

Image-Guided Minimally Invasive Treatment of Pulmonary Arterial Hypertension Due to Embolic Disease

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OBJECTIVE: Although surgical pulmonary thromboendarterectomy is the treatment of choice for pulmonary hypertension due to chronic thrombotic and/or embolic disease, minimally invasive endovascular techniques such as angioplasty or placement of a metallic stent can provide acceptable results when surgery is not indicated or has been refused by the patient.

PATIENTS AND METHODS: Eight patients (5 men, 3 women; mean age, 62.6 years) were treated. The patients were in New York Heart Association (NYHA) class III or IV and had a mean pulmonary artery pressure of 40 mm Hg or more, a capillary wedge pressure of 15 mm Hg or less, and a Miller index greater than 0.5. In all cases, diagnosis was based on Doppler echocardiography, pulmonary angiography, hemodynamic evaluation, and ventilation-perfusion scintigraphy. All patients received fibrinolytic therapy and underwent angioplasty. A metallic stent was implanted in 3 patients. Follow-up echocardiographic assessment and ventilation-perfusion scans were scheduled at 1, 3, 6, and 12 months.

RESULTS: The procedures were technically successful in all cases. The mean follow-up period was 18.7 months. Minor complications were extrasystoles (3 cases), slight bruising at the site of puncture (1 case), and rectal bleeding that resolved without treatment (1 case). One patient died from an unknown cause 24 hours after the procedure. In all other cases, improvements were noted in NYHA functional class, in hemodynamics demonstrated by echocardiography, and in vascular structure as shown by arteriography and scintigraphy.

CONCLUSIONS: Minimally invasive endovascular interventions can help improve pulmonary arterial hypertension due to chronic thrombotic and/or embolic disease in patients for whom medical or surgical treatment is not possible.

Key words: *Minimally invasive surgical procedures. Chronic pulmonary embolic disease. Pulmonary artery hypertension.*

Tratamiento de la hipertensión arterial pulmonar postembólica mediante técnicas mínimamente invasivas guiadas por imagen

OBJETIVO: Aunque la tromboendarterectomía pulmonar quirúrgica es el tratamiento de elección en la hipertensión arterial crónica de origen tromboembólico, cuando no hay indicación quirúrgica o el paciente rechaza la cirugía se puede recurrir a técnicas endovasculares de mínima invasión (angioplastia y prótesis metálica) con aceptables resultados.

PACIENTES Y MÉTODOS: Se trató a 8 pacientes (5 varones y 3 mujeres) con una media de edad de 62,6 años, en clase III o IV de la clasificación de la New York Heart Association (NYHA), con presión arterial pulmonar media de 40 mmHg o superior, presión capilar enclavada de 15 mmHg o menor e índice de Miller mayor de 0,5. En todos los casos el diagnóstico se estableció por ecografía Doppler cardíaca, angiografía pulmonar, estudio hemodinámico y gammagrafía de ventilación-perfusión. Se realizó tratamiento fibrinolítico seguido de angioplastia en todos los casos, y se colocó una prótesis metálica en 3. Se realizaron revisiones clínicas al cabo de 1, 3, 6 y 12 meses mediante ecografía y gammagrafía.

RESULTADOS: El éxito técnico del procedimiento fue del 100%. El seguimiento medio fue de 18,7 meses. Como complicaciones menores se produjeron extrasístoles en 3 casos; hematoma leve en la zona de punción en un caso, y rectorragia, que remitió sin tratamiento, en otro. Una paciente murió por causa desconocida al cabo de 24 h. En todos los casos revisados se observaron una mejoría en la clasificación de la NYHA, mejora hemodinámica evidenciada por ecografía y mejora morfológica objetivada por arteriografía y gammagrafía.

CONCLUSIONES: Las técnicas endovasculares de mínima invasión pueden contribuir a mejorar la hipertensión arterial pulmonar crónica debida a tromboembolia en la que no es posible otro tratamiento (farmacológico o quirúrgico).

