Medical Therapy for Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by chronic organized thrombi obstructing the pulmonary vasculature. Thromboembolic obstruction of the pulmonary arteries leads to increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and right ventricular failure. Studies following pulmonary hypertension (PH), and right ventricular failure.1 Studies following pulmonary emboli suggest that about 1% to 4% of patients develop chronic thromboemboli.2,3 In addition, about 25% of CTEPH patients never have an identifiable preceding acute pulmonary embolus.4 Therefore, the number of patients with CTEPH is no doubt underestimated. Despite it being a mechanical problem, CTEPH can result in a secondary arteriopathy similar to that seen in PAH. Pathologic examinations of surgical biopsies or postmortem specimens have shown pulmonary hypertensive changes indistinguishable from pulmonary arterial hypertension (PAH), including intimal thickening of the small pulmonary arteries and plexiform lesions.5 Interestingly, the small vessel changes were distal to patent pulmonary arterial segments, whereas arteries distal to embolic obstruction were normal. This is likely a result of increased blood flow to unobstructed areas.

In addition to histopathologic similarities, CTEPH and PAH can have comparable clinical presentations. It is very important to distinguish CTEPH from PAH by performing the necessary imaging studies, such as ventilation/perfusion scanning and pulmonary angiography. A correct diagnosis is of utmost importance, as PAH can be improved by PAH-targeted therapies, whereas the optimal treatment for CTEPH is surgical removal of chronic thrombi by pulmonary thromboendarterectomy (PTE). PTE often results in normal or near normal hemodynamics, and requires no therapy other than anti-coagulation. Many patients return to New York Heart Association (NYHA) functional class I. This highly successful procedure is described elsewhere in this issue.

Even though PTE is the treatment of choice for CTEPH, there is a group of patients that will not be operative candidates. Patients can have obstruction of subsegmental and more distal arteries that are not surgically accessible. In addition, there is a set of patients with CTEPH who will have persistent or recurrent PH despite successful PTE. Persistent PH is due to distal disease or arteriolar remodeling of unobstructed vessels, which cannot be corrected with surgery. Recently published data from an international registry of 679 newly diagnosed patients with CTEPH found that 37% of patients were considered inoperable.4 Nonoperability was mostly due to inaccessibility of disease (45%), followed by comorbidities and high PVR >1500 dynes-cm⁻².5 It cannot be overemphasized that determination of operability requires great expertise and should only be made at centers that evaluate and treat many patients with CTEPH.

Rationale for Medical Therapy

Given the clinical and pathological similarities between CTEPH and PAH, there may be a benefit to using PAH-targeted therapies in this disease, specifically in nonoperable CTEPH or persistent PH after PTE. There is evidence that endothelin-1 (ET-1), a potent vasoconstrictor upregulated in

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PAH, is also elevated in CTEPH. Animal models of CTEPH have shown elevated ET-1 levels. In humans, ET-1 levels have been shown to be higher in patients with CTEPH when compared to healthy controls. ET-1 levels in 35 patients with CTEPH correlated with the clinical severity of disease and hemodynamic outcome after PTE. Patients with higher preoperative ET-1 levels had worse postoperative outcomes and were more likely to have persistent PH after PTE. Nitric oxide and prostacyclin pathways are also known to be important in the development of PAH. However, less is known about the significance of these mechanisms in CTEPH.

**Medical Therapy As a Bridge to Surgery**

Recent series of CTEPH patients undergoing PTE have reported in-hospital mortality rates of 2.2% to 5%. Risk of mortality seems to be related to preoperative hemodynamic severity, in particular an elevated PVR. A series of 275 patients who underwent PTE had a 4% mortality rate when PVR was less than 900 dynes-cm⁻⁵. Mortality increased to 10% when PVR was above 900 dynes-cm⁻⁵. Another large series reported a mortality rate of 1.6% when PVR was less than 1000 dynes-cm⁻⁵, as compared to 4.1% when PVR was greater than 1000 dynes-cm⁻⁵. Postoperative PH with a PVR greater than 500 dynes-cm⁻⁵ was associated with an even higher mortality of 10.3%. Whether surgical outcomes can be improved by refining preoperative hemodynamics with targeted PAH therapies remains unknown.

Small studies have aimed to answer the question regarding medical treatment prior to surgery. Treatment with intravenous (IV) epoprostenol in patients with CTEPH and severe PH (PVR >1000 dynes-cm⁻⁵) was associated with preoperative improvements in PVR, mean pulmonary artery pressure (mPAP), and cardiac index. However, the impact on surgical morbidity or mortality could not be established from these small uncontrolled studies. Similar hemodynamic improvements were also seen in patients treated preoperatively with bosentan. Twenty-five CTEPH patients, candidates for PTE, were randomized to bosentan vs no bosentan. After 16 weeks of treatment, the bosentan group had significant improvements in mPAP, total pulmonary resistance (TPR), and 6-minute walk distance (6MWD). However, outcomes after surgery were similar in both groups.

