Ultrasound Accelerated Thrombolysis May Be an Effective and Safe Treatment Modality for Intermediate Risk/Submassive Pulmonary Embolism

Caglar Ozmen, MD, Ali Deniz, MD, Rabia Eker Akilli, MD, Onur Sinan Deveci, MD, Caglar Emre Cagliyan, MD, Halil Aktas, MD, Aziz İnan Celik, MD, Ayça Acikelin Akpinar, MD, Nezihat Rana Disel, MD, Hüseyin Tugsan Balli, MD, İsmail Hanta, MD, Mesut Demir, MD, Ayhan Usal, MD, and Mehmet Kanadasi, MD

Summary

Pulmonary embolism (PE) is a potentially life-threatening condition and the fact that 90% of PE originate from lower limb veins highlights the significance of early detection and treatment of deep vein thrombosis.1 Massive/high risk PE involving circulatory collapse or systemic arterial hypotension is associated with an early mortality rate of approximately 50%, in part from right ventricular (RV) failure.2 Intermediate risk/submassive PE, on the other hand, is defined as PE-related RV dysfunction, troponin and/or B-type natriuretic peptide elevation despite normal arterial pressure.3 Without prompt treatment, patients with intermediate risk PE may progress to the massive category with a potentially fatal outcome. In patients with PE and right ventricular dysfunction (RVD), in hospital mortality ranges from 5% to 17%, significantly higher than in patients without RVD.4-6 (Int Heart J 2016; 57: 91-95)

Key words: Right ventricular dysfunction, Circulatory collapse, Hypotension

In patients with massive PE, systemic thrombolysis has been demonstrated to reduce mortality rates.7 Patients with high-risk PE and a low risk of bleeding should receive thrombolysis, as may patients with intermediate risk PE.8 In comparison to anticoagulation alone, systemic thrombolysis can reverse RV dilatation within 24 hours of treatment.9,10 Despite these effects, thrombolytic therapy is associated with a higher incidence of major bleeding complications defined as intracranial or retroperitoneal hemorrhage or bleeding leading directly to death, hospitalization, or transfusion.11

Ultrasound-accelerated thrombolysis (USAT) using the EkoSonic® Endovascular System (EKOS corporation; Bothell, WA) uses low-intensity, high-frequency ultrasound that dissolves fibrin strands without causing thrombus fragmentation. The acoustic energy enhances thrombolytic penetration into the thrombus, and increases thrombus surface area exposed to lytic drug.12 This method enhances dissolution of more organized thrombus.

There is a need for effective treatment alternatives for acute PE that facilitate the reversal of RVD without causing an excess in systemic bleeding complications. The purpose of this study was to evaluate the results of clinical efficacy and safety of USAT in patients with intermediate risk PE, retrospectively.

Patients: The study population was composed of patients who underwent USAT at Cukurova University Faculty of Medicine between October 2012 and August 2013. Ten intermediate risk PE patients were included in the study. The clinical records of all patients were reviewed and clinical data were recorded. We used recombinant tissue plasminogen activator (rt-PA) as a thrombolytic agent for this procedure. Intermediate risk PE patients were treated with this therapy if they fulfilled all of the following criteria: a) dyspnea, hypoxia with no hemodynamic instability, b) evidence of PE by multi-detector contrast-enhanced computed tomography (CT), and c) RVD found from transhilar echocardiography defined as the case that had shown any of the following 3 findings; 1) The ratio of the right ventricular end-diastolic diameter to the left ventricular end-diastolic diameter is ≥ 0.9; 2) wall motion abnormality of right ventricle; and 3) tricuspid regurgitation jet velocity (TRV) ≥ 2.8 m/sec.13 Patients with any contraindications to thrombolytic therapy according to the European Society of Cardiology (ESC) guidelines regarding acute PE did not undergo USAT.14 Written informed consent was obtained in all patients prior to the procedure. This study was approved by the local Institutional Review Board (2013/26-7).

EkoSonic device: The EkoSonic® system includes a multiple-lumen infusion catheter with a removable coaxial ultrasound...
core wire containing a series of miniature ultrasound transducers, which are connected to a control unit that delivers low-intensity ultrasound with concomitant thrombolytic drug infusion into the thrombus. A 5.2 Fr multilumen side port infusion catheter, with infusion lengths of 6 to 50 cm, accommodates the coaxial 0.035-inch ultrasound core wire. The system delivers ultrasound energy (2.2 MHz) radially along the coaxial infusion zone with simultaneous rt-PA infusion. The control unit continuously monitors variables, including temperature and ultrasound energy power output in the treatment zone, by means of thermocouples incorporated into the catheter, and automatically adjusts delivered ultrasound power to optimize thrombolysis. 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.