Palabras clave: *Mínima invasión. Embolia pulmonar crónica. Hipertensión arterial pulmonar.*

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Introduction

The term pulmonary hypertension describes a hemodynamic state shared by many clinical entities. While the name chronic pulmonary arterial hypertension (PAH) has disappeared, that of primary PAH remains in use.¹ In

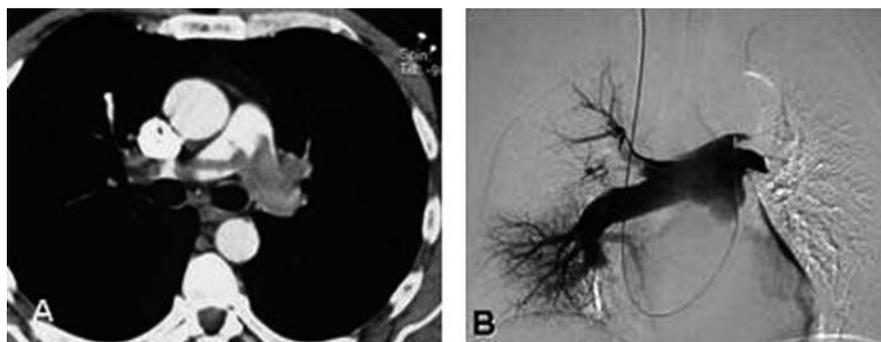


Figure 1. Chronic obstruction of the left pulmonary artery and partial obstruction on the right.

recent international classifications² and consensus statements,³ PAH due to thrombotic and/or embolic disease has been classified within a specific group. Although there is no unanimously accepted definition of PAH, the Patient Registry for Primary Pulmonary Hypertension of the US National Institutes of Health describes it as persistently abnormal pulmonary hemodynamics with a mean pulmonary arterial pressure of 25 mm Hg or more at rest, or 30 mm Hg or more with exercise, and a capillary wedge pressure of 15 mm Hg or less determined through right heart catheterization.²

Pulmonary thromboendarterectomy is the treatment of choice for chronic hypertension due to thrombotic and/or embolic disease. Over 2000 procedures with acceptable outcomes have been reported, and although no controlled studies have been undertaken, pulmonary thromboendarterectomy is currently considered fully curative in hospitals with experience and when the correct selection criteria are applied.⁴ Thirty-day postoperative mortality in uncontrolled studies ranges from 7% to 35%.^{4,5} When a patient refuses surgery or when it is deemed contraindicated, medical treatment and minimally invasive endovascular procedures (angioplasty and metallic stenting) are the next line of treatment.

We report our experience in treating PAH due to chronic thrombotic and/or embolic disease.

Patients and Methods

Patients

Eight patients (5 men, 3 women) with a mean age of 62.6 years (range, 49-73 years) underwent endovascular

procedures in this prospective, descriptive study in a single hospital. Inclusion criteria were age less than 80 years, informed consent, New York Heart Association (NYHA) functional class III or IV, mean pulmonary arterial pressure of 40 mm Hg or more and capillary wedge pressure of 15 mm Hg or less, diagnosis supported by computed tomography (CT) angiography or other arteriography showing stenosis or occlusion of the main pulmonary or lobar arteries due to chronic thrombosis or embolism, refusal of surgery (endarterectomy) or high surgical risk, and an unobstructed pathway to the inferior or superior vena cava. Exclusion criteria were a contraindication for anticoagulation therapy and/or fibrinolysis and serious concomitant disease with life expectancy of less than a year.

The NYHA functional class was used to evaluate clinical status. Class I corresponded to a patient with no symptoms during ordinary physical activity; class II, a patient with mild symptoms and slight limitation during ordinary activities; class III, marked limitation in activity due to symptoms, even during less-than-ordinary activity; and class IV, symptoms even while at rest.

Table 1 shows the main characteristics of the patients included in the study.

