

Balloon Pulmonary Angioplasty for Treatment of Chronic Thromboembolic Pulmonary Hypertension

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Background—Although pulmonary thromboendarterectomy is increasingly successful for the definitive treatment of chronic thromboembolic pulmonary hypertension (CTEPH), not all patients have surgically accessible disease. Others are poor surgical candidates because of comorbid illness. Therefore, for selected patients, we defined and implemented an alternative interventional strategy of balloon pulmonary angioplasty (BPA).

Methods and Results—Eighteen patients (mean age, 51.8 years; range, 14 to 75 years) with CTEPH underwent BPA; they averaged 2.6 procedures (range, 1 to 5) and 6 dilations (range, 1 to 12). Selection of pulmonary artery segments for dilation required (1) complete occlusion, (2) filling defects, or (3) signs of intravascular webs. After an average of 36 months of follow-up (range, 0.5 to 66 months), the average New York Heart Association class improved from 3.3 to 1.8 ($P<0.001$), and 6-minute walking distances increased from 209 to 497 yards ($P<0.0001$). Pulmonary artery mean pressures decreased from 43.0 ± 12.1 to 33.7 ± 10.2 mm Hg ($P=0.007$). Eleven patients developed reperfusion pulmonary edema; 3 required mechanical ventilation.

Conclusions—BPA reduces pulmonary artery hypertension in patients with CTEPH and is associated with long-term improvement in New York Heart Association class and 6-minute walking distances. BPA is a promising interventional technique that warrants randomized comparison with medical therapy in CTEPH patients who are not surgical candidates. (*Circulation*. 2001;103:10-13.)

Key Words: balloon ■ angioplasty ■ embolism ■ thrombus ■ pulmonary heart disease

Although pulmonary thromboendarterectomy is increasingly successful for the definitive treatment of chronic thromboembolic pulmonary hypertension (CTEPH), not all patients have surgically accessible disease.^{1,2} Others are poor surgical candidates because of comorbid illness. Therefore, we implemented an alternative interventional strategy of balloon pulmonary angioplasty (BPA) for patients without surgical potential. We report our initial results in 18 patients who had an average 3.0-year follow-up.

Methods

Patients

Patients referred for CTEPH were evaluated with a detailed medical history, physical examination, chest radiography, nuclear lung scintigraphy, high-resolution chest computed tomography scanning or magnetic resonance angiography, and measurement of exercise limitation (6-minute walking capacity). Patients were considered for BPA if angiographic studies confirmed distal branch pulmonary artery obstructions with either surgically inaccessible disease (no lesions in the proximal branch pulmonary arteries, with obstructions beginning primarily in the third-order branches after the main pulmonary artery), or if they were poor surgical candidates because

of the presence of severe concomitant medical comorbidity. Studies were reviewed by at least 2 members of the CTEPH team, including a surgeon with regional expertise in management of CTEPH, to determine suitability for BPA versus surgery.

CTEPH was defined at catheterization by the presence of a mean pulmonary artery pressure >30 mm Hg and angiographic demonstration of multiple bilateral pulmonary artery obstructions associated with vascular cutoffs and webs.

Cardiac Catheterization

Before catheterization, informed procedural consent was obtained from all patients. Full anticoagulation was maintained. Standard right heart catheterization was performed. A highly maneuverable, soft-tipped, 0.035-inch wire facilitated entry into distally stenosed and occluded vessels. We modified a 7-French high-flow pigtail catheter by removing most of the curled tip. For each contrast injection (5 to 7 mL over 1 second), we maintained the distal guiding wire in place.

Selection of a pulmonary artery segment for dilation required at least 1 of the following 3 criteria: (1) complete occlusion, (2) filling defects, or (3) signs of intravascular webs. Segments were sequentially dilated in an order chosen to maximally restore balance in pulmonary blood flow. Lower lobe vessels were preferentially dilated. Initial 3- to 6-mm balloons were sized to be 75% to 100% of