Despite the lack of good data, the use of medical treatment prior to PTE has significantly increased in the past decade. A prospective analysis found that the use of disease-modifying PAH therapies had increased from 29% in 2001 to 65% in 2006. Another study reported an increase in medical treatment before PTE from 20% in 2005 to 37% in 2007. This high number was confirmed in the CTEPH registry, where up to 54% of patients were on at least one PAH-targeted therapy. A retrospective analysis of CTEPH patients referred for PTE compared 244 patients not on PAH therapy to 111 who were on therapy prior to surgery. The patients on medical therapy had a lower mPAP at the time of surgery. However, there were no significant differences in hemodynamic parameters, mortality, or complications after PTE between the 2 groups. The only significant difference was the time to referral for surgery. The median time to referral was 9 months in those on medical therapy vs 4 months in those without therapy. Therefore, preoperative medical therapy does not seem to improve outcomes and may lead to an unwarranted delay in surgery.

**Medical Therapy in Lieu of Surgery or After Surgery**

In patients deemed inoperable or with persistent or recurrent PH after PTE, several PAH-targeted agents have been evaluated, mostly in uncontrolled case series. Table 1 summarizes the studies of targeted PAH therapies in CTEPH.

### PROSTANOIDS

There are limited data on medical treatment for inoperable CTEPH. A small, retrospective study showed that the use of the oral prostacyclin beraprost was associated with improved hemodynamics, functional class, and mortality in patients with CTEPH compared to retrospectively matched untreated controls. Treatment with IV epoprostenol in 11 inoperable CTEPH and 16 idiopathic PAH (IPAH) patients resulted in improved clinical status, exercise tolerance, and NYHA functional class after 12 months. Another retrospective study found improvement in hemodynamics and 6MWD after 3 and 20 months of IV epoprostenol in 27 patients with inoperable CTEPH. Only half of the patients had improvement in NYHA functional class. By the end of the study, only 9 patients remained on epoprostenol (5 got transplants and 13 patients died).

Inhaled and subcutaneous prostanooids have also been considered for treatment of inoperable CTEPH. A multicenter retrospective study examined the effects of subcutaneous treprostinil in 99 patients with IPAH and 23 patients with distal CTEPH. After 3 years, patients in both groups had significant improvement in 6MWD, dyspnea score, and NYHA functional class. Subsequently, an open-label case-control study of 25 patients with inoperable CTEPH or persistent PH after PTE found significant improvements in 6MWD, NYHA functional class, B-type brain natriuretic peptide (BNP) plasma levels, cardiac output, and PVR when treated with subcutaneous treprostinil. Survival was also better when compared to historical controls.

Regarding inhaled prostacyclin, the Aerosolized Iloprost Randomized (AIR) study included 47 patients with CTEPH (23% total patients). A post-hoc analysis in this patient group found improvement in quality of life and dyspnea scores, without improvement in 6MWD.

**PHOSPHODIESTERASE TYPE 5 INHIBITORS**

A small, open-label study treated 12 patients with inoperable CTEPH and severe PH with sildenafil. Sildenafil was well tolerated and improved walk distance and PVR after 6 months. A larger open-label trial of 104 inoperable CTEPH patients found similar positive results after 1 year of treatment. This was followed by a single-center, double-blind, placebo-controlled pilot study that randomized 12 inoperable CTEPH patients to 12 weeks of sildenafil vs placebo. This was the first randomized
controlled trial ever done on CTEPH patients. The sildenafil group had improvements in NYHA functional class and PVR, but did not achieve the primary outcome of improvement in exercise capacity. This lack of improvement in 6MWD may be attributed to the study being under-powered. Based on these small trials, it

