Hemodynamic Effects of Ultrasound-Assisted, Catheter-Directed, Very Low-Dose, Short-Time Duration Thrombolysis in Acute Intermediate−High Risk Pulmonary Embolism (from the EKOS-PL Study)

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Ultrasound-assisted, catheter-directed, low-dose thrombolysis (USAT) at an average alteplase dose of 20 mg infused over 12 to 24 hours reversed right ventricular disfunction and improved pulmonary hemodynamics in intermediate−high-risk pulmonary embolism patients. As bleeding risk increases with the thrombolytic dose, establishing a minimal effective USAT dosing regimen is of clinical importance. We aimed to investigate hemodynamic effects and safety of a very low-alteplase-dose USAT of 10 mg administered within 5 hours. We included 12 consecutive intermediate−high-risk pulmonary embolism patients with symptoms duration of <14 days and proximal thrombi location in pulmonary arteries. Pulmonary Embolism Response Team decision-based fixed, bilateral ultrasound-assisted alteplase infusions at the rate of 1mg/hour/catheter for 5 hours through EKOS system catheters were made. The primary efficacy measure was the change in invasive systolic and mean pulmonary arteries pressure, and in cardiac index from USAT start to termination. Safety measures were 180-day all-cause death or cardiopulmonary decompensation and bleeding complications. The systolic pulmonary arteries pressure and mean pulmonary arteries pressure decreased from 53 (45.5 to 59) to 37.5 (27.5 to 40.5) mm Hg (p = 0.02) and from 29.5 (27.5 to 32) to 21.5 (15.5 to 25) mm Hg (p = 0.02), respectively. The cardiac index increased from 1.6 (1.5 to 1.8) to 2.2 (1.9 to 2.4) l/min/m^2, (p = 0.02). No deaths, decompensations, or need for therapy intensification occurred. There was 1 episode of access-site bleeding, which subsided after conservative management. No intracranial hemorrhages appeared. In conclusion, reduced dose and duration USAT improved pulmonary hemodynamics and cardiac function leading to cardiopulmonary stabilization in intermediate-high risk pulmonary embolism patients at a low periprocedural risk. **(Am J Cardiol 2021;141:133−139)**

Catheter-directed interventions are becoming valuable methods for the treatment of acute pulmonary embolism (PE).[1] Ultrasound-assisted thrombolysis (USAT) is a form of local fibrinolytic therapy enhanced by acoustic energy, which facilitates penetration of the lytic drug into the thrombi.[2] It allows the use of lower lytic doses as compared with systemic thrombolysis. Previous studies have shown that an average 20 to 24 mg of alteplase administered through USAT over 12 to 24 hours efficiently reversed right ventricular (RV) dilatation and improved pulmonary hemodynamics in intermediate-high risk (IHR) PE patients, and was associated with up to 10% of bleeding complications.[3−6] As the risk of hemorrhagic events increases with the thrombolytic dose, establishing a minimal effective dose for USAT is clinically important. A recent study suggested that even smaller doses may efficiently reduce RV enlargement, but their effect on pulmonary hemodynamics has not been reported to date.[7] Therefore, we aimed to investigate changes in invasive pulmonary hemodynamics during very low-alteplase-dose USAT of 10 mg administered within reduced 5-hour infusion in patients with IHR-PE.

Methods

This was a prospective, observational study conducted in a tertiary cardiology center in Krakow, Poland by the institutional Pulmonary Embolism Response Team (PERT).[8] The protocol was developed in compliance with the ESC guidelines and approved by the Bioethical Committee of Physicians and Dentists Chamber in Krakow, Poland (186/KBL/OIL/2017), and the study was performed with respect for the principles of the Declaration of Helsinki.

Adult PE patients at IHR of early death and symptoms duration of ≤ 14 days were eligible for enrolment. According to contemporary ESC guidelines, IHR-PE patients were

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See page 138 for disclosure information.