Diagnostic Methods

In all patients, Doppler ultrasound imaging of the heart and lower extremities was performed in all patients in order to detect extrapulmonary venous thrombosis. Coagulation and biochemical analyses were also carried out. A diagnosis of pulmonary embolism was based on findings of structural (CT angiography, except in 1 patient) and functional (ventilation-perfusion scan) studies.

The hemodynamic/angiographic evaluation was carried out by right-heart catheterization (Swan-Ganz catheter, Medtronic Ibérica, Madrid, Spain) to measure pressures in the atrium, ventricle, and pulmonary arteries, including the pulmonary wedge pressure. The location and morphology of thrombi or emboli in

TABLE 1
Main Patient Characteristics

Case	Diagnosis	NYHA	Sex	Age, y	Indication	Initial mPAP	MI	Follow-up, mo
1	Chronic PE + DVT	III	W	64	Declined surgery	42	0.5	13
2	Chronic PE	III	M	58	Severe COPD	53	0.7	–
3	Chronic PE + DVT	IV	M	73	Renal insufficiency	51	0.6	26
4	Chronic PE	III	W	66	Declined surgery	54	0.8	17
5	Chronic PE + DVT	III	M	54	Declined surgery	47	0.7	23
6	Chronic PE + DVT	IV	W	49	Breast cancer	58	0.7	–
7	Chronic PE + DVT	III	M	69	Severe COPD	46	0.6	11
8	Chronic PE + DVT	III	M	68	Declined surgery	53	0.7	8

Abbreviations: COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; M, man; MI, Miller index; mPAP, mean pulmonary arterial pressure; NYHA: New York Heart Association functional class; PE, pulmonary embolism; W, woman.

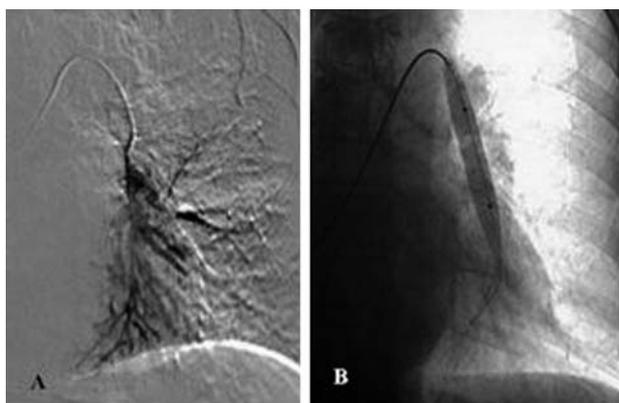


Figure 2. Massive pulmonary embolism. A: Chronic obstruction of the artery of the left lower lobe. B: Inflated angioplasty balloon in the same artery.

the pulmonary arterial system were evaluated using a pigtail catheter with a 145° angle and the Optitorque perforated catheter (Terumo Europe, Leuven, Belgium) (Figure 1). The extent of obstruction and vascular perfusion were assessed (Miller index).

Endovascular Treatment

All treatments were carried out in the theater for image-guided minimally invasive surgery. The room contains equipment mounted on a C-shaped structure to provide real-time digital imaging for 3-dimensional mapping and the possibility of CT (Allura Xper FD 20/10, Philips Ibérica, Madrid, Spain). Monitoring included oxygen saturation, invasive and noninvasive pressures, and electrocardiogram. Using aseptic technique and local anesthetic, the surgeon introduced catheters into the right femoral and jugular veins. General anesthesia was unnecessary, but sedation and analgesia were provided with 1-5 mg of midazolam and 100-150 µg of fentanyl. Oxygen was administered through a nasal canula at a rate of 2-4 L/min.