Treatment regimen: All patients received unfractionated heparin using a standard weight-based algorithm and doses were adjusted according to the activated partial thromboplastin time prior to, during, and after USAT treatment. The placement of the EkoSonic Endovascular System was performed in the cardiac catheterization laboratory. Venous access was obtained via the common femoral vein using a micropuncture needle and a 6 Fr introducer sheath. Following placement of the introducer sheath, a 260 cm, 0.035-inch guidewire and a 6 Fr pigtail catheter were advanced into the desired location in the PA and then pulmonary arteriograms were obtained. Once the location of a pulmonary arterial thrombus was identified, the pigtail catheter was then removed and the EkoSonic infusion catheter was advanced over the guidewire until the distal catheter tip was positioned at the distal edge of the thrombus under fluoroscopy. In case of bilateral PE, an EkoSonic catheter was introduced into the PA containing higher thrombus load. After final positioning, the guidewire was then removed and replaced by the ultrasound core wire (endowave catheter) which was connected to the control unit for ultrasound energy transmission. Continuous infusion of thrombolytic was initiated through the drug lumen of the infusion catheter, and ultrasound energy was delivered with simultaneous infusion of the thrombolytic drug. Normal saline was continuously infused through a central lumen (60–70 mL/hour) to provide baseline cooling in the endowave catheter. Thrombolysis was performed using rt-PA. Patients were transported to the coronary care unit. Patients received rt-PA and ultrasound for 12 hours. Follow-up angiography was performed with the Vivid S5 cardiovascular ultrasound system (3S 1.5–3.6 MHz probe for transthoracic GE Medical Systems, Buckinghamshire, UK). Preinterventional and postinterventional standard color 2-dimensional echocardiographic Doppler examinations were performed by experienced echocardiographers. The end-diastolic dimensions of the right and left ventricles were measured in the apical 4-chamber views from the septal endocardial border to the lateral wall endocardial border at their widest point just above the mitral valve and tricuspid valve annulus. Also, the end-diastolic dimensions of the right and left ventricles were measured in the parasternal long axis view. The RV/LV ratio was then determined for each view. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode recordings from the apical 4-chamber view, with the cursor placed at the free wall of the tricuspid annulus. From the apical 4-chamber view, the tricuspid gradient derived from tricuspid regurgitation jet velocity (TRV) was measured. The RV outflow tract velocity integral (RVOT VTI) was recorded from the parasternal short axis view at the aortic valve level with the pulsed-wave (PW) Doppler sample volume positioned in the center of the RV outflow tract just proximal to the pulmonary valve. The area under the velocity curve was traced. Pulmonary acceleration time (PAT) was measured from the parasternal short-axis view with the PW Doppler sample volume placed at the annulus of the pulmonary valve. PAT was defined as the interval between the onset of systolic pulmonary arterial flow and peak flow velocity.

Statistical analysis: Statistical analysis was performed using the statistical package SPSS v 17.0. For each continuous variable, normality was checked by the Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. Comparisons of pre and post operation days were conducted using the Wilcoxon test and the Friedman test was used for data that was not normally distributed. Line plots were obtained using Microsoft Excel. Values of P < 0.05 were considered statistically significant.

Results

Demographics and procedural details: Mean age was 53.2 ± 14.1 years and 60% of patients were male. All patients had a symptom duration of less than 14 days and were at intermediate risk (normotensive, RV dysfunction or dilatation). On CT, PE with a median Qanadli score of 19 (18-27) was detected in all patients. Baseline median RV end diastolic diameter was 41 (36-52) mm and the baseline median RV/LV ratio was 1.26 (0.76-1.84) on CT. On echocardiography the RV/LV ratio in the 4-chamber view was 0.99 (0.71-1.22) with a median TRV of 3.35 (2.8-4.1) m/s. All patients underwent pulmonary angiography. The median of mean pulmonary artery pressure (PAP) wall at the widest point in the chamber, which was typically in the basal third of the RV. The LV diameter was measured on the transverse image that showed the mitral valve at its widest and, like the diameter of the RV, was measured from the inner wall to the inner wall at the widest portion of the LV. The right-to-left ventricular dimension ratio (RV/LV ratio) was then calculated. For evidence of thrombus removal, the Qanadli score was used. Preinterventional and postinterventional Qanadli scores were calculated for each patient. Echocardiographic analysis: Transthoracic (TTE) echocardiography was performed with the Vivid S5 cardiovascular ultrasound system (3S 1.5–3.6 MHz probe for transthoracic GE Medical Systems, Buckinghamshire, UK). Preinterventional and postinterventional standard color 2-dimensional echocardiographic Doppler examinations were performed by experienced echocardiographers. The end-diastolic dimensions of the right and left ventricles were measured in the apical 4-chamber views from the septal endocardial border to the lateral wall endocardial border at their widest point just above the mitral valve and tricuspid valve annulus. Also, the end-diastolic dimensions of the right and left ventricles were measured in the parasternal long axis view. The RV/LV ratio was then determined for each view. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode recordings from the apical 4-chamber view, with the cursor placed at the free wall of the tricuspid annulus. From the apical 4-chamber view, the transtricuspid gradient derived from tricuspid regurgitation jet velocity (TRV) was measured. The RV outflow tract velocity integral (RVOT VTI) was recorded from the parasternal short axis view at the aortic valve level with the pulsed-wave (PW) Doppler sample volume positioned in the center of the RV outflow tract just proximal to the pulmonary valve. The area under the velocity curve was traced. Pulmonary acceleration time (PAT) was measured from the parasternal short-axis view with the PW Doppler sample volume placed at the annulus of the pulmonary valve. PAT was defined as the interval between the onset of systolic pulmonary arterial flow and peak flow velocity.