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identified by the presence of RV dysfunction (RV-to-left ventricular diameter ratio [RV/LV] ≥ 0.9) on cardiac echo study or computed tomography angiography (CTPA), elevated serum levels of cardiac troponin or N-terminal pro-B-type natriuretic peptide, and pulmonary embolism severity index class III-V or simplified pulmonary embolism severity index score ≥ 1.[9] Potential candidates were enrolled if they (1) showed clinical signs of severe PE including at least 1 of the after: heart rate (HR) ≥ 100/min or systolic blood pressure (SBP) 90 to 100 mm Hg or room air arterial oxygen saturation ($SatO_2$) ≤ 90%; (2) had central location of thrombi in at least 1 main or lobar PA documented in CTPA; (3) were deemed to be at increased risk of bleeding complications if treated with full-dose systemic thrombolysis (Supplementary Table 1); and (4) were disqualified from surgical embolectomy by the local PERT, composed of an interventional cardiologist and a cardiac surgeon. Patients with SBP < 90 mm Hg despite catecholamine support, or at cardiac arrest requiring active resuscitation upon qualification, or with absolute contraindications to thrombolysis were excluded from the study. All patients provided their written informed consent.

The procedure of USAT was performed with the use of the EkoSonic Endovascular System − the EKOS system (Boston Scientific Company, Boston, Massachusetts) composed of endovascular catheters and a control unit as previously described.[2–4] Placement of the EKOS system catheters into PAs was performed at the cardiac catheter suite through femoral vein access under fluoroscopic guidance in all patients directly after the study enrolment and was followed by immediate initiation of alteplase infusion. The ultrasound-assisted alteplase infusion was further continued in the Intensive Cardiac Care Unit at a rate of 1 mg/h per catheter for a total duration of 5 hours. All patients received therapeutic anticoagulation with unfractionated heparin intravenously with targeted activated prothrombin time of 46 to 70 seconds.

The primary efficacy end point was improvement of invasively measured systolic and mean PA pressures and cardiac index (sPAP, mPAP, and cardiac index [CI], respectively) from baseline, before placement of EKOS system catheters, to USAT termination, during catheters removal (Figure 1). Pulmonary pressure was recorded with the use of a 7 French SwanGanz catheter before the EKOS system catheters implantation and with 1 of the EKOS system catheters on their removal. The Fick method was applied to calculate the CI both at baseline and USAT completion. Secondary efficacy measures were the (1) change in the RV/LV ratio assessed in the CTPA before and after 12 hours from the USAT start, and (2) reduction of symptoms and HR, improvement in pulse oximetry $SatO_2$, and change in SBP.

The primary safety measure was all-cause mortality within 180 days from inclusion to the study. Secondary safety outcomes were (1) in-hospital cardiopulmonary decompensation defined as sudden cardiac arrest, occurrence of shock, or refractory hypotension requiring treatment intensification and (2) major bleeding according to the International Society of Thrombosis and Haemostasis classification within 72 hours from the procedure initiation.[10]

Categorical variables were described as counts and percentages, and continuous variables as median, and interquartile ranges. Postprocedural results were compared with the baseline using the Wilcoxon signed-rank test. The significance level was set at $p < 0.05$. Statistical analyses were performed with Statistica PL software (StatSoft, Inc. [2017]. STATISTICA [data analysis software system], version 13.1 www.statsoft.com).

Results

During the 15-month recruiting period we had evaluated 39 IHR acute PE patients, of whom 12 were qualified for the study (Figure 2). The decision to use USAT was supported by the PERT's recommendation in all cases. The study group was composed of a similar proportion of males (58%) and females, at a median age of 64 (43.5 to 70) years. Table 1 presents the patients' clinical data and procedural characteristics. Eleven (91.6%) patients had tachycardia upon enrolment, 12 (100%) had hypoxemia, and 3 (25%) required vasopressor support to maintain SBP > 90 mm Hg (Supplementary Table 2). Levels of troponin T were elevated in all patients with a median value of 0.143 (0.078 to 0.2) ng/ml, and the median RV/LV ratio was 1.5 (1.3 to 1.6).

