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

Miguel Ángel de Gregorio, Alicia Laborda, Rosario Ortas, Teresa Higuera, Javier Gómez-Arrue, Joaquín Medrano, and Antonio Mainar

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, an unknown cause 24 hours after the procedure. In all other cases, improvements were noted in NYHA functional class, and hemodynamic 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.

PATIENTES 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, angiógrafia 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; hematomas que resolvió sin tratamiento, en otro. Una paciente murió por causa desconocida al cabo de 24 h. En todos los casos se observaron mejoría en la clasificación de la NYHA, mejoría 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).

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recent international classifications and consensus statements, 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.

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. Thirty-day postoperative mortality in uncontrolled studies ranges from 7% to 35%. 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 patients and methods are provided in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>NYHA</th>
<th>Sex</th>
<th>Age, y</th>
<th>Indication</th>
<th>Initial mPAP</th>
<th>MI</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chronic PE + DVT</td>
<td>III</td>
<td>W</td>
<td>64</td>
<td>Declined surgery</td>
<td>42</td>
<td>0.5</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>Chronic PE</td>
<td>III</td>
<td>M</td>
<td>58</td>
<td>Severe COPD</td>
<td>53</td>
<td>0.7</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Chronic PE + DVT</td>
<td>IV</td>
<td>M</td>
<td>73</td>
<td>Renal insufficiency</td>
<td>51</td>
<td>0.6</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>Chronic PE</td>
<td>III</td>
<td>W</td>
<td>66</td>
<td>Declined surgery</td>
<td>54</td>
<td>0.8</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>Chronic PE + DVT</td>
<td>III</td>
<td>M</td>
<td>54</td>
<td>Declined surgery</td>
<td>47</td>
<td>0.7</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>Chronic PE + DVT</td>
<td>IV</td>
<td>W</td>
<td>49</td>
<td>Breast cancer</td>
<td>58</td>
<td>0.7</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Chronic PE + DVT</td>
<td>III</td>
<td>M</td>
<td>69</td>
<td>Severe COPD</td>
<td>46</td>
<td>0.6</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>Chronic PE + DVT</td>
<td>III</td>
<td>M</td>
<td>68</td>
<td>Declined surgery</td>
<td>53</td>
<td>0.7</td>
<td>8</td>
</tr>
</tbody>
</table>

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.
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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, Bjaeverakav, 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 fibrinolitics 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 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

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

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.

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.
angioplasty.

of PAH due to pulmonary embolism.

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a coagulation study. All had been referred to our unit once
a lung function study complete the evaluation. In our study,
evaluation of hemodynamics and morphology confirms
of hypertension.

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 coworkers8 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
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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.19 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.

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
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stent to reopen a vessel occluded by a massive embolism
that could not be treated with anticoagulants.

TABLE 3
Findings During Follow-up

<table>
<thead>
<tr>
<th>Case</th>
<th>Treatment</th>
<th>Follow-up, mo</th>
<th>NYHA</th>
<th>mPAP</th>
<th>Ventilation-Perfusion Lung Scan</th>
<th>Clinical Course</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>PTA + MS</td>
<td>36</td>
<td>III</td>
<td>I</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
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<td>36</td>
<td>III</td>
<td>II</td>
<td>53</td>
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</tr>
<tr>
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<td>25</td>
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<tr>
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<td>21</td>
<td>III</td>
<td>II</td>
<td>54</td>
<td>24</td>
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Abbreviations: mPAP, mean pulmonary arterial pressure; MS, metallic stent; NYHA, New York Heart Association functional class; PTA, percutaneous transluminal balloon angioplasty.
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.

REFERENCES