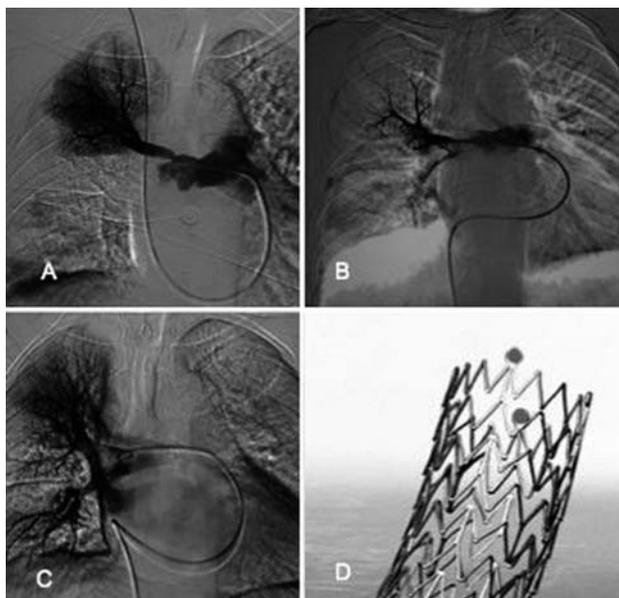


Figure 3. A: Obstruction of lobar vessels (arteries of the right and left lower lobes). B: Results after 24 hours of urokinase infusion. C: Poor results of angioplasty; insertion of a Zilver metallic stent. D: Close-up of a Zilver metallic stent.

Once the structural and hemodynamic evaluation had been completed, the occluded arteries were selected and the pigtail catheter was rotated and moved back and forth inside the artery to break up the thrombus. Throughout this procedure, which lasted approximately 20 minutes, 250 000 U of urokinase was administered. Urokinase was then infused continuously at a rate of 100 000 U/h over a period of 24 hours in the zone of greatest obstruction in order to dissolve fresh thrombi. Sodium heparin was also administered, with activated partial thromboplastin time adjusted to a ratio of 2. Points of bleeding and coagulation abnormalities were monitored in order to prevent possible complications related to fibrinolysis. Fibrinolytic therapy was discontinued if blood was observed in bodily fluids, on the appearance of bruising or neurological symptoms, or if the level of fibrinogen fell below 100 mg/dL. After 24 hours, angioplasty was performed using balloons of different diameters (Advance PTA Dilatation Catheter, William Cook Europe, Bjaeverakov, Denmark) adapted to the caliber of the artery (Figure 2). When balloon angioplasty failed in 3 cases, we inserted self-expanding metallic stents made of nitinol (Zilver Vascular Stent, William Cook Europe) of a caliber appropriate to the vessel (Figure 3). Multiple dilatation maneuvers were applied in all vessels with stenosis exceeding 50% of the nonthrombosed vessel (mean number of vessels per patient, 2.8; range, 2-7 vessels). Also in all patients, the optional Günther Tulip filter (William Cook Europe) was placed in the inferior vena cava, to be removed after 3 months. A final angiographic structural and hemodynamic study of pressures was then performed to evaluate the results.

Structural, Hemodynamic, and Clinical Follow-up

All patients were re-evaluated in the image-guided minimally invasive surgery unit 1, 3, 6, and 12 months after treatment and yearly thereafter. At each follow-up visit the NYHA functional class was noted, Doppler echocardiography and scintigraphy were performed to assess right heart abnormalities, and pressures were measured indirectly. Six-minute walk tests were not performed. Scintigraphic evaluation was based on the extension and number of poorly perfused segments that were different from those found before treatment, but they were not quantified. At the 3-month follow-up visit, during which the filter was removed from the inferior vena cava, pulmonary angiography was performed (Figure 4).

Statistical Analysis

Given that the sample was small, results for quantitative variables are expressed in percentages, means, and ranges. The α error was set at .05 and the means of dependent variables were compared between groups with the nonparametric Wilcoxon test. Statistics were calculated with SPSS version 13.0 (SPSS Inc, Chicago, Illinois, USA) for Windows.