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Drug</th>
<th>Type of Study</th>
<th>Length of Study</th>
<th>Number of Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olschewski et al, 2002&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Inhaled iloprost</td>
<td>Multicenter randomized controlled trial (AIR)</td>
<td>12 weeks</td>
<td>● 101 iloprost (33 CTEPH) ● 102 placebo (24 CTEPH)</td>
<td>● 16.8% iloprost patients reached combined primary endpoint (improvement in NYHA class and at least 10% improvement in 6MWD) vs 4.9% in placebo group</td>
</tr>
<tr>
<td>Olschewski et al, 2002&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Beraprost</td>
<td>Retrospective</td>
<td>2 months</td>
<td>● 20 beraprost ● 23 matched controls</td>
<td>● Improved NYHA in 50% of treated patients ● Decrease in mPAP ● Decrease in PVR ● 15% mortality on beraprost ● 70% mortality in controls</td>
</tr>
<tr>
<td>Scelsi et al, 2004&lt;sup&gt;17&lt;/sup&gt;</td>
<td>IV epoprostenol</td>
<td>Retrospective</td>
<td>12 months</td>
<td>● 16 PAH ● 11 inoperable CTEPH</td>
<td>● Improved exercise capacity ● Improved NYHA functional class</td>
</tr>
<tr>
<td>Cabrol et al, 2007&lt;sup&gt;18&lt;/sup&gt;</td>
<td>IV epoprostenol</td>
<td>Retrospective</td>
<td>3 months</td>
<td>● 27 NYHA III-IV</td>
<td>● Increase in 6MWD ● Decrease in mPAP ● Increased cardiac index ● Decreased TPR ● 50% Improved NYHA</td>
</tr>
<tr>
<td>Lang et al, 2006&lt;sup&gt;19&lt;/sup&gt;</td>
<td>SQ treprostinil</td>
<td>Multicenter retrospective</td>
<td>26 months</td>
<td>● 99 PAH ● 23 inoperable CTEPH</td>
<td>● Increased 6MWD ● Improvement in NYHA ● Survival 89% 1 year, 71% 2 years</td>
</tr>
<tr>
<td>Scoro-Sajer et al, 2007&lt;sup&gt;20&lt;/sup&gt;</td>
<td>SQ treprostinil</td>
<td>Open-label case control</td>
<td>19 months</td>
<td>● 25 ● 31 historical matched controls</td>
<td>● Increased 6MWD ● 50% improved NYHA class ● Improvement in BNP ● Increase in cardiac output ● Decrease in PVR</td>
</tr>
<tr>
<td>Ghofrani et al, 2003&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Sildenafil</td>
<td>Open label</td>
<td>6 months</td>
<td>● 12</td>
<td>● Decrease in PVR ● Increase in cardiac index ● Increase in 6MWD</td>
</tr>
<tr>
<td>Reichenberger et al, 2007&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Sildenafil</td>
<td>Open label</td>
<td>1 Year</td>
<td>● 104</td>
<td>● Decrease in PVR ● Increase in 6MWD</td>
</tr>
<tr>
<td>Suntharalingam et al, 2007&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Sildenafil</td>
<td>RCT</td>
<td>12 Weeks</td>
<td>● 8 sildenafil ● 10 placebo</td>
<td>● Improvement in NYHA class ● Decrease in PVR ● No significant change in 6MWD</td>
</tr>
<tr>
<td>Hoope et al, 2005&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Bosentan</td>
<td>Open label</td>
<td>3 months</td>
<td>● 19</td>
<td>● Decrease in PVR ● Increase in 6MWD ● No change in NYHA class or MVO2</td>
</tr>
<tr>
<td>Hughes et al, 2006&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Bosentan</td>
<td>Open-label retrospective</td>
<td>1 year</td>
<td>● 47</td>
<td>● Increase in 6MWD ● Decrease in PVR</td>
</tr>
<tr>
<td>Jais et al, 2008&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Bosentan</td>
<td>Multicenter RCT (BENEFIT)</td>
<td>16 weeks</td>
<td>● 77 bosentan ● 80 placebo</td>
<td>● Decrease in PVR ● No change in 6MWD</td>
</tr>
<tr>
<td>Gofrani et al, 2013&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Riociguat</td>
<td>Multicenter RCT (CHEST-1)</td>
<td>16 weeks</td>
<td>● 173 riociguat ● 88 placebo</td>
<td>● Increased 6MWD ● Decrease in PVR ● Improvement in NYHA class ● Improvement in NT-proBNP</td>
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</table>
seems that sildenafil is well tolerated and leads to improvement in hemodynamics and functional class, without obvious improvement in exercise capacity. However, further larger studies would need to be conducted to better answer this question.

**ENDOTHELIN RECEPTOR ANTAGONISTS**

Several uncontrolled trials suggested that bosentan was not only safe, but may improve exercise capacity and hemodynamics in patients with inoperable CTEPH or persistent PH after PTE. An open-label safety study used bosentan for the treatment of 19 patients with inoperable CTEPH. After 3 months of treatment, patients had improvement in PVR and 6MWD, but no improvement in peak oxygen uptake or NYHA functional class. Similar results were seen in a subsequent small case series of 16 patients with inoperable CTEPH receiving bosentan for 6 months. A larger open-label retrospective study found that bosentan was well tolerated in 47 patients with inoperable CTEPH or PH after PTE. After 1 year of treatment there was improvement in 6MWD and hemodynamics, with no significant side effects.

