (\(<240 \text{ mL in 24 h}\)), most physicians still recommend conservative therapy. An additional option for patients with less severe blood loss is early BAE, before bleeding becomes more extensive. One reason is that massive hemoptysis, invariably a sign of severe bronchial alterations and often a life-threatening event, is frequently associated with poor outcome and quality of life. In many patients, although BAE may significantly lower the rate of recurrent hemoptysis, it often leaves long-term survival unchanged. However, early control of bleeding by BAE may help to reinforce a patient’s psychological well-being and enhance compliance with further treatments, thus improving patients’ readiness for lung transplantation.

Our aim in this study was to evaluate retrospectively the impact of early BAE on the clinical course of CF (recurrent hemoptysis, pulmonary exacerbations, lung function) and on the quality of life in adult patients with nonmassive hemoptysis managed with conservative medical therapy and BAE or conservative medical therapy alone.

**MATERIALS AND METHODS**

**Subject Selection**

We reviewed the clinical records of the 52 consecutive patients with CF who presented with nonmassive hemoptysis (minor bleeding) observed in our Cystic Fibrosis Service during the 4 years from 1992 to 1996. From the series of 52 patients, we analyzed the data for the 8 patients who had received conservative medical treatment and BAE; as a control group, we selected 8 patients managed with conservative medical treatment alone, matched for age, number of bleeding episodes, severity of the disease (FEV\textsubscript{1} and number of pulmonary exacerbations), and prognosis (Shwachman score) in the preceding year.

**Clinical Characteristics**

FEV\textsubscript{1} data were the mean percentage of predicted values for at least three different measurements obtained, in accordance with American Thoracic Society recommendations,\textsuperscript{16} at routine clinical examinations in the preceding year and the 3 ensuing years. The mean number of minor episodes of bleeding and the mean number of respiratory exacerbations were calculated for each patient in the BAE group and control group in the preceding year and the 3 ensuing years. Episodes of bleeding were classified as follows: minor hemoptysis, bleeding \(<240 \text{ mL in 24 h}\) (usually from 50 to 200 mL in 24 h); and massive hemoptysis, acute bleeding involving a large blood loss (\(>240 \text{ mL in 24 h}\)). Pulmonary exacerbations were defined as any episode of increased cough, sputum production, shortness of breath, decreased exercise tolerance, decreased appetite and fatigue requiring combined IV antibiotic therapy.

Prognosis was assessed with the modified Shwachman score (radiologic findings with the Crispin-Norman score). The quality of life was evaluated with part 2 of the Nottingham Health Profile (NHP) by determining the percentage of patients with problems (home, social, home life, hobbies, and holidays).\textsuperscript{17}

All patients in both groups received daily chest physiotherapy and nebulized treatment with bronchodilators. All patients received nebulizer treatments with antibiotics (IV preparations) once daily for 20 days every month. One patient in the BAE group and two control patients had mucolytic therapy with deoxyribonuclease.

Physicians caring for the patients proposed and described both procedures (medical therapy with or without BAE). In all patients, conservative medical therapy consisted of administration of vitamin K and tranexamic acid. All patients received IV antibiotic therapy for pulmonary exacerbations as indicated by the last sputum culture result. Chest physiotherapy and nebulized treatment (bronchodilators, antibiotics, and deoxyribonuclease) were stopped until full control of bleeding. At hospital admission, all patients underwent chest radiography, complete blood cell counts, and coagulation tests.

**BAE**

Patients scheduled for BAE were hospitalized and underwent preoperative thoracic aortography and selective bronchial artery catheterization. Under local anesthesia, a 5F catheter was introduced into the right femoral artery. During BAE, the bronchial circulation anatomy was studied to identify the site of bleeding. None of the patients had systemic collateral vessels. The embo- lizing substances used in all patients consisted of polyvinyl alcohol particles (Ivalon; Target Therapeutics; Freemont, CA) from 150 to 200 \(\mu\)m in size.\textsuperscript{18,19} Larger-sized polyvinyl alcohol particles (500 \(\mu\)m) were used in patients with large bronchial arteries. BAE was considered successful when one or more BAE procedures arrested bleeding during the same hospital stay. Written informed consent was obtained from all subjects before arteriography. All cases of recurrent bleeding (at least 50 mL of blood) after the hospital discharge were considered a recurrence.