The median time from the onset of symptoms to the USAT initiation was 12 (7.5 to 18) hours (Supplementary Table 3). All patients were anticoagulated with unfractionated heparin before the USAT start for a median period of 5.5 (4 to 12.5) hours and continued throughout the procedure up to the 3rd (2 to 4) postprocedural day. Anticoagulation was further continued with the use of direct oral

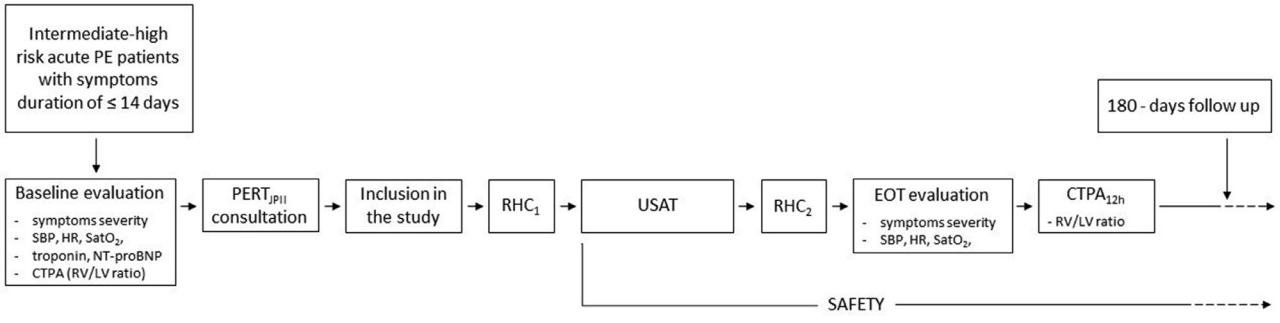

Figure 1. Study protocol diagram. CTPA = computed tomography pulmonary angiography; EOT = end of treatment; HR = heart rate; PE = pulmonary embolism; PERT = pulmonary embolism response team; RHC = right heart catheterization; RV/LV ratio = right to left ventricular diameters ratio; $SatO_2$ = arterial blood saturation; SBP = systolic blood pressure; USAT = ultrasound-assisted, catheter-directed, very low-dose, short-time duration thrombolysis.