Statistical analysis: Statistical analysis was performed using the statistical package SPSS v 17.0. For each continuous variable, normality was checked by the Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. Comparisons of pre and post operation days were conducted using the Wilcoxon test and the Friedman test was used for data that was not normally distributed. Line plots were obtained using Microsoft Excel. Values of P < 0.05 were considered statistically significant.
was 34 (22–50) mmHg during catheterization. USAT were performed successfully in all patients. Overall, we used rt-PA 0.05 mg/kg/hour for each patient. The mean rt-PA dose was 31.7 mg ± 3.22 and infusion time was 12 hours. The EkoSonic device was removed quickly when the infusion was completed. The rt-PA infusion time was considered to be 12 hours for all patients as there was no bleeding complication during this period.

**Endpoint analyses:** We performed follow-up echocardiography in all patients 2 days and 6 months later in the follow-up, except for the patient who died on the 13th day of hospitalization. Baseline characteristics of the patients are presented in Supplemental Table I, and laboratory data and symptoms are presented in Supplemental Table II. Preintervention, postintervention, and 6 month follow-up variables are shown in Supplemental Table III. Echocardiographic parameters showing RV dysfunction significantly improved after treatment and this significant difference was maintained during the 6 months of follow-up. The RV/LV ratio in the 4-chamber view decreased from 0.99 (0.71–1.22) to 0.82 (0.55–0.93) after treatment and to 0.73 (0.54–0.88) 6 months later (P = 0.005, P < 0.001, respectively) (Supplemental Figure 1A). TRV decreased from 3.35 (2.8–4.1) m/s to 2.50 (2.1–3.8) m/s after treatment and to 2.20 (2.0–2.7) m/s 6 months later (P = 0.004, P < 0.001, respectively). Pulmonary acceleration time increased from 86 (66–112) ms to 113 (76–135) ms after treatment and to 133 (110–147) ms 6 months later (P = 0.008, P < 0.001, respectively). TAPSE increased from 14 (12–21) mm to 21 (15–34) mm after treatment and to 24 (13–34) mm 6 months later (P = 0.005, P = 0.001 respectively).

Follow-up CT angiography was performed in all patients after 2 days of USAT treatment. The RV/LV ratio decreased from 1.26 (0.76–1.84) to 0.91 (0.62–1.10) at follow-up (P = 0.005) (Supplemental Figure 1B). The median RV end diastolic diameter was reduced from 41 (36–52) mm to 34 (29–41) mm (P = 0.005). The Q nadli score was significantly reduced from 19 (18–27) to 11 (3–15) (P = 0.005).

We performed follow-up pulmonary angiography in all patients after the USAT procedure. The pre- and postinterventional pulmonary angiography results are shown in Supplemental Figure 2 and Supplemental Figure 3. PA systolic and mean pressures decreased significantly from the baseline values of 49 (31–80) and 34 (22–50) mmHg, to 29 (14–63) and 6 (2–27) mmHg, respectively. (P = 0.005 for each) (Supplemental Figure 1C). The Miller score was significantly reduced from 21 (13–28) to 8 (4–16) (P = 0.005).

**Clinical outcomes:** All patients except one survived to hospital discharge with an average hospital stay of 9 ± 4 days (range, 4–16 days; median 6 days). This patient had been hospitalized in the ICU due to organophosphate intoxication, and PE was detected on the 6th day of her hospital stay. Seven days after USAT she died of liver failure. The average duration of stay in the intensive care unit was 3 days (median, 2 days). We suspected no recurrent PE during the hospital stay of the patients. No minor or major bleeding complications were observed.

**DISCUSSION**

In the present study, we observed that catheter-directed USAT treatment resulted in a reduced thrombolytic dose, reversed RV dilatation, improved RV dysfunction, and decreased pulmonary clot burden and PA pressures in intermediate risk PE patients. In addition no bleeding event was reported.