**Data Analysis**

Statistical analysis was performed with the software (Statistical Package for Social Sciences, Graduate Pack 9.0 for Windows; SPSS; Chicago, IL). Data are reported as mean and SD. Non-parametric tests (the Friedman and Wilcoxon signed-rank tests) were used to compare clinical variables in the two groups. All \(p\) values \(\leq 0.05\) were considered to indicate statistical significance.

**RESULTS**

During the year after embolization, one patient in the BAE group died of a severe acute pulmonary exacerbation and was excluded from the analysis. The matched control subject remained in the follow-up. This left 15 patients for follow-up: 7 patients (3...
men and 4 women) in the BAE group and 8 control subject (2 men and 6 women). The two groups had a similar mean age (19 years and 20 years, respectively). They also had a comparable number of minor bleeding episodes (2.1 ± 0.7 episodes in the group who underwent embolization and 2.1 ± 0.8 episodes in the group who did not); mean percentage of predicted FEV1 (49% ± 19% and 50% ± 8); and mean modified Shwachman scores (63 ± 4 and 64 ± 3, respectively) in the preceding year.

Sputum cultures grew the following organisms: Staphylococcus aureus (two BAE patients and two control subjects), Burkholderia cepacia (one BAE patient), and Aspergillus fumigatus (two BAE patients and one control subject). None of the sputum cultures yielded multidrug-resistant organisms. Two patients in the BAE group had an altered prothrombin time.

Chest radiography and the patient’s medical history (sense of fullness, gurgling) were able to identify the site of bleeding in 12 patients. In a further three patients, the bleeding site remained unknown. No patient underwent bronchoscopy.

In the BAE group, the vessel supplying bleeding was the right bronchial artery in six patients and the left bronchial artery in two patients. Two of the eight patients needed two repeat procedures for complete control of bleeding. None of the procedures led to major BAE-related complications. In two patients, low-grade fever and chest pain developed during the 24 h immediately after BAE.

All patients in both groups had recurrent hemoptysis. Patients who underwent BAE had significantly fewer episodes of hemoptysis during the 3-year follow-up than during the year before (p < 0.001); in control patients, the number remained unchanged (Fig 1). Patients who underwent BAE also had significantly fewer episodes of hemoptysis than control patients during the third year of follow-up (1.3 ± 1 episodes vs 2.6 ± 0.9 episodes, respectively; p < 0.04; Table 1).

During the 3-year follow-up, the mean number of pulmonary exacerbations in the BAE group diminished significantly (p < 0.006; Fig 1), but in control subjects remained unchanged. During the third year, patients who underwent BAE also had fewer, but not significantly fewer, pulmonary exacerbations than control subjects (1.8 ± 0.7 episodes vs 2.6 ± 1.4 episodes; p = not significant [NS]; Table 1).

During the 3-year follow-up, pulmonary function, as evaluated by FEV1, declined significantly in both groups (p < 0.001; Fig 1). During the third year,
pulmonary function declined similarly in BAE patients and controls (8.7% ± 5 vs 7.1% ± 6; p = NS; Table 1).

During the 3-year follow-up, the modified Shwachman score in BAE patients decreased slowly and nonsignificantly but in control subjects decreased significantly (p < 0.001; Fig 1). In the third year, the mean modified Shwachman score diminished less in the BAE group than in control subjects (1.5 ± 4.1 vs 6.2 ± 3; p < 0.04; Table 1).

NHP part 2 scores were higher in patients who underwent BAE than in those who did not (p < 0.05), indicating a better quality of life (Fig 2). Patients who received medical therapy alone had greater difficulties in social life, home life, and holidays. One patient from the BAE group underwent a successful double-lung transplantation 36 months after BAE.

### DISCUSSION

The distinctive finding in this study is that in adult patients with CF complicated by minor hemoptysis, early BAE reduced the frequency of recurrent bleeding and pulmonary exacerbations inducing only minor, transient complications, but left the clinical course of CF as assessed by lung function tests unchanged. Early BAE also improved these patients’ quality of life.