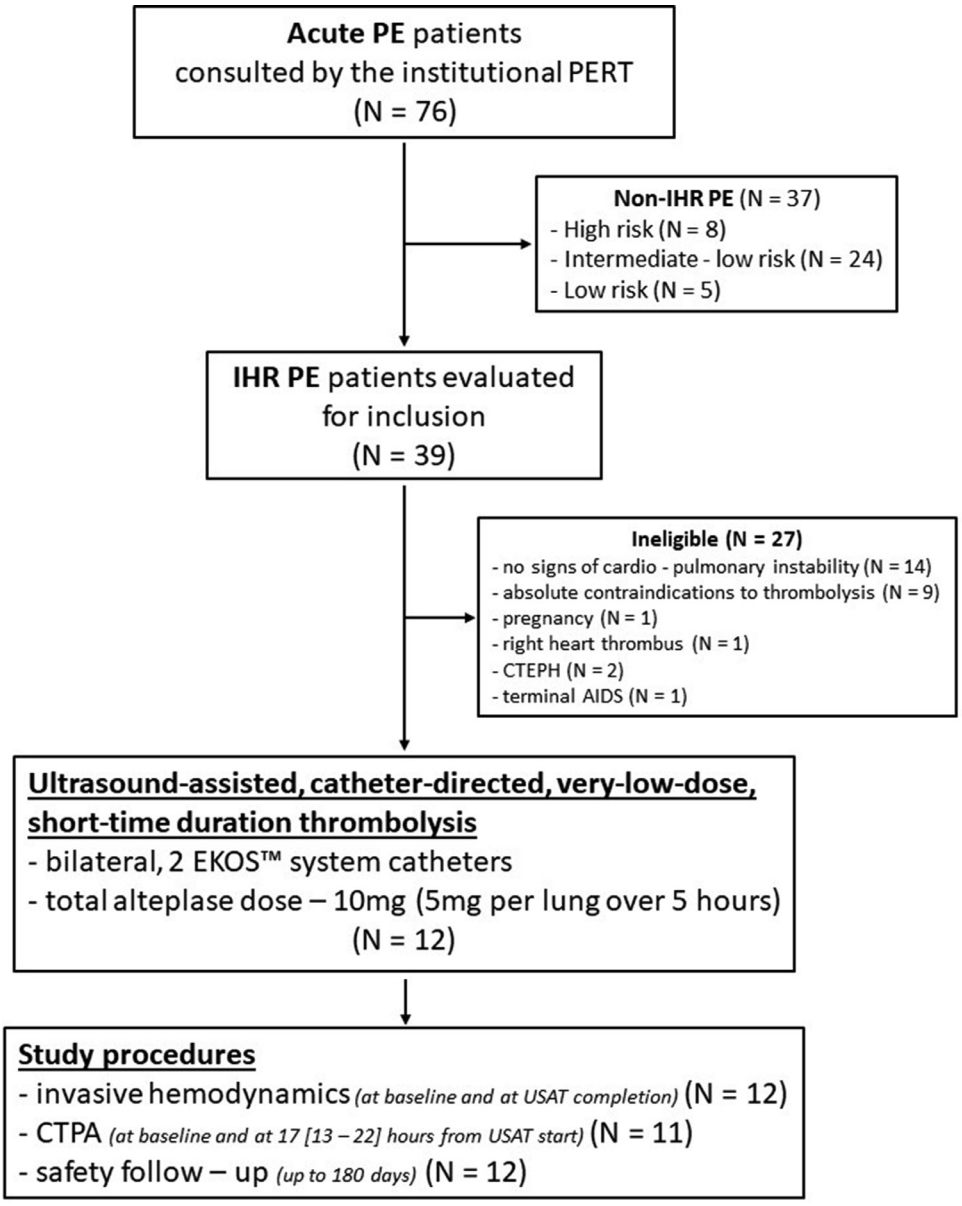

Figure 2. Study flow chart. CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; IHR = intermediate-high risk; PE = pulmonary embolism; PERT = Pulmonary Embolism Response Team; USAT = ultrasound-assisted, catheter-directed, very low-dose, short-time duration thrombolysis.

anticoagulants in 9 (75%) patients, low molecular weight heparin in 2 (16.7%) and vitamin K antagonist in 1 (8.3%) for the complete 180-day follow-up. The procedure of USAT was performed with the use of 2 EKOS system catheters in all patients, inserted bilaterally. Every patient received a total of 10 mg of alteplase (5 mg per lung), during the 5-hour infusion. No device-related complications were recorded.

At completion of USAT all patients reported remission of resting symptoms, decrease in HR from 115 (111 to 120) beats/min to 94 (83 to 100) beats/min ($p = 0.002$), and increase in $SatO_2$ from 89 (88 to 89) % to 95 (93 to 96) % ($p = 0.002$). Vasopressor support had been discontinued by the end of USAT in all 3 patients requiring it at baseline. Hemodynamic parameters improved significantly (Figure 3). Systolic PAP and mPAP decreased and CI improved (sPAP: from 53 (46 to 59) mm Hg to 38 (28 to 41) mm Hg, $p = 0.002$; mPAP: from 30 (28 to 32) mm Hg to 22 (16 to 25) mm Hg, $p = 0.002$; CI: from 1.67 (1.53 to 1.83) l/min/m^2 to 2.18 (1.93 to 2.37) l/min/m^2, $p = 0.002$). The follow-up CTPA was performed in all but 1 patient with poor renal function, at median 17 (13 to 22) hours after the initiation of USAT. Comparison of the follow-up CTPA to baseline showed a significant decrease in the RV/LV ratio, from 1.44 (1.32 to 1.58) to 0.98 (0.95 to 1.14) ($p = 0.003$). The median length of hospital stay was 7 days (4.5 to 8.5).

There were no in-hospital or 180-day follow-up deaths observed in the study (Table 1). In all patients cardiopulmonary stabilization was achieved and no decompensations

