Pulmonary embolism (PE) is a life-threatening condition that is responsible for more than 300,000 deaths every year in the United States. It is estimated that more than 600,000 patients develop symptomatic PE annually.\[1,2\] The mortality rate in the first 3 months following a diagnosis of PE ranges from 15%-18%.\[3,4\] Massive PE, characterized by circulatory collapse or hemodynamic instability from acute PE, is a highly lethal condition associated with a 3-fold increased inpatient mortality compared with patients who do not have hemodynamic instability.\[5,6\] Most PE-associated deaths are the result of acute massive PE and typically occur within 1 hour of presentation.\[7\] It is noteworthy that although PE lethality data are comparable to those of acute myocardial infarction, the overall mortality rate associated with this devastating condition has not improved significantly in the past 3 decades.\[3,8-10\]

The optimal treatment strategies for patients with acute PE have been a subject of controversy, because no randomized controlled trials exist to support an ideal therapeutic modality. For patients with hemodynamic instability from massive PE, systemic thrombolysis is considered to be the standard of care.\[2,11-15\]

Researchers have reported that catheter-directed thrombolytic (CDT) therapy can facilitate thrombus dissolution through the infusion of a high concentration of thrombolytic agents directly into the thrombus, resulting in shorter infusion times and lower thrombolytic doses. Recent advances in catheter-based thrombolytic therapy have led to the development of ultrasound-accelerated CDT therapy, a novel therapeutic strategy with promising application in patients with acute PE. In this article, treatment indications for acute PE and the therapeutic modality of ultrasound-accelerated thrombolysis for acute massive PE are discussed.

### Indications for Advanced Therapy for Acute Pulmonary Embolism

In the 2008 publication, *Evidence-Based Clinical Practice Guidelines*, by the American College of Chest Physicians, treatment of PE, therapeutic strategies, and advanced interventions such as anticoagulation, thrombolysis, percutaneous embolectomy, and/or inferior vena cava filter placement were recommended on the basis of appropriate risk stratification in highly selected patients who have PE-related hemodynamic instability.\[16\] A separate consensus guideline by the 2008 European Society of Cardiology Task Force on PE Management outlined many similar diagnostic criteria and therapeutic recommendations in patients with massive PE who have experienced cardiogenic shock. Table 1 highlights the treatment recommendation from these 2 consensus guidelines for patients with PE-related hemodynamic compromise.

### Table 1. Treatment Guidelines for Advanced Therapy in Patients With Acute Pulmonary Embolism
<table>
<thead>
<tr>
<th>Treatment Variable</th>
<th>2008 ACCP&lt;sup&gt;a&lt;/sup&gt; Guidelines&lt;sup&gt;[16]&lt;/sup&gt;</th>
<th>2008 ESC&lt;sup&gt;b&lt;/sup&gt; Guidelines&lt;sup&gt;[29]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk stratification</td>
<td>All patients should undergo rapid risk stratification</td>
<td>All patients should undergo risk stratification on the basis of presence of shock and hypotension, as well as further stratification on the basis of imaging or biochemical markers of right ventricular dysfunction and myocardial injury</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>Use if hemodynamic compromise, unless contraindications. If high-risk without hypotension, use depends on clinician's assessment of PE severity, prognosis, and bleeding risk</td>
<td>First-line treatment for cardiogenic shock or persistent arterial hypotension. Consider in selected intermediate-risk patients after assessing bleeding risk</td>
</tr>
<tr>
<td>Catheter embolectomy</td>
<td>Selected highly compromised patients with too high bleeding risk for thrombolysis or insufficient time for systemic thrombolysis to be effective</td>
<td>Consider as an alternative to surgical treatment in high-risk patients when thrombolysis is absolutely contraindicated</td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>Selected highly compromised patients with too high bleeding risk for thrombolysis or insufficient time for systemic thrombolysis to be effective</td>
<td>Valuable therapeutic option in patients with high-risk PE in whom thrombolysis is absolutely contraindicated or has failed</td>
</tr>
<tr>
<td>Vena caval filter</td>
<td>Place if anticoagulation is not possible because of the risk for bleeding. If the bleeding risk resolves, administer a conventional course of anticoagulant therapy</td>
<td>Use when there are absolute contraindications to anticoagulation and a high risk of PE recurrence. Remove retrievable filters as soon as it is safe to use anticoagulants</td>
</tr>
</tbody>
</table>

<sup>a</sup>ACCP: American College of Chest Physicians  
<sup>b</sup>ESC: European Society of Cardiology

On the basis of clinical evidence,<sup>[17-20]</sup> clinical parameters that warrant early and aggressive catheter-based interventions for acute massive PE require 1 or more of the following conditions:

- Arterial hypotension, defined as systolic arterial pressure ≤ 90 mm Hg, a drop in systolic arterial pressure ≥ 40 mm Hg for ≥ 15 minutes, or ongoing administration of catecholamine for the treatment of systemic arterial hypotension;
- Cardiogenic shock with peripheral hypoperfusion and hypoxia;
- Circulatory collapse, including syncope or need for cardiopulmonary resuscitation;
- Echocardiographic findings indicating right ventricular dilatation and/or pulmonary hypertension;
- Subtotal or total filling defect in the left and/or right main pulmonary artery determined by chest computed tomography (CT) scan or by conventional pulmonary angiography; or
- Widened arterial-alveolar O2 gradient (> 50 mm Hg).