Current ESC guidelines support the use of thrombolysis in the management of intermediate risk PE patients without an elevated risk of bleeding. In randomized trials and clinical practice, systemic PE thrombolysis is associated with high bleeding risk. Anticoagulation with heparin is a widely used therapy in intermediate risk PE patients, but this treatment does not remove thrombus burden or restore vascular flow. In the ULtrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial, a randomized, prospective, controlled study of PE patients at intermediate risk of death, catheter-directed USAT was superior to anticoagulation with heparin alone in reversing RV dilatation and dysfunction at 24 hours, without an increase in bleeding complications. In their trial, USAT reduced the RV/LV ratio from 1.28 at baseline to 0.99 over 24 hours, which was comparable to the effect seen with tenecteplase in the TIPES trial. The control group in the ULTIMA study received unfractionated heparin without thrombolysis, and there was no significant reversal of right ventricular dilatation with an RV/LV ratio of 1.20 at baseline and 1.17 at 24 hours (RV/LV ratio mean absolute reduction 0.03). In our study, USAT reduced the RV/LV ratio from 0.99 (0.71–1.22) to 0.82 (0.55–0.93) on echocardiography and from 1.26 (0.76–1.84) to 0.91 (0.62–1.10) on CT at two days. RV dysfunction is known to be associated with adverse prognosis in PE patients. We also examined the alteration in other parameters related to RV dysfunction on echocardiography and long-term follow-up as RV echocardiography provides valuable information about chronic thromboembolic pulmonary hypertension. After the procedure and at 6th months of follow-up, we found improvements in TRV, PAT, and TAPSE.

In the ULTIMA trial there were significant reductions in systolic, diastolic, and mean PAP measured invasively. In our study, systolic, mean, and diastolic PA pressures all decreased like in the ULTIMA trial. In the ULTIMA trial, rtPA was used up to 20 mg over 15 hours during the USAT procedure, and no significant increase in bleeding complications was reported compared to heparin. In our study, we used 31.7 mg rt-PA over 12 hours. During the USAT procedure we did not observe any bleeding complications. In the ULTIMA trial, the significant decrease in the RV/LV ratio at 90 days follow-up was maintained (from 1.28 to 0.95). Also in our study, the difference between the basal and 6 month follow-up RV/LV ratio remained significant. Although the ULTIMA study and our study demonstrated a hemodynamic benefit from USAT therapy, further studies are warranted to determine whether this benefit translates into improved clinical outcomes. All patients except one were discharged alive in our study. Treatment success as evidence of thrombus removal was also examined using the Q nadli and Miller scoring systems. We observed a reduction of the Miller score from 21 (13–28) to 8 (4–16) and the Q nadli score from 19 (18–27) to 11 (3–15).

One of our patients who died of organophosphate intoxication did not reflect the reduced clinical efficacy of USAT since she did not die due to PE. Related complications of interventional therapy for PE such as dissemination, pericardial tamponade, pulmonary hemorrhage, distal embolization, arrhythmia, contrast nephropathy, anaphylaxis, hemorrhage and groin hematoma, pseudoaneurysm, or AV fistula were not ob-
served in our study. Ultrasound exposure does not cause mechanical fragmentation of the clot, however, it does increase the flow rate through thrombi, probably by disaggregation of un-crosslinked fibrin fibers into smaller fibers. This results in increased transport of the lytic agent into the clot, alteration of binding affinity, and increased maximum binding. Thereby, USAT reduces the amount of drug required for thrombolysis.

The EkoSonic® system has been studied in the treatment of patients with stroke, peripheral arterial occlusion, DVT, and PE. Chamsuddin, et al concluded that USAT was an effective method for treating massive thrombolysis in their study of 10 acute massive PE patients. They emphasized that low-dose USAT rapidly reverses RV dilatation and pulmonary clot burden.

There are some limitations in our study. It was retrospective and without a control group, and in addition, the limited length of follow-up and small number of patients indicate the findings should be interpreted cautiously.

In conclusion, USAT improved RV dysfunction, decreased clot burden, and caused no bleeding complications in intermediate risk PE patients. USAT therapy may be a safe and effective treatment option for intermediate risk PE patients. Additional prospective, randomized clinical studies are necessary to validate our results with this USAT therapy in acute PE patients.

**DISCLOSURE**

**Conflicts of interest:** The authors declare that there is no conflict of interest.

**REFERENCES**


SUPPLEMENTAL FILES

Supplemental Table I, II, III
Supplemental Figure 1, 2, 3
Please find supplemental files; https://www.jstage.jst.co.jp/article/ihj/57/1/57_15-271/_article/supplement