Pulmonary Hypertensive Medical Therapy in Chronic Thromboembolic Pulmonary Hypertension Before Pulmonary Thromboendarterectomy

Kurt W. Jensen, MD; Kim M. Kerr, MD; Peter F. Fedullo, MD; Nick Hyong Kim, MD; Victor J. Test, MD; Ori Ben-Yehuda, MD; William R. Auger, MD

Background—The currently recommended treatment for chronic thromboembolic pulmonary hypertension is pulmonary thromboendarterectomy (PTE). No convincing evidence for the use of pulmonary hypertensive medical therapy (PHT) exists in operable candidates. We sought to determine the prevalence of the use of PHT on referral for PTE and the effects on pre-PTE hemodynamics and post-PTE outcomes/hemodynamics.

Methods and Results—We performed a retrospective analysis of chronic thromboembolic pulmonary hypertension patients referred for PTE during 2005–2007. The prevalence of PHT was determined for all patients referred to our institution. Hemodynamic and outcomes analysis involved only those undergoing PTE. Data included baseline demographics, PHT medication(s), dosage, duration of therapy, and time to referral. Hemodynamic data were acquired from the time of diagnosis, the time of referral visit, and after PTE. Outcomes included intensive care unit, hospital, and ventilator days; bleeding and infection rates; incidence of reperfusion lung injury; and in-hospital mortality. The control group (n=244) was compared with the PHT group (n=111); subgroups included monotherapy with bosentan, sildenafil, or epoprostenol and combination therapy. The prevalence of PHT significantly increased from 19.9% in 2005 to 37% in 2007. There was minimal benefit of treatment with PHT on pre-PTE mean pulmonary artery pressure, but its use was associated with a significant delay in time to referral for PTE. Both groups experienced significant improvements in hemodynamic parameters after PTE. The 2 groups did not differ significantly in any post-PTE outcome. Similar results were obtained for each subgroup.

Conclusions—Our results suggest that PHT use has minimal effect on pre-PTE hemodynamics and no effect on post-PTE outcomes/hemodynamics. (Circulation. 2009;120:1248-1254.)

Key Words: embolism ■ hypertension, pulmonary ■ pulmonary heart disease ■ surgery ■ thrombus

Clinical Perspective on p 1254

Pulmonary thromboendarterectomy (PTE) surgery is considered the treatment of choice for patients with surgically accessible CTEPH. Experience with PTE surgery is well documented, and excellent outcomes can be achieved for most patients deemed surgical candidates. The mortality rates in experienced centers are ~6% to 8%. Persistent pulmonary hypertension is observed in ~10% to 15% of patients who undergo PTE for CTEPH despite careful preoperative evaluation. Higher preoperative PVR, especially >1000 dyne×s/cm², is associated with increased morbidity and mortality, and residual postoperative pulmonary hypertension (PVR >500 dyne×s/cm²) is even more strongly correlated with perioperative mortality.

Optimization of pulmonary hemodynamics before PTE surgery has the potential for improving the morbidity and mortality associated with this operation. Alternatively, delaying PTE while administering a trial of medical therapy might lead to worsening pre-PTE hemodynamics and worse clinical outcomes if that therapy is ineffective. There is no convincing evidence that such therapy (eg, phosphodiesterase-5 inhibi-
tors, endothelin receptor antagonists, and prostanoids) before PTE is beneficial. Only 4 small studies have incompletely addressed these issues.7–10

Two small retrospective studies by Bresser et al7 and Nagaya et al8 examined a total of 21 patients treated with intravenous epoprostenol before PTE. These studies demonstrated improvement in pre-PTE hemodynamics but no change in post-PTE hemodynamics compared with controls. In a prospective study of perioperative and post-PTE inhaled iloprost in 10 consecutive patients undergoing PTE, Kramm et al9 demonstrated worsening hemodynamics in the operating room with iloprost. However, they noted improved hemodynamics in the intensive care unit after PTE with continued inhalation of iloprost versus inhaled saline. In a prospective randomized study of 26 CTEPH patients treated with pre-PTE bosentan for 6 months, Reesink et al10 demonstrated a reduction in pre-PTE PVR, mean pulmonary artery pressure (mPAP), and mean right atrial pressure (mRAP) but no difference in post-PTE hemodynamics compared with controls.