The long-term outcome of patients with CF depends crucially on the various complications that inevitably develop, predominantly involving the respiratory tract. Among the most dangerous is hemoptysis, often a life-threatening event. Recurrent hemoptysis is a debilitating complication that may reduce patients’ compliance with physical and daily activities, and often precludes routine postural drainage of other lung regions. In many patients with CF, these unwelcome episodes might help to increase

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**Table 1—Clinical Outcome of Patients With CF Who Underwent BAE and Those Who Did Not, During the Third Year of Follow-up**

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Patients With CF</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Therapy</td>
<td>Medical Therapy Alone</td>
<td></td>
</tr>
<tr>
<td>Total recurrent episodes, † episode/patient/yr</td>
<td>1.3 ± 1</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>Pulmonary exacerbations, episode/patient/yr</td>
<td>1.8 ± 0.7</td>
<td>2.6 ± 1.4</td>
</tr>
<tr>
<td>Mean FEV₁ decrease, % from baseline</td>
<td>8.7 ± 5</td>
<td>7.1 ± 2.6</td>
</tr>
<tr>
<td>Mean modified Shwachman score, † decrease/increase</td>
<td>1.5 ± 4.1</td>
<td>6.2 ± 3</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†p values by Wilcoxon test.

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**Figure 2.** Quality of life assessed by the NHP scores in patients with CF who received medical therapy with early BAE and those managed with conservative medical therapy alone. Data are presented as mean values: *NS; **p < 0.05 by the Wilcoxon test. Note that early BAE significantly decreased patients’ problems related to social activities, home life, and holidays.

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[brachial artery embolization] [medical therapy]
the number of pulmonary exacerbations and hospitalizations. By progressively destroying the lung parenchyma, they may also worsen pulmonary function. The final result in many cases might be a lower survival rate. The treatment of choice for massive, life-threatening hemoptysis is BAE. Less severe forms of bleeding respond well to conservative treatment,\(^20,21\) intended to control pulmonary infections and correct coagulation defects. All the BAE procedures in the series we reviewed had a successful outcome (complete control of bleeding). None of the eight patients had severe BEA-related complications and only two patients had minor complications (fever) that did not lengthen the hospital stay. Our experience therefore agrees with published reports\(^{14,15,22}\) describing BEA as a safe procedure that achieves complete control of bleeding in from 85 to 95% of cases, with complications ranging in most series from 10 to 30%, an acceptable rate.\(^{5,8,9,13,14,23}\)

Recurrent bleeding after BAE is a frequent event, and reported recurrence rates range from 30 to 60% of cases.\(^{9,10,14,24}\) Although some patients in both groups we studied had recurrent episodes of hemoptysis, our review suggests that early BAE significantly reduces recurrent bleeding.

Patients who underwent early BAE also had fewer pulmonary exacerbations. The probable reason why BAE reduced the number of pulmonary exacerbations is that by reducing recurrent bleeding it improved patients’ quality of life, as assessed by NHP, and encouraged compliance with rehabilitation programs. It also improved the prognosis, as assessed by the modified Shwachman score.

By reducing the number of pulmonary exacerbations, early BAE should therefore in theory also help to maintain good pulmonary functional reserve. Yet, in our patients it did not because FEV\(_1\) measurements after BAE suggested a similar decline in lung function in both groups. We are not surprised that early embolization had no influence on FEV\(_1\). Unfortunately, at present we can only slow down the course of the disease. However, if these patients have fewer infections, hence fewer antibiotic courses, FEV\(_1\) will probably remain more stable. BAE presumably left FEV\(_1\) decline unchanged overtime because this index of lung depends primarily on the natural history of the disease. In addition, we strongly believe that reducing the number of bleeding episodes not only markedly improves these patients’ lifestyles, but also increases their awareness and compliance with therapy. Ultimately, it enhances their readiness for lung transplantation. Insofar as patients who underwent BAE had fewer pulmonary exacerbations, this procedure in some way helped to improve life expectancy.

Our experience suggests that future candidates for BAE should be not only patients with massive hemoptysis, but also those patients with CF who have minor episodes of bleeding and who are strongly motivated to treat themselves. However, even if BAE leaves the natural history of the disease as assessed by lung function tests unchanged, the benefits accrued by reducing the number of pulmonary exacerbations and improving the quality of life in these patients surely constitute a success.

We conclude that in patients with CF and minor hemoptysis, early BAE may reduce recurrent bleeding, thus offering patients a better quality of life and possibly improving the long-term prognosis. A possible limitation of our study is bias arising from the fact that patients who opted for embolization, after discussing the advantages and disadvantages with their physicians, may have been those who achieved better compliance with the therapeutic strategies and were more motivated to self-management. Our encouraging preliminary findings need confirmation from a randomized prospective study.

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