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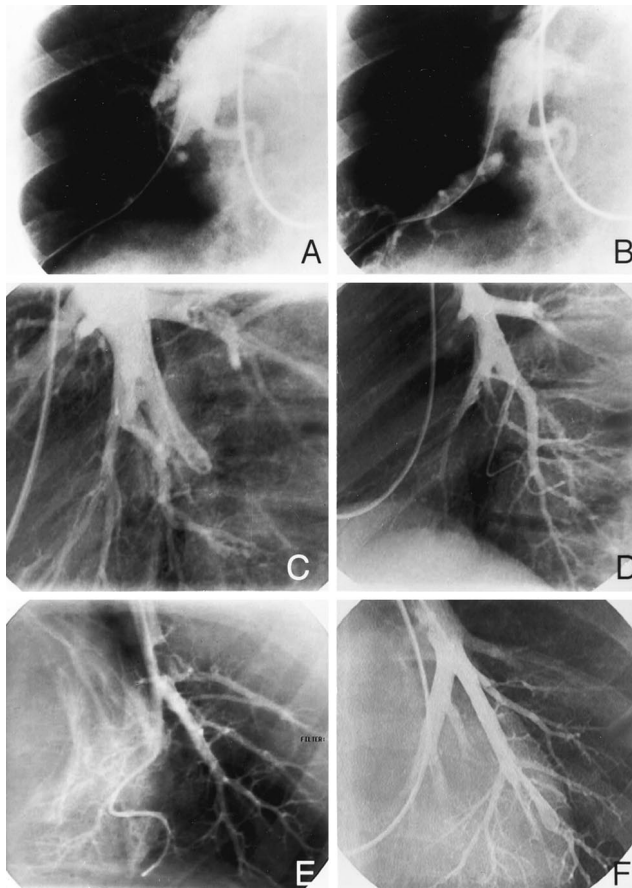


Figure 1. Angiographic appearance of occluded (A, C), and stenotic (E) lower lobe pulmonary artery segmental branches that were deemed surgically inaccessible. They are horizontally paired with angiograms performed immediately after successful BPA (B, D, and F).

the vessel diameter. Balloons were inflated by hand for 1 to 5 seconds until the fluoroscopic waist disappeared or until the balloon was fully expanded. After inflation, fluoroscopy and angiography were performed to determine vessel size and flow and to look for evidence of intimal disruption, aneurysm formation, vessel rupture, or pulmonary edema. Repeat dilation was performed if there was <50% increase in angiographic vessel size. Additional pulmonary artery segments were dilated in up to 3 lobes. After catheterization, patients were observed for 2 days for the possible development of reperfusion pulmonary edema.

Repeat catheterization at an interval of 6 to 12 weeks after BPA was recommended for all patients with a resultant mean pulmonary artery pressure >30 mm Hg and residual lesions that were thought to be amenable to BPA. Follow-up was suggested at subsequent intervals of 3 months and included a history, physical examination, and reassessment of exercise capacity. Comparison of continuous variables and of categorical data were performed using 2-tailed paired *t*-tests and χ^2 analysis, respectively, with $P=0.05$ considered significant.

Results

From October 1994 through January 1999, 18 patients (mean age, 52.9 years; range, 14 to 75 years) evaluated for BPA for CTEPH underwent intervention (Figure 1). Distal surgically inaccessible disease was present in 16 patients; 9 were deemed “nonsurgical” on additional referral to other national centers of expertise for surgical thromboendarterectomy.