Given the lack of beneficial evidence for PAH medical therapy before PTE for patients with CTEPH, we conducted a retrospective chart analysis of CTEPH patients referred to the University of California at San Diego (UCSD) during 2005–2007 for PTE. The aims of the study were 2-fold: (1) to determine the prevalence of pulmonary hypertensive medical therapy used in these patients before PTE referral and (2) to determine the effects of pre-PTE pulmonary hypertensive medical therapy on pre-PTE hemodynamics and post-PTE outcomes in patients with operable CTEPH.

Methods

Study Design and Patient Selection

We conducted a retrospective chart analysis of all patients referred to UCSD for PTE surgery during 2005–2007 to evaluate the prevalence of the use of PAH medications in CTEPH patients. Only consecutive patients who underwent PTE surgery at UCSD from 2005–2007 were included in the retrospective chart analysis examining the effects of pulmonary hypertensive medical therapy on pre-PTE hemodynamics and post-PTE outcomes. This study was approved by the institutional review board at our institution.

Data Collection

The use of PAH medications was recorded for all subjects in the study, including prostanoids, phosphodiesterase-5 inhibitors, and endothelin receptor antagonists. For the hemodynamic and outcomes portion of the study, baseline data for all subjects were recorded, including age, sex, and standard heart failure medication use (antiarrhythmics, diuretics, spironolactone, digoxin, and dopamine) and the dose and duration of use for each PAH medication used at the time of referral. Time of diagnosis was defined as the time of initial diagnosis of pulmonary hypertension either by echocardiography or right heart catheterization. Time of referral was defined as the time of initial evaluation at UCSD. When available, invasive hemodynamic data at the time of diagnosis were recorded. Invasive hemodynamic data were recorded for all subjects at the time of referral (either in the cardiac catheterization laboratory or in the operating room before incision for PTE) and after PTE in the intensive care unit when subjects were off all vasoactive medications. For all hemodynamic data, rather than using PVR, total pulmonary resistance (TPR) was recorded because the pulmonary artery catheter balloon could not be inflated safely postoperatively. TPR was calculated with the use of the following formula: TPR (dyne×s/cm²) = (mPAP/CO)×80, where mPAP is mean pulmonary artery pressure (mm Hg), CO is cardiac output (L/min), and 80 is the conversion factor from Wood’s units to dyne×s/cm².

Outcomes including hospital days, intensive care unit days, ventilator days, in-hospital mortality, and complications including postoperative infections, reperfusion lung injury, and excessive bleeding were recorded for each subject. Because of unforeseen delays for some surgeries, hospital days were counted from the day of surgery to the day of discharge. Bleeding was defined as any amount of bleeding that required intervention either with esophagogastroduodenoscopy or with surgery. Infection diagnoses required either clinical suspicion with positive cultures and/or the presence of fever (temperature >38.4°C) and elevated white blood cell count (>12 000) with a response to empiric antibiotic treatment. Reperfusion lung injury was defined as hypoxia associated with a new radiographic infiltrate in a reperfused lung segment without evidence for infection.

Data Analysis

The prevalence data for pulmonary hypertensive medications are presented as percentages and were compared between each of the years 2005, 2006, and 2007. For the analysis of pulmonary hypertensive medical therapy on PTE outcomes, the subjects who went on to PTE surgery were divided into 2 groups: those on pulmonary hypertensive medical therapy (PHT group) before referral for PTE and those who were not (control group). The PHT group was also divided into subgroups: sildenafil monotherapy, bosentan monotherapy, and epoprostenol monotherapy and combination therapy with any combination of ≥2 medications. The baseline demographic data of age, sex, and standard heart failure medication use were compared between the 2 groups. The dosage of and the length of therapy with each PAH medical therapy were also compared, as was the length of time from diagnosis to first referral visit for both groups.

Hemodynamic data were compared between the control and PHT groups and the control and PHT subgroups at each of 3 time points: at diagnosis, at time of referral visit, and after PTE surgery. They were also compared within the PHT group and the subgroups from diagnosis to time of referral visit to evaluate the effects of PAH medical therapy on pre-PTE hemodynamics. Post-PTE outcomes and complications were also compared between the control and PHT groups and between the control group and the PHT subgroups.