Table 1
Patients' clinical data, procedural characteristics and safety outcomes

	Gender, age	Symptom duration / Pre-procedural anticoagulation (*hours*)	PESI/sPESI	Thrombi location	No. of catheters inserted	Fluoroscopy time (min)	Total alteplase dose (mg)	Hospitalization [days]	Safety outcome / adverse events
1	*M*, 24	12 / 5	94 / 2	Saddle & BC	2	9	10 (5 per lung)	8	None
2	*F*, 30	17 / 12	90 / 2	BC	2	10.5	10 (5 per lung)	4	None
3	*M*, 37	58 / 55	106 / 2	BC	2	10.5	10 (5 per lung)	6	None
4	*F*, 50	12 / 10	90 / 2	BC	2	6.5	10 (5 per lung)	3	None
5	*F*, 55	9 / 7	95 / 2	BC	2	5	10 (5 per lung)	13	Access site bleeding
6	*M*, 62	6 / 4	142 / 3	Saddle & BC	2	8.5	10 (5 per lung)	4	None
7	*M*, 66	2.5 / 2	156 / 4	Saddle & BC	2	7	10 (5 per lung)	9	None
8	*M*, 67	35.5 / 33	147 / 3	BC	2	11	10 (5 per lung)	3	None
9	*M*, 68	6.5 / 4	118 / 1	Saddle & BC	2	14	10 (5 per lung)	6	None
10	*M*, 72	13 / 3.5	142 / 2	BC	2	39.5	10 (5 per lung)	8	None
11	*F*, 74	8.5 / 5.5	134 / 2	Saddle & BC	2	12	10 (5 per lung)	9	None
12	*F*, 81	19 / 4	171 / 5	BC	2	9	10 (5 per lung)	8	None

BC = bilateral thrombi, centrally located in the major left and right pulmonary artery; M = male; F = female; PESI (sPESI) = pulmonary embolism severity index (simplified); Saddle = thrombus located on the bifurcation of the pulmonary trunk.

happened. We recorded 1 access-site bleeding event, which occurred when the patient removed the compression dressing individually, and it was resolved after applying re-compression. Eventually, 2 blood units were transfused at the 5th postoperative day to restore the hemoglobin concentration. Further hospital stay of this patient was uneventful.

Discussion

We report in our study that reduced-dose USAT with a total 10 mg of alteplase delivered within a 5-hour infusion resulted in substantial improvement of pulmonary and RV hemodynamics and clinical stabilization in acute PE patients at IHR of early death with a very low periprocedural risk. This is, to our best knowledge, the first study reporting on the acute hemodynamic effects of very low-dose USAT of short time duration.

Although favorable outcomes of USAT have been previously shown, most of the evidence comes from studies which used higher average doses of alteplase of 20 to 24 mg, delivered within a longer 12- to 24-hour period.[3–6] Recently, a multicenter, randomized parallel-group study found that also lower alteplase doses and shorter infusion protocols may bring benefit to IHR-PE patients in terms of reduction of RV dilatation.[7] However, the effects on pulmonary hemodynamics have not been reported. The authors evaluated 4 different USAT protocols. Alteplase dose as low as 8 mg total delivered within 2 hours was associated with a decrease in the RV/LV ratio by 0.40 ± 0.37 as measured in the CTPA after 48 hours. The other 3 protocols, 8 mg over 4 hours, 12 mg over 6 hours, and 24 mg over 6 hours, showed similar improvement (-0.35 ± 0.27, -0.42 ± 0.32, -0.48 ± 0.51, respectively). Correspondingly, in our study the total alteplase dose of 10 mg over 5 hours resulted in a RV/LV ratio decrease by a median of 0.39 (0.54 to 0.34). This improvement was observed already at 17 (13 to 22) hours after therapy initiation. Taking into account that the rate of the RV/LV ratio improvement assessed at 24 to 48 hours showed to be at similar levels in studies using higher doses and USAT durations (-0.35 [95% CI -0.40 to -0.30]), it may suggest that the benefits of USAT could be more immediate. Evaluation of the RV/LV ratio at the timepoints distant to the termination of the USAT therapy may therefore not reflect a direct effect of the method. Thus, we chose in our study to use invasive hemodynamic parameters recorded before USAT start and at USAT completion as the measures of the tested USAT protocol efficacy. Moreover, PA pressures have been found to be valuable prognostic markers in acute PE.[11] We found in our study a significant improvement in CI, sPAP, and mPAP during USAT treatment. Previous studies showed that an average ultrasound-assisted alteplase dose of 20 to 24 mg delivered within 12 to 24 hours was associated with improvement similar to that achieved in our study (CI by a mean of 0.68 [95% CI 0.49 to 0.87]) l/min/m^2, reductions in sPAP by 16.69 (95% CI -19.73 to -13.65) mm Hg and mPAP by 12.13 (95% CI -14.67 to -9.59) mm Hg.[3,12,13] This may suggest that the hemodynamic effect of USAT can be achieved at lower alteplase doses and USAT prolongation may not always be needed. This concept may also be supported by the observation that HR, a clinical