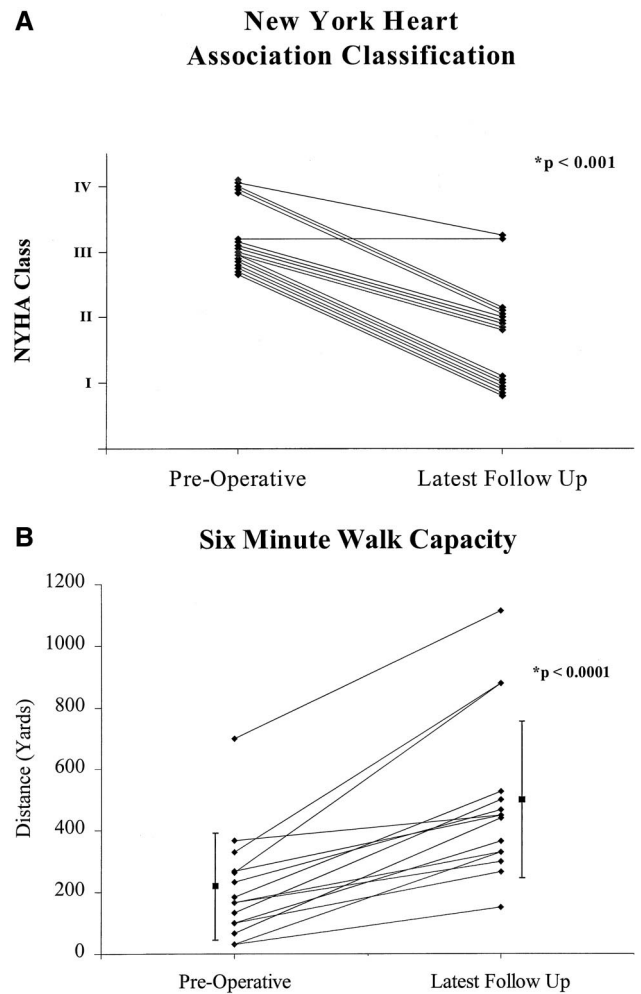


Figure 2. NYHA classification (A) and 6-minute walk capacity (B) before BPA and at latest follow up.

Proximal disease with severe concomitant medical illness was present in 2 patients; the proximal disease was morbid obesity in one and a combination of severe coronary artery disease and chronic obstructive pulmonary disease in the other. One patient died of right ventricular failure on postcatheterization day 7 (see below). The average follow-up of the remaining 17 patients was 35.9 months (median, 36.0 months; range, 0.5 to 66 months). Overall, New York Heart Association (NYHA) class improved ($P<0.001$; Figure 2A), and 6-minute walk distances increased ($P<0.0001$, Figure 2B).

The 18 patients with CTEPH underwent a total of 47 catheterizations (median, 3; range, 1 to 5). Patients underwent a total of 107 balloon dilations (mean, 2.3 ± 1 ; range, 1 to 7 per catheterization).

Hemodynamic data are summarized in the Table. Overall, when comparing pre-BPA values to those obtained at latest catheterization, right ventricular systolic pressure decreased ($P=0.004$), as did pulmonary artery mean pressure ($P=0.002$) and the right ventricular/systemic pressure ratio ($P=0.007$). No significant change was observed in calculated cardiac index ($P=0.46$). All vessels previously dilated were patent at angiographic reassessment at repeat catheterizations performed 1 to 40 months after initial BPA.