**Ultrasound-Accelerated Thrombolytic Therapy for Pulmonary Embolism**

The efficacy of CDT therapy with intrapulmonary thrombolytic infusion in patients with acute massive PE has been reported in several studies to lead to an overall remarkable treatment success.<sup>[8,21-27]</sup> This strategy requires selective infusion catheter placement in the pulmonary artery within the embolus, followed by continuous infusion of thrombolytic drugs for a specified period of time.

Ultrasound-accelerated catheter-directed thrombolysis is a novel treatment in which pulmonary artery thrombolytic therapy is delivered through an infusion catheter that emits ultrasound energy to accelerate the thrombolytic...
cascade. This treatment is achieved using the EkoSonic® Endovascular System (EKOS Corporation; Bothell, WA), which is approved by the US Food and Drug Administration for pulmonary artery infusion. The system uses a 5.2-French multilumen sideport infusion catheter, with infusion lengths of 6-50 cm depending on the length of the thrombotic occlusion. Once the EkoSonic catheter is positioned in the pulmonary artery, an ultrasound core wire containing a series of ultrasound transducer elements (2.2 MHz, 0.45 W) is positioned within the infusion catheter (Figure 1). The ultrasound catheter is then connected to a control unit that provides continuous monitored variables, including temperature and ultrasound energy power output in the treatment zone by means of thermocouples incorporated in the catheter, and automatically adjusts power to optimize lysis of the intravascular thrombosis. The acoustic streaming energy dissociates the fibrin and increases the fibrin porosity without causing distal embolization, which also facilitates the penetration of thrombolytic agents into the thrombus for receptor binding. Two recent clinical reports (including our own institutional experience) about patients who have experienced acute massive PE and who were treated with ultrasound-accelerated thrombolytic therapy, showed promising clinical outcomes with dramatic hemodynamic improvement. [21,25]

Figure 1. (A) The EkoSonic Endovascular System consists of a multilumen infusion catheter with a removable coaxial ultrasound transducer core, which is connected to a control unit that delivers lower-energy high-frequency ultrasound energy with concomitant thrombolytic drug infusion into the thrombus. (B) Schlieren photograph of an EkoSonic catheter that emits ultrasound energy. The acoustic streaming energy dissociates the fibrin and increases the fibrin porosity without causing distal embolization, which also facilitates the penetration of thrombolytic agent into the thrombus for receptor binding.

Clinical Experience With Ultrasound-Enhanced Catheter-Directed Thrombolysis for Pulmonary Embolism

Clinical experience with interventional treatment in patients with acute massive PE from our institution was recently reported. [25] A total of 25 patients underwent 33 catheter-directed interventions for massive PE during a 10-year period. Interventional treatment strategies in these patients included CDT therapy (CDT group, n = 11) or ultrasound-accelerated thrombolytic therapy using the EkoSonic system (EKOS group, n = 15). Preinterventional and postinterventional pulmonary angiography were analyzed for evidence of thrombus removal on the basis of published criteria as reported by Miller and associates. [28] The Miller score (MS) was calculated on the basis of degree of pulmonary artery obstruction and perfusion indexes, which range from 0 (best) to 34 (worst). A diagnosis of massive PE was confirmed with an MS > 17. Preinterventional MS, postinterventional MS, and relative MS improvement (defined as the preinterventional MS minus the postinterventional MS divided by the preinterventional MS) were calculated for each patient.
Relevant clinical factors, including hypercoagulable risk factors for PE, thrombolytic dose, infusion time, percentage lysis on the basis of angiographic analysis, and treatment complications were compared between the 2 treatment groups. Complete thrombolysis was defined as more than 90% thrombus removal, near complete lysis was defined as 75%-90% thrombus removal, and partial lysis was defined as 50%-75% thrombus removal. Follow-up pulmonary angiography was performed 12-48 hours after the initiation of catheter-based interventions to determine the need to continue or stop thrombolysis. Helical CT angiogram of the chest was performed whenever clinical indications were present (Figure 2).

Figure 2. (A) Helical CT angiogram showing emboli in bilateral pulmonary arteries with large thrombus in the left main pulmonary artery (short arrow) and multiple thrombi in the right main pulmonary artery (long arrow) prior to ultrasound-accelerated thrombolytic therapy. (B) Follow-up CT angiogram performed 5 days after successful thrombolytic therapy using the EkoSonic device, demonstrating complete resolution of bilateral pulmonary emboli.