Statistical Analysis

For dichotomous variables, Pearson χ² or Fisher exact test was used. The Anderson-Darling and Shapiro-Wilk tests for normality revealed that not all of the data were normally distributed. We thus utilized nonparametric analysis. Data are presented as median (interquartile range [IQR]). Mann-Whitney tests were used for continuous variables. Changes in hemodynamic data between time points within each group were compared with Friedman ANOVAs. Significant associations found with the Friedman test were followed by pairwise comparisons with the Wilcoxon signed rank test. For all tests, a 2-sided P value of 0.05 was determined to be significant. Statistical analysis was performed with the use of SPSS software.

Results

Prevalence of Medical Therapy

A total of 487 patients were referred to UCSD for PTE surgery during 2005–2007; 355 (73%) went on to undergo PTE surgery. The most common reasons for not undergoing PTE surgery were inoperable disease or an alternative diagnosis made at the time of evaluation. The prevalence of
pulmonary hypertensive medical therapy in all CTEPH patients referred to UCSD for PTE evaluation significantly increased from 2005 to 2006 (19.9% versus 31.8%; P=0.012). The increase from 2006 to 2007 was nonsignificant (31.8% versus 37.0%; P=0.66). The most commonly utilized medications were sildenafil and bosentan (Table 1). The overall prevalence of pulmonary hypertensive medical therapy in those who went on to PTE surgery from 2005 to 2007 was not significantly different from the prevalence in all subjects referred during the same time period (31.3% versus 29.2%; P=0.41).

### Effect of Preoperative Medical Therapy on Pre-PTE Hemodynamics and Post-PTE Outcomes

The baseline characteristics for the PHT and control groups are presented in Table 2. The PHT group at the time of referral for PTE was utilizing diuretics, digoxin, and spironolactone more frequently than those in the control group (Table 2). The PHT group had a significantly longer median time to referral for PTE (8.9 [IQR, 4–13] versus 4.4 [IQR, 2.5–7] months; P<0.01). The average duration of use for sildenafil was 6.5 months, for bosentan 10.7 months, for epoprostenol 9.3 months, for treprostinil 4.8 months, and for iloprost 5 months (Table 3). At the time of referral visit, we found a significantly higher mPAP in the PHT group compared with the control group (48.0 [IQR, 42 to 55] mm Hg versus 46.0 [IQR, 37 to 53] mm Hg; P=0.04) (Table 3). After PTE, there were no significant differences in any hemodynamic parameter observed between the PHT and control groups (Table 3). Subgroup analysis revealed no significant differences between the bosentan, sildenafil, and the combination subgroups compared with the control group at any time point (Table 3). In the epoprostenol subgroup, we observed a significantly higher mRAP at all 3 time points, a significantly higher mPAP at diagnosis and referral, and a significantly higher TPR at diagnosis and after PTE compared with the control group (Table 3).

Changes in hemodynamic values within each group/subgroup for those subjects with measurements at all 3 time points are presented in Figures 1 and 2, respectively. There were no statistically significant differences in any hemodynamic parameter at any time point between those subjects who had data at all 3 time points compared with their group/subgroup at each time point as a whole (data not shown). We observed a significant decrease in mPAP in the PHT group (50.0 [IQR, 42 to 55] mm Hg versus 46.0 [IQR, 41 to 54] mm Hg; P<0.03) and a significant decrease in the CO in the control group from the time of diagnosis to the time of referral visit for PTE evaluation (4.2 [IQR, 3.4 to 5.2] L/min to 4.0 [IQR, 3.1 to 4.7] L/min; P=0.01) (Figure 1). For both groups, significant improvements in all hemodynamic parameters except mRAP were seen after undergoing PTE surgery (Figure 1).

Subgroup analysis demonstrated no significant changes seen in any hemodynamic parameter from time of diagnosis to referral visit within the bosentan and combination subgroups (Figure 2). Within the sildenafil subgroup, we observed a significant decrease in mPAP from the time of diagnosis to the time of referral (50.0 [IQR, 42 to 56] mm Hg to 45.0 [IQR, 41 to 51] mm Hg; P=0.03), but no other hemodynamic parameter was found to change significantly between those time points (Figure 2). Within the epoprostenol subgroup, a significant improvement was seen in TPR from...
Within the epoprostenol subgroup, a significant improvement was seen in TPR and mPAP from the time of the referral visit to after PTE, but CO and mRAP did not change significantly after PTE (Figure 2).