Given these positive findings, a large, multicenter, randomized, placebo-controlled trial was performed. The Bosentan Effects in nOpErable Forms of chronic Thromboembolic pulmonary hypertension (or BENEFIT) study, a 16-week randomized trial of bosentan therapy in 100 patients with CTEPH, was the first large randomized trial that looked exclusively at this patient population. One hundred fifty-seven patients with either inoperable CTEPH due to distal disease or PVR out of proportion to obstruction, or patients with persistent or recurrent PH more than 6 months after PTE, were randomized to bosentan or placebo. After 16 weeks of treatment, there was a statistically significant improvement in PVR (-24% of baseline) in the bosentan group. Despite improvements in PVR, there was no significant difference in exercise capacity. The reasons for this “disconnect” between the hemodynamic and exercise capacity effects of bosentan in the BENEFIT trial are not clear; patient selection may have played a role, as many patients were deemed “inoperable” due to other comorbidities and not necessarily anatomically inaccessible disease.

**RIOCIGUAT**

Riociguat is a member of a new class of drugs, soluble guanylate cyclase (sGC) stimulators. Riociguat acts both by enhancing the sensitivity of sGC to nitric oxide (NO), and as a direct sGC stimulator that will activate sGC to synthesize cyclic guanosine monophosphate (cGMP) in the absence of NO. Once sGC is activated, it converts guanosine triphosphate (GTP) to cGMP, which then leads to vasodilation. The Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial (CHEST-1) was a large, multicenter, randomized, double-blind, placebo-controlled trial of 261 patients, randomized to riociguat vs placebo. Patients included had anatomically inoperable CTEPH or persistent or recurrent PH after undergoing PTE. After 16 weeks of treatment, 6MWD increased by a mean of 39 meters in the riociguat group, compared with a mean decrease of 6 meters in the placebo group ($P<0.001$) (Figure 1). There were also significant improvements in secondary endpoints, including hemodynamics. Pulmonary vascular resistance decreased by 226 dyne $\cdot$ cm$^{-5}$ in the riociguat group, compared with an increase of 23 dyne $\cdot$ cm$^{-5}$ in the placebo group. There was significant improvement in other hemodynamic variables in the riociguat group, including pulmonary artery pressure and cardiac output (see Table 2). Patients treated with riociguat also had improvement in NYHA functional class and reduction in NT-proBNP, when compared to placebo. Riociguat was recently approved in the United States for the treatment on inoperable CTEPH or persistent PH following PTE.

**SURGICAL VS MEDICAL THERAPY**

When thinking about medical therapy in CTEPH, early referral to a center of excellence with experience in pulmonary endarterectomy needs to be emphasized. Starting medical therapy should never delay referral for surgery. PTE has the potential to normalize hemodynamic and symptomatic impairments, whereas medical therapy cannot. Patients with operable disease have been found to have a 5-year survival of 90%, whereas inoperable patients have a 3-year survival of 70%. The decision to operate is dependent on whether the disease is surgically accessible, if the anatomic lesions “fit” the hemodynamics, and the severity of comorbidities. Currently there is no consensus or accepted algorithm to guide operability. This decision is based on center and surgical expertise.

The international CTEPH registry found a large variation between countries and centers regarding the number of patients deemed operable. Low-volume centers reported up to 47% of patients evaluated as inoperable, whereas high-volume centers performing >50 PTEs a year reported 34% of patients inoperable. Therefore, more experienced centers may operate on cases others would deem inoperable. A recent large retrospective study from San Diego analyzed 1500 patients with symptomatic CTEPH who underwent pulmonary endarterectomy between 1999 and 2010. Despite having more distal disease, the most recent 500 patients had a comparable decrease in PVR and mPAP and an in-hospital mortality of 2.2%, compared to 5.2% in the first 1000 patients. Therefore, in an experienced center, the outcomes of
PTE are favorable even in patients with segmental level CTEPH.

CONCLUSION
CTEPH should be considered and ruled out in any patient with newly diagnosed PH. Clinically it can mimic PAH. It is important to distinguish between the two because the treatment strategies are different. The initial step in management of CTEPH should be referral to a specialized center with expertise in CTEPH, in order to assess operability. If PTE is successful, patients may return to normal or near-normal hemodynamics and exercise capacity after surgery. In those patients who are not surgical candidates or have recurrent or persistent PH after PTE, medical management with riociguat is appropriate.

References
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