Our clinical experience showed that successful catheter-based interventions were initiated, because the infusion catheters were positioned appropriately within the thrombus in all patients in both groups. In the EKOS group, tissue plasminogen activator (tPA) was administered to all patients, with a mean tPA dose rate of 0.86 ± 0.16 mg/hour for a mean total tPA dose of 17.2 ± 2.36 mg (range 8-28 mg). The mean infusion time was 17.4 ± 5.23 hours (range 13-38 hours). No hemorrhagic complications occurred in this patient group. The preinterventional MS was 18.65 ± 3.25, which decreased to a postinterventional MS level of 5.84 ± 1.57 (Table 2). In the CDT group, 5 patients received urokinase, and 10 patients received tPA as thrombolytic agents. The mean infusion duration was 26.7 ± 8.64 hours (range 14-46 hours). The mean tPA dose rate was 0.93 ± 0.22 mg/hour for a mean total tPA dose of 25.43 ± 5.27 mg (range 16-45 mg). For patients who received urokinase thrombolytic therapy, the mean starting dose was 60,000 units/hour, which was increased at 6 hours to a mean dose of 90,000 units/hour. The mean total urokinase dose was 2.04 ± 0.56 million units (range 1.65-2.87 million units) delivered over a mean duration of 25.3 ± 7.35 hours (range 17-39 hours). Complete thrombus resolution was achieved in 7 patients (50%) and partial thrombolysis was achieved in 2 patients (14.3%).

Comparative analysis between the 2 treatment groups on the basis of thrombus removal showed that the EKOS group had improved treatment success compared with the CDT group (P < .02). The preinterventional MS was 17.29 ± 3.86 which was reduced to 7.38 ± 2.26 following CDT therapy (Table 2). With respect to tPA dosage and infusion time, these were lower in the EKOS group compared with the CDT group (P < .001). The MS scores were statistically significant in both EKOS and CDT groups following respective interventional treatment (P < .002). No significant difference in relative MS improvement was observed between groups.

Table 2. Treatment Outcome in the EKOS and CDT Treatment Groups
<table>
<thead>
<tr>
<th>Variable</th>
<th>EKOS Therapy</th>
<th>CDT Therapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11</td>
<td>15</td>
<td>n/a</td>
</tr>
<tr>
<td>No. of PE lesions</td>
<td>15</td>
<td>18</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean age</td>
<td>59 ± 17 years</td>
<td>62 ± 18 years</td>
<td>NS</td>
</tr>
<tr>
<td>Men (%)</td>
<td>5 (45%)</td>
<td>7 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Complete thrombolysis</td>
<td>11 (100%)</td>
<td>7 (50%)</td>
<td>.01</td>
</tr>
<tr>
<td>Partial thrombolysis</td>
<td>0</td>
<td>2 (14.3%)</td>
<td>.03</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (9.1%)</td>
<td>2 (14.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemorrhagic complications</td>
<td>0</td>
<td>3 (21.4%)</td>
<td>.02</td>
</tr>
<tr>
<td>Thrombolytic dosage (Urokinase, units x 10^6)</td>
<td>n/a</td>
<td>2.04 ± 0.56</td>
<td>n/a</td>
</tr>
<tr>
<td>Thrombolytic dose rate (tPA, mg/hr)</td>
<td>0.86 ± 0.16</td>
<td>0.93 ± 0.22</td>
<td>.04</td>
</tr>
<tr>
<td>Thrombolytic dose (tPA, mg)</td>
<td>17.2 ± 2.36</td>
<td>25.43 ± 5.27</td>
<td>.03</td>
</tr>
<tr>
<td>Thrombolytic infusion (hrs)</td>
<td>17.4 ± 5.23</td>
<td>26.7 ± 8.64</td>
<td>.03</td>
</tr>
<tr>
<td>Preintervention MS</td>
<td>18.65 ± 3.25</td>
<td>17.29 ± 3.86</td>
<td>NS</td>
</tr>
<tr>
<td>Postintervention MS</td>
<td>5.84 ± 1.57a</td>
<td>7.38 ± 2.26b</td>
<td>NS</td>
</tr>
<tr>
<td>Relative MS improvement</td>
<td>0.63 ± 0.18</td>
<td>0.68 ± 0.26</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a*Comparison of preintervention and postintervention Miller Score (MS) within EKOS group showed a significant difference (P < .002)

*b*Comparison of preintervention and postintervention MS within CDT group showed a significant difference with P < .002

This study demonstrated remarkable therapeutic efficacy of both CDT and ultrasound-accelerated thrombolytic therapy in patients with acute massive PE. The treatment success of CDT and EKOS interventions is evidenced by the 30-day survival rates, which were 86% and 91%, respectively. The findings of this study underscored the beneficial role for endovascular interventions in patients with acute massive PE.

**Conclusions**

The results of our own institutional experience highlight a potential therapeutic benefit in patients with acute massive PE whose hemodynamic instability or cardiogenic shock could be improved with endovascular interventions using ultrasound-accelerated CDT therapy. This modality is a beneficial treatment option in patients who have acute massive PE with contraindications to systemic thrombolysis, when time to administer systemic thrombolytic agents is lacking, or when no improvement follows standard intravenous thrombolytic administration. In institutions with appropriate clinical expertise, ultrasound-accelerated CDT therapy is an important component of the therapeutic armamentarium for patients with acute massive PE.

**References**