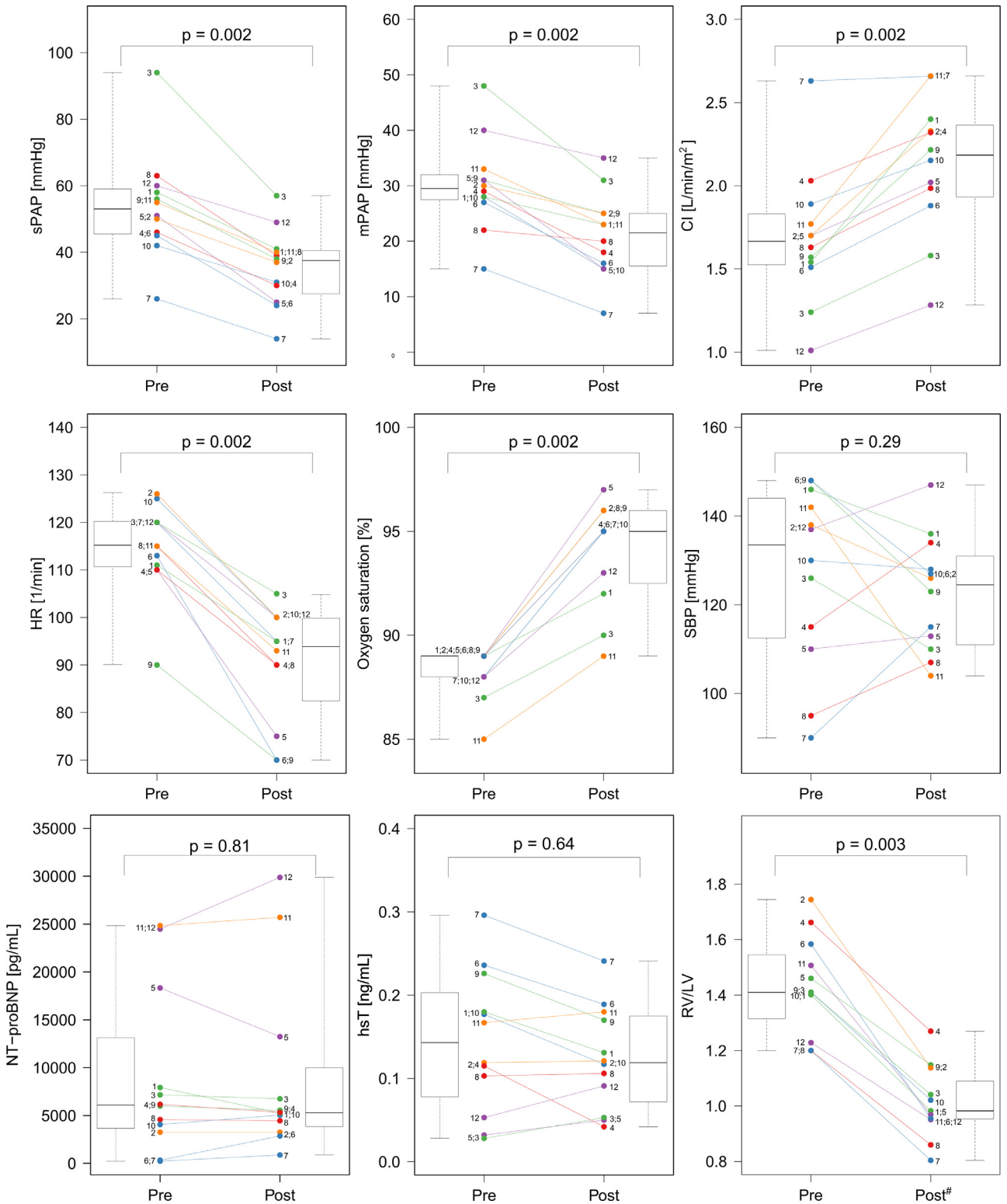

Figure 3. Changes in primary and secondary efficacy measures from baseline (Pre) to completion (Post) of the ultrasound-assisted, catheter-directed, very low-dose, short-time duration thrombolysis (USAT). # = measurement of the post treatment RV/LV ratio was conducted 17 (13 − 22) hours after the initiation of USAT; CI = cardiac index; HR = heart rate; hsT = high sensitivity troponin T; mPAP = mean pulmonary artery pressure; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RV/LV = ratio of right to left ventricular diameters; SBP = systolic blood pressure; sPAP = systolic pulmonary artery pressure.

sign of RV dysfunction, significantly decreased during the treatment parallelly with a significant improvement in $SatO_2$.

Importantly, decreasing the alteplase dose and USAT duration was not associated with increased risk of cardiopulmonary decompensation or death. In fact, in all 3 patients requiring pharmacological circulatory support at baseline it had been discontinued by the end of USAT. Similarly to most previous studies with various USAT regimens, we did not observe any intracranial bleeding, deaths, or recurrent PE. We experienced 1 access-site bleeding event due to patient incompliance. When compared with previous studies, the rate of bleeding events in our study was at a similar level.

Results of our investigation show that reduced-dose and short-time duration USAT was safe and effective in reversing RV dysfunction and impaired pulmonary hemodynamics. Although we found a clear benefits of a tested USAT regimen, it may not always suit all IHR-PE patients. Apart from the dosing, the optimal timing of the procedure has not been established yet. We managed in our study to implement the USAT at a median time of 12 (7.5 to 18) hours from the onset of symptoms and after 5.5 (4 to 12.5) hours of anticoagulation. Previous data support earlier (< 24 to 48 hours after presentation) rather than delayed (> 48 hours) initiation of USAT in terms of improvement of pulmonary hemodynamics and RV function.[14] Nonetheless, a larger study is required to prove our approach regarding both USAT dosing and timing. Also, it remains unknown whether such a reduced-dose USAT protocol could affect the incidence of long-term acute PE consequences such as post-PE syndrome or chronic thromboembolic pulmonary hypertension .[15,16]