Results

The endovascular procedure was completed in all cases (technical success rate of 100%). Extrasystoles occurred in 3 patients when the catheter or other instruments were near the heart, but they resolved with no need for medication or special maneuvers. One patient had slight rectal bleeding in the first few hours of fibrinolysis, obliging discontinuation of the infusion, after which the endovascular intervention could be completed. At the end of fibrinolytic therapy, another patient had moderately serious bruising at the puncture site on the neck; no treatment other than

compression was required. A female patient died suddenly of cardiorespiratory arrest 24 hours after fibrinolytic treatment and balloon dilatation. During the procedure, she had had extrasystoles, which resolved on the hospital ward without electrical cardioversion or medical treatment. Signs of bleeding were not observed, but the family refused an autopsy. Table 2 shows the early posttreatment results, after 24 hours of urokinase infusion.

Angioplasty, carried out in all patients, was performed with balloon catheters ranging in caliber from 8 mm to 14 mm. A metallic stent was inserted in the lobar branches of the pulmonary arteries of 3 patients (right lower lobe in 2 patients and left lower lobe in 1). The mean dose of urokinase infused in 24 hours was 2.68 million units. All patients were given intermediate doses of sodium heparin as anticoagulant therapy, with activated partial thromboplastin time adjusted to a ratio of 2. The NYHA classification varied, though not substantially, in the first 24 hours, although it was difficult to establish the different classification ranges while the patient was hospitalized. The improvement in mean pulmonary artery pressure after administration of fibrinolytics and angioplasty with or without implantation of a metallic stent was 21.9 mm Hg, a level that was clinically significant ($P < .001$). The Miller index fell to 0.26, reflecting an improvement of 0.37 points, which was also significant ($P < .001$).

Patients were prescribed coumarin agents for anticoagulation when discharged home (target international normalized ratio, 2.5). Therapy was supervised by the hematology department.

During follow-up, which took place in the minimally invasive surgery unit but in coordination with other specialist departments, we observed improvement in clinical status (NYHA classification) as well as in hemodynamics (Doppler ultrasound) and structure (arteriography and lung perfusion scan) (Table 3). The mean duration of follow-up was 18.7 months (range, 11-36 months). Six patients experienced evident clinical improvement as shown by lower NYHA classifications. The mean pulmonary arterial pressure measured by Doppler ultrasound fell to 24 mm Hg, representing a significant improvement of 25.4 mm Hg ($P < .005$). The lung scan was normal in 2 patients; small perfusion defects were detected in 3, and larger defects in 2. The 3-month pulmonary arteriography findings demonstrated evident improvement in 6 patients, as shown