Cardiac Catheterization Hemodynamic Data

| Patient | Age, y | Duration, y | No. of Catheterizations | No. of Dilations | RV Pressure, mm Hg | | Mean PA Pressure, mm Hg | | % Systemic Pressure | | Cardiac Index, L · m ⁻¹ · m ⁻² | | TPR WU · m ² | |
|---------|--------|-------------|-------------------------|------------------|--------------------|----------|-------------------------|----------|---------------------|-----------|--|----------|-------------------------|----------|
| | | | | | Pre-BPA | Post-BPA | Pre-BPA | Post-BPA | Pre-BPA | Post-BPA | Pre-BPA | Post-BPA | Pre-BPA | Post-BPA |
| 1 | 62 | 3 | 1 | 4 | 105/24 | 60/30 | 60 | 40 | 0.95 | 0.5 | 1.9 | 1.7 | 32 | 24 |
| 2 | 74 | 4 | 2 | 5 | 70/14 | 60/12 | 30 | 25 | 0.64 | 0.55 | 2.1 | 1.9 | 14 | 13 |
| 3 | 48 | 4 | 2 | 4 | 50/9 | 55/14 | 29 | 30 | 0.4 | 0.42 | 2.2 | 2.6 | 13 | 12 |
| 4 | 14 | 3 | 3 | 11 | 90/10 | 55/6 | 58 | 38 | 0.75 | 0.46 | 1.9 | 1.9 | 31 | 20 |
| 5 | 66 | 3 | 3 | 5 | 90/20 | 76/10 | 48 | 42 | 0.86 | 0.61 | 1.1 | 1.8 | 44 | 23 |
| 6 | 29 | 4.5 | 2 | 6 | 78/10 | 75/9 | 43 | 40 | 0.77 | 0.68 | 2.1 | 2.3 | 20 | 17 |
| 7 | 54 | 2.5 | 1 | 3 | 60/14 | 52/14 | 40 | 30 | 0.44 | 0.38 | 2.6 | 2.6 | 15 | 12 |
| 8 | 33 | 0.5 | 3 | 3 | 55/10 | 48/12 | 26 | 30 | 0.41 | 0.38 | 2.3 | 2.2 | 11 | 14 |
| 9 | 67 | 1.25 | 3 | 9 | 86/15 | 90/22 | 50 | 50 | 0.72 | 0.84 | 1.3 | 1.6 | 38 | 31 |
| 10 | 58 | 2.5 | 4 | 6 | 68/15 | 44/10 | 42 | 24 | 0.55 | 0.34 | 2.9 | 3.2 | 14 | 8 |
| 11 | 46 | 1.5 | 4 | 12 | 110/12 | 45/4 | 56 | 25 | 1 | 0.32 | 1.7 | 3.2 | 33 | 8 |
| 12 | 49 | 2.5 | 4 | 8 | 80/15 | 60/10 | 45 | 40 | 0.62 | 0.51 | 2.3 | 2 | 20 | 20 |
| 13 | 69 | 2.5 | 3 | 8 | 80/10 | 70/18 | 52 | 45 | 0.8 | 0.58 | 2.2 | 2.5 | 24 | 18 |
| 14 | 37 | 2 | 5 | 6 | 67/10 | 40/10 | 31 | 10 | 0.66 | 0.35 | 1.8 | 1.7 | 17 | 6 |
| 15 | 49 | 1.25 | 3 | 10 | 70/5 | 50/8 | 36 | 29 | 0.54 | 0.36 | 2.1 | 1.9 | 17 | 15 |
| 16 | 75 | 1 | 1 | 1 | 45/8 | 55/10 | 23 | 30 | 0.38 | 0.45 | 2.1 | 1.7 | 11 | 18 |
| 17 | 58 | 2 | 1 | 4 | 55/13 | 57/11 | 31 | 29 | 0.46 | 0.44 | 1.4 | 1.4 | 22 | 21 |
| 18 | 45 | 1.5 | 3 | 5 | 80/22 | 75/20 | 60 | 50 | 0.64 | 0.6 | 1.7 | 1.3 | 35 | 38 |
| Mean±SD | 52±12 | 2.4±0.9 | 2.7±1 | 6±3 | 74±18 | 58±12 | 42±12 | 33±10 | 0.64±0.15 | 0.48±0.11 | 2.0±0.4 | 2.1±0.6 | 22±9 | 17±8 |

RV indicates right ventricular; PA, pulmonary artery; and TPR, total pulmonary resistance.

Medical complications occurred during 4 procedures. Perforation of a right lower lobe pulmonary artery with a stiff wire necessitated subsequent coil occlusion of the vessel, with maintenance of clinical stability. Femoral arterial pseudoaneurysms were noted in 3 obese patients who had femoral arterial access for monitoring during BPA; all were successfully treated with either surgical repair or mechanical compression.

Eleven patients developed reperfusion pulmonary edema (defined as radiographic opacity in the dilated segment and worsening hypoxemia): 4 at the time of catheterization and 7 during the subsequent 48 hours. Development of reperfusion pulmonary edema correlated with a pre-BPA mean pulmonary artery pressure >35 mm Hg ($P=0.04$; odds ratio, 4.8), but it did not correlate with patient age, cardiac index, or the size of the dilated pulmonary artery segment. All patients with reperfusion pulmonary edema were managed with diuretics and oxygen, and 3 required mechanical ventilation. One of the 3 (patient 1) developed segmental pulmonary edema in all dilated areas. Despite mechanical ventilatory support and administration of inhaled nitric oxide, she died of right ventricular failure 1 week after BPA.