There were no significant differences observed between the PHT and control groups in any of the post-PTE outcomes or complications (Table 4). Subgroup analysis also revealed no significant differences between any subgroup compared to the control group.
with the control group with regard to post-PTE outcomes or complications (Table 4).

**Discussion**

Our study demonstrates that the use of PAH medical therapies is increasing in patients with CTEPH. Their use is also associated with a delay in the time to referral for PTE surgery with only a minimal improvement in preoperative mPAP. Moreover, their use did not result in any significant differences in postoperative outcomes or hemodynamics.

Only 4 studies have addressed the issue of utilizing PAH medications in CTEPH patients before PTE.7–10 Despite the lack of evidence for their use in operable CTEPH, PAH medications are being increasingly utilized in patients with CTEPH before referral for PTE. This is likely due to the relatively recent Food and Drug Administration approval of new oral medications for the treatment of PAH, as evidenced by their being the majority of PAH medications used in our study population. These medications are simpler to prescribe for physicians and easier for patients to use than the intravenous, subcutaneous, and inhaled prostanoids. The use of PAH therapies was associated with a significant delay in referral for definitive surgical therapy. In addition, the use of PAH medical therapies added to patients’ medical expenses and healthcare resource utilization because these medications are extremely expen-

**Table 4. Post-PTE Outcomes and Complications**

<table>
<thead>
<tr>
<th>Group</th>
<th>Bleeding</th>
<th>Infection</th>
<th>Reperfusion</th>
<th>Mortality</th>
<th>Intensive Care Unit</th>
<th>Ventilator Days</th>
<th>Hospital Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td>n (%)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Control (n=243)</td>
<td>18 (7.4)</td>
<td>NA</td>
<td>48 (19.8)</td>
<td>NA</td>
<td>9 (3.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PHT (n=110)</td>
<td>15 (13.6)</td>
<td>0.06</td>
<td>22 (20.0)</td>
<td>0.96</td>
<td>25 (22.7)</td>
<td>0.77</td>
<td>NA</td>
</tr>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosentan (n=31)</td>
<td>8 (25.8)</td>
<td>0.16</td>
<td>5 (16.1)</td>
<td>0.48</td>
<td>4 (12.9)</td>
<td>0.36</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Sildenafil (n=46)</td>
<td>3 (6.5)</td>
<td>0.24</td>
<td>5 (10.9)</td>
<td>0.21</td>
<td>9 (19.6)</td>
<td>0.57</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Combination (n=20)</td>
<td>2 (10.0)</td>
<td>0.66</td>
<td>4 (20.0)</td>
<td>1.00</td>
<td>7 (35.0)</td>
<td>0.29</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Epoprostenol (n=11)</td>
<td>2 (20.0)</td>
<td>0.18</td>
<td>4 (40.0)</td>
<td>0.13</td>
<td>4 (40.0)</td>
<td>0.27</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

NA indicates not applicable. P values are for comparison with control group.
sive. For example, the annual costs range from $12 761 for sildenafil to $97 615 for treprostinil (for a 70-kg person).11

The PHT group had hemodynamic parameters similar to those of the control group with the exception of a slightly, but significantly, higher mPAP at diagnosis. The PHT group also was prescribed significantly more diuretics, digoxin, and spironolactone. This may indicate that their physicians perceived them to be more seriously ill than those in the control group. In addition, edema is a side effect of endothelin receptor antagonists, which may also explain why more diuretics were utilized in the PHT group.

Overall, our PHT subjects experienced a small reduction in preoperative mPAP while receiving comparable doses of PAH medications used in previous studies.7–9 There was, however, no change in preoperative TPR from the time of diagnosis to time of referral. The reduction in the preoperative mPAP in the sildenafil subgroup was also not associated with any change in TPR from the time of diagnosis to time of referral. The control subjects experienced a significant decline in preoperative CO, but their preoperative TPR was also unchanged from time of diagnosis to time of referral. Whether these small changes in mPAP (in the PHT group and sildenafil subgroup) and CO (in the control group) found during the preoperative period are clinically meaningful could be debated because PVR is most closely associated with morbidity and mortality in PTE surgery, and neither group experienced any significant change in TPR before PTE surgery.