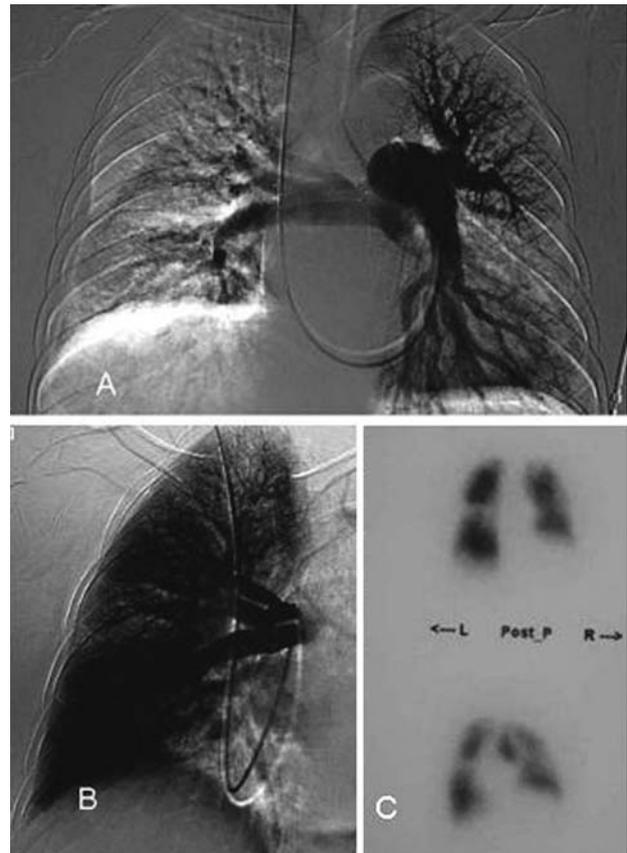


Figure 4. Three-month follow-up images coinciding with removal of the filter in an asymptomatic patient (functional class I of the New York Heart Association) with a mean pulmonary arterial pressure of 27 mm Hg. A: Arteriography of the pulmonary arteries showing a patent metallic stent and patent right lobe branches. B: Angiography, right anterior oblique projection in which the metallic stent and patent branches can be seen. Distal perfusion is good. C: Perfusion scan showing acceptable distribution of the isotope with bilateral segmental perfusion defects.

in Figure 4. Six of the 7 filters were removed via the jugular vein at 3 months without complications. In 1 patient, the upper hook of the filter was more difficult to remove because it had become embedded in the wall of the vena cava. The filter was left in place in 1 case because the patient had a new episode of deep vein thrombosis and declined the removal procedure.

TABLE 2
Outcome After Fibrinolytic and Endovascular Treatment

Case	Treatment	UK Dose, Million Units	NYHA		mPAP		MI		Complications
			Pre	Post	Pre	Post	Pre	Post	
1	PTA + MS	3.3	III	II	42	31	0.6	0.4	Rectal bleeding
2	PTA	3.1	III	II	53	28	0.8	0.3	Extrasystoles
3	PTA + MS	2.8	IV	III	51	29	0.7	0.2	No
4	PTA	3.2	III	II	54	25	0.6	0.1	Extrasystoles
5	PTA	2.7	III	I	47	29	0.7	0.3	Small hematoma at puncture site
6	PTA	3.2	IV		58	31	0.6	0.4	Extrasystoles, sudden death
7	PTA	3.2	III	II	46	26	0.5	0.2	No
8	PTA + MS	3.3	III	I	53	30	0.6	0.2	No

Abbreviations: MI, Miller index; mPAP, mean pulmonary arterial pressure; MS, metallic stent; NYHA, New York Heart Association functional class; PTA, percutaneous transluminal balloon angioplasty; UK, urokinase.

TABLE 3
Findings During Follow-up

Case	Treatment	Follow-up, mo	NYHA		mPAP		Ventilation-Perfusion Lung Scan	Clinical Course
			Pre	Post	Pre	Post		
1	PTA + MS	36	III	I	42	24	Normal	Improvement
2	PTA	36	III	II	53	22	Small perfusion defects	Improvement
3	PTA + MS	25	IV	III	51	33	Perfusion defects	Little change
4	PTA	21	III	II	54	24	Small perfusion defects	Improvement
5	PTA	20	III	I	47	21	Normal	Improvement
6	PTA		IV		58			Death
7	PTA	12	III	II	46	23	Perfusion defects	Improvement
8	PTA + MS	11	III	I	53	21	Small perfusion defects	Improvement

Abbreviations: mPAP, mean pulmonary arterial pressure; MS, metallic stent; NYHA, New York Heart Association functional class; PTA, percutaneous transluminal balloon angioplasty.

Discussion

The incidence of PAH following an episode of pulmonary thromboembolism is unknown, though it has been reported to be a rare complication estimated to occur in 0.1% to 0.5% of cases.⁷ Some authors have even suggested that this type of hypertension might not be related to pulmonary embolism.⁸ Hemodynamic values become normal in over 90% of patients who suffer pulmonary embolism and survive 30 days, and it has therefore been said that this must only rarely be the cause of hypertension.⁷ However, in a multicenter study with a follow-up period of 8 years, Pengo and coworkers⁹ found that the cumulative incidence of chronic hypertension due to thromboembolism might be as high as 3.8%. Our results show that PAH due to chronic embolic disease is not as rare as has been believed.⁸