Sixteen of the 18 patients remained alive at an average of 34.2 months after initial catheterization. None were lost to follow-up. One patient (patient 4) died of recurrent aspiration pneumonia 16 months after initial BPA. No other patients have had clinical deterioration. Average NYHA class at latest follow-up improved from 3.3 preoperatively to 1.8 ($P\leq 0.001$; Figure 2A), and 6-minute walking capacity increased from

209 yards preoperatively to 497 yards ($P\leq 0.0001$; Figure 2B). Ten patients initially required oxygen inhalation to sustain a peripheral oxygen saturation >92%; none required supplemental oxygen at latest follow-up.

Discussion

Pulmonary thromboendarterectomy is so successful that alternative approaches to CTEPH may seem heretical. However, CTEPH patients who are not candidates for this surgery are currently doomed to a life of increasing disability and premature death.^{3,4} Therefore, we sought to devise a catheterization-based interventional management strategy for these nonsurgical patients. BPA improves pulmonary blood flow distribution and increases pulmonary vascular capacitance, decreasing right ventricular afterload. We think that improvement in these parameters explains the improved NYHA classification and 6-minute walk tests that we observed.

Our approach was possible, in part, by technical advances and accumulating experience in the congenital heart disease catheterization laboratory with dilation of congenital and acquired pulmonary artery stenoses.^{5,6} Over the past decade, improvements have included use of (1) soft-tipped, highly maneuverable guidewires; (2) a modified pigtail catheter that permits angiography while maintaining wire position⁷; (3) low profile balloons; (4) improved nonionic contrast agents; and (5) full heparin anticoagulation before, during, and after the procedure.

The BPA of experimentally induced pulmonary arterial narrowings in animals, in conjunction with registry collection of clinical experience in patients with congenital peripheral pulmonary stenoses, has confirmed that optimal dilation can be obtained with balloons sized 200% to 400% the diameter of the stenotic region but $\leq 150\%$ the diameter of the surrounding vessel.⁶ At present, there are insufficient pathological studies of the vascular wall and its response to injury in distal vessels affected by CTEPH. Therefore, to minimize the potential for vessel rupture, we reasoned that the maximal balloon size should be less than or equal to the surrounding vessel size. Our results, to date, do not suggest the need for larger balloon sizing.

As with any novel procedure, we experienced a learning curve. We found that (1) access through the right internal jugular vein allowed greater ease of catheter manipulation, (2) a flexible wire was safer and more effective than stiffer wires in crossing stenoses, (3) systemic arterial cannulation was not necessary, and (4) reperfusion pulmonary edema was common, suggesting that BPA should be performed in a staged fashion over multiple, separate procedures.

Our results are consistent with the successful outcome in a case report of BPA for CTEPH published in 1988.⁸ Voorburg and colleagues⁸ dilated 4 stenoses in 3 sessions in a 30-year-old man with CTEPH. Pulmonary artery pressures decreased from 90/25/46 to 78/13/35 mm Hg, with a concomitant increase in systemic arterial pressure. As far as we know, these results were not followed-up in other CTEPH patients until our present series.

Our report is limited by the small number of patients who have undergone this procedure and by the lack of a controlled comparison with patients who were managed with medical therapy alone. The most serious complication of BPA currently seems to be reperfusion pulmonary edema, which is the principal cause of death among patients undergoing surgical thromboendarterectomy.⁹ Despite a recognized correlation with a pre-BPA mean pulmonary artery pressure >35 mm Hg, the extent and potential severity of reperfusion pulmonary edema warrants an anticipation of its occurrence in all patients treated with BPA. Mean cardiac index did not seem to improve after BPA, despite symptomatic improve-

ment and patient survival. To better define the mechanism of improvement, extent of risk, and survival determinants, BPA patients may benefit from a more extensive preoperative and postoperative evaluation, which would routinely include cardiopulmonary exercise testing with oximetry and maximal oxygen uptake, quantitative perfusion lung scanning, pulmonary function testing, and echocardiographic assessment of right ventricular function.

We think that our results are sufficiently promising to justify extension of BPA to CTEPH patients at other institutions with special expertise in pulmonary vascular diseases and cardiopulmonary catheterization. BPA, however, is an expensive and labor-intensive approach to management and has potentially lethal complications. Therefore, after specialists at other centers familiarize themselves with these techniques, we strongly urge collaboration to undertake a randomized, controlled trial of BPA plus maximal medical therapy versus maximal medical therapy alone in CTEPH patients who are not surgical candidates.

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