Unlike the study of Reesink et al,10 there was no significant improvement in preoperative hemodynamic parameters within the bosentan subgroup. As in the studies by Bresser et al7 and Nagaya et al,8 the preoperative TPR in the epoprostenol subgroup was significantly reduced. This group, however, also had a significantly higher TPR after PTE compared with the control group. This may suggest that this subgroup, which had higher mPAP and TPR, may have more small-vessel disease (ie, small-vessel remodeling), which might be more responsive to epoprostenol therapy. Overall, this subgroup was too small to make any firm conclusions about hemodynamics. As in the studies by Bresser et al, Nagaya et al, and Reesink et al, our study demonstrated no significant difference in post-PTE hemodynamics between the PHT group and the control group. There were also no differences in hospital, ventilator, or intensive care unit days and in the post-PTE complications of bleeding and infection between the PHT and control groups and the control group and all the subgroups.

Limitations of our study include its retrospective nature and lack of randomization. Because of this, there could be a referral bias in that CTEPH patients who either do well on PAH medications or die on PAH medications may not make it to referral to UCSD for PTE evaluation. In addition, some of the subgroups contained relatively small sample sizes. Moreover, approximately one quarter of the PHT group was initiated on PAH medical therapy without diagnostic hemodynamics, which could limit the ability to detect hemodynamic improvements in the PHT group’s hemodynamics before PTE. A strength of the study is the use of a concurrently treated control group, thus limiting any bias that may have been introduced with changing surgical procedures or post-PTE care. Another strength is the large size of the 2 main study groups in a relatively rare disease such as CTEPH.

Conclusion
Our retrospective study suggests that there is no benefit to the use of PAH medical therapy in patients with operable CTEPH with the possible exception of improved TPR preoperatively in those treated with epoprostenol. The use of these medications delayed the time to referral with presumed associated increased health resource utilization without any apparent postoperative outcome benefits. Future prospective studies involving PAH medications, particularly epoprostenol, are warranted to determine whether there is any value in treating CTEPH patients with these agents before surgery.

Sources of Funding
All funding for this research project was provided by the Division of Pulmonary and Critical Care Medicine, UCSD Medical Center.

Disclosures
Dr. Kerr serves on the Consultant/Advisory Board for Gilead Sciences. Dr. Fedullo has received honoraria from the American College of Chest Physicians and has also served as an expert witness with no company representation. Dr. Kim is the recipient of a research grant from United Therapeutics, is on the Speakers Bureau for Actelion and Gilead, and is a member of the Consultant/Advisory Board for Actelion and Bayer. Dr. Test is the recipient of a research grant from Actelion and United Therapeutics. Dr. Ben-Yehuda has received honoraria and consultation from Gilead Sciences (unrelated to pulmonary hypertension). Dr. Auger received honoraria from Henry Ford Hospital and served as an expert witness in October 2008.

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The estimate of the number of pulmonary emboli per year in the United States is 500,000. The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in those who develop a pulmonary embolus is estimated to be from 0.1% to 3.8%. Given these estimates, the incidence of CTEPH in the United States ranges from 500 to 2500 patients per year up to 19,000 over 2 years. The pulmonary arterial hypertension medications being used in patients with CTEPH before pulmonary thromboendarterectomy (PTE) are unproven for this indication. In addition, they come with a high financial cost in an overburdened medical system. Significant side effects can also be involved with the use of these medications. It is possible that these medications may worsen PTE outcomes in patients with CTEPH undergoing PTE. Conversely, if some form of medical therapy improves pre-PTE hemodynamics, this may decrease surgical risk and improve immediate surgical outcomes. The University of California at San Diego Pulmonary Thromboendarterectomy Program is a world leader in CTEPH/PTE. Our center is one of a very few, if not the only center, that is able to gather data on hundreds of patients with CTEPH who are undergoing PTE. Given this, we hope to provide valuable data/analysis on the effects of medical therapy before PTE in patients with CTEPH. This is a very important question because, as it stands to date, there is no evidence to support the use of medications indicated for other forms of pulmonary arterial hypertension in CTEPH before PTE.
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_Circulation_. 2009;120:1248-1254; originally published online September 14, 2009;
doi: 10.1161/CIRCULATIONAHA.109.865881
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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