The diagnosis and management of this disease is the responsibility of many participating specialists—cardiologists, pneumologists, radiologists, surgeons, and interventional cardiologists. Echocardiography, which establishes the severity of pulmonary hypertension, is undertaken on the basis of clinical suspicion.¹ Ventilation-perfusion scintigraphy will determine whether the cause is thromboembolic, and a normal scan rules out a diagnosis of PAH due to pulmonary embolism.¹ Angiographic evaluation of hemodynamics and morphology confirms the diagnosis and establishes the prognosis. Chest CT and a lung function study complete the evaluation. In our study, all patients underwent Doppler echocardiography, ventilation-perfusion scintigraphy, spirometry, plain chest x-ray and CT, Doppler ultrasound of the extremities, and a coagulation study. All had been referred to our unit once surgery had been ruled out by physicians in other departments (respiratory medicine and cardiology).

Surgery is the treatment of choice for PAH due to thrombotic and/or embolic disease.¹⁻⁵ The first thromboendarterectomy was performed over 40 years ago by the San Diego group.¹⁰ Since then, over 2000 surgical procedures have been performed with acceptable rates of morbidity and mortality that range from 7% to 35% depending on a group's surgical experience.^{4,5,11} Such clear improvement is achieved that some authors have questioned the use of alternative treatments.¹¹ The surgical procedure

consists of endarterectomy of the pulmonary arteries in which the media of the artery wall is removed along with the organized thrombotic material.⁴ Outcome assessment has demonstrated significant decreases in mean pressures from 45-50 mm Hg to 20-25 mm Hg in addition to significant improvements in cardiac index.¹²⁻¹⁶ Similar outcomes have been seen in the change in NYHA classification, with clinical improvement in over 70% of cases.¹⁷ For patients who refuse endarterectomy or for whom the risk is high, the fifth guidelines of the American College of Chest Physicians on the treatment of PAH due to pulmonary thromboembolism establish 3 options: pharmacologic treatment, balloon dilatation, and lung transplant.¹⁸ Feinstein and coworkers¹⁹ observed improvement in NYHA classification from 3.3 to 1.1 and a decrease of 10 mm Hg in mean pulmonary arterial pressure in a study of angioplasty performed in 18 patients. The only complication those authors recorded was sudden death due to reperfusion edema. Our results using a different technique for balloon angioplasty are consistent with those of Feinstein and coworkers. None of our patients developed reperfusion edema, although the reason for the death of our case number 6 remains unclear. All patients in our series were treated with fibrinolytic agents during the 24 hours before balloon dilatation or insertion of a metallic stent. The purpose of such treatment is based on the unproven theory that urokinase will act on the thrombotic material most recently deposited on the organized clot.²⁰ We also used a metallic stent when angioplasty failed or the results were unsatisfactory. Metallic stents have been used to recanalize an acute arterial occlusion due to embolism.²¹⁻²⁴ The satisfactory use of metallic stents in the pulmonary artery of a 38-year-old man with Williams syndrome and PAH who had several stenoses in lobar branches was recently described.²⁵ Initially, a single stenotic lesion was treated by insertion of a metallic stent and several others were opened by means of balloon angioplasty. Early restenoses of the arteries dilated by angioplasty were also treated with stents, which were still patent at the 3-year follow-up evaluation. The work of Schmitz-Rode and colleagues²² suggests that this approach can lead in many directions. Those authors used a temporary metallic stent to reopen a vessel occluded by a massive embolism that could not be treated with anticoagulants.

There is insufficient information for evaluating the efficacy of inferior vena caval filters in preventing re-embolization or for assessing lifelong anticoagulation therapy.⁴ We chose to use temporary filters for 3 months in order to prevent early re-embolism and to prescribe lifelong anticoagulation.²³

In conclusion, we believe that minimally invasive endovascular interventions can contribute to improving chronic PAH due to thrombotic and/or embolic disease when other pharmacologic or surgical treatments have been ruled out. Nonetheless, we have noted the recent report of Otero González et al²⁶ concerning clinical improvements with sildenafil monotherapy in class II and III patients with PAH, although improved pulmonary artery systolic pressure was not demonstrated by echocardiography. Prospective studies of larger series of patients are needed.

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