There are several limitations to our analysis. The results of our study should be taken with caution due to the limited number of study participants. As the study was a nonrandomized, 1-arm, observational investigation it remains unknown whether our approach is more effective than heparin-only treatment. As well, we did not directly compare the very low-dose USAT protocol with the most commonly used higher USAT doses, however indirect comparison of published data may suggest an existing equivalence.

Although there exists some evidence on the efficacy of reduced-dose USAT regimens, to the best of our knowledge their effect on pulmonary hemodynamics has not been reported yet. Our study used 1 of the lowest-dose alteplase and shortest-duration USAT protocols ever tested. In order to evaluate an immediate effect of the investigated USAT regimen of reduced dose and duration, we used invasive pulmonary hemodynamic parameters measured before and directly at completion of treatment. Despite the limited number of study patients, we believe that the consistency of the results validates our observations and helps to improve understanding of potential benefits of such a USAT approach.

In conclusion, USAT of reduced dose and duration improved pulmonary hemodynamics and cardiac function leading to cardiopulmonary stabilization in patients with IHR- PE at a minimal risk of bleeding complications.

Authors' Contribution

Jakub Stępniewski: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - Original Draft, Visualization, Project administration; Grzegorz Kopeć: Conceptualization, Methodology, Investigation, Resources, Supervision Writing - Review & Editing, Funding acquisition; Piotr Musiałek: Conceptualization, Methodology, Investigation, Resources, Supervision Writing - Review & Editing, Funding acquisition; Wojciech Magoń: Formal analysis, Data Curation, Investigation, Resources, Writing - Review & Editing; Kamil Jonas: Investigation, Resources, Writing - Review & Editing; Marcin Waligóra: Investigation, Resources, Writing - Review & Editing; Dorota Sobczyk: Investigation, Resources, Supervision Writing - Review & Editing, Funding acquisition; Piotr Podolec: Investigation, Resources, Supervision Writing - Review & Editing, Funding acquisition.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary Material

Supplementary data related with this article can be found, in the online version, at

Supplementary materials

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