Relationship of left ventricular outflow tract velocity time integral to treatment strategy in submassive and massive pulmonary embolism

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Abstract

Pulmonary embolism is associated with high rates of mortality and morbidity. It is important to understand direct comparisons of current interventions to differentiate favorable outcomes and complications. The objective of this study was to compare ultrasound-accelerated thrombolysis versus systemic thrombolysis versus anticoagulation alone and their effect on left ventricular outflow tract velocity time integral. This was a retrospective cohort study of subjects ≥18 years of age with a diagnosis of submassive or massive pulmonary embolism. The primary outcome was the percent change in left ventricular outflow tract velocity time integral between pre- and post-treatment echocardiograms. Ultrasound-accelerated thrombolysis compared to anticoagulation had a greater improvement in left ventricular outflow tract velocity time integral, measured by percent change. No significant change was noted between the ultrasound-accelerated thrombolysis and systemic thrombolysis nor systemic thrombolysis and anticoagulation groups. Pulmonary artery systolic pressure only showed a significant reduction in the ultrasound-accelerated thrombolysis versus anticoagulation group. The percent change of right ventricular to left ventricular ratios was improved when systemic thrombolysis was compared to both ultrasound-accelerated thrombolysis and anticoagulation. In this retrospective study of submassive or massive pulmonary embolisms, left ventricular outflow tract velocity time integral demonstrated greater improvement in patients treated with ultrasound-accelerated thrombolysis as compared to anticoagulation alone, a finding not seen with systemic thrombolysis. While this improvement in left ventricular outflow tract velocity time integral parallels the trend seen in mortality outcomes across the three groups, it only correlates with changes seen in pulmonary artery systolic pressure, not in other markers of echocardiographic right ventricular dysfunction (tricuspid annular plane systolic excursion and right ventricular to left ventricular ratios). Changes in left ventricular outflow tract velocity time integral, rather than echocardiographic markers of right ventricular dysfunction, may be considered a more useful prognostic marker of both dysfunction and improvement after reperfusion therapy.

Introduction

Pulmonary embolism (PE) is a subset of venous thromboembolism that is associated with high rates of mortality and morbidity. Overall, 30-day and 1-year mortality has been

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reported at 3.9 and 12.9%, respectively,[1] with mortality rates increasing with age and severity of PE. Patients who survive an initial event may have marked impairment in quality of life and are at increased risk for development of long-term complications such as chronic thromboembolic pulmonary hypertension.[2–4]

The treatments available for PE are currently individualized based on clinical parameters such as hemodynamic status, location of PE, personnel and resource availability to perform advanced PE management strategies, and risks associated with each treatment modality.[4] PE management has previously been limited to systemic thrombolysis, transcatheter mechanical clot fragmentation with or without thrombectomy, infusion catheters, or anticoagulation alone. The PEITHO trial, which is the largest thrombolytic trial in PE patients to date, studied normotensive intermediate risk PE patients randomized to heparin plus tenecteplase versus heparin plus placebo. This pivotal trial showed that the systemic thrombolysis reduced the composite outcome of all-cause mortality and hemodynamic compromise but increased the risk of major hemorrhage and stroke.[5] In the same year the PEITHO study was published, the EKOS[TM] ultrasonic device was approved by the FDA, which combines catheter-delivered fibrinolytic therapy with mechanical disruption of the thrombus via ultrasound therapy, or ultrasound-accelerated thrombolysis (USAT). Several clinical trials focusing on catheter-based management of PE have subsequently been published including the ULTIMA,[6] SEATTLE,[7] PERFECT,[8] and OPTALYSE[9] trials. Although much smaller than the PEITHO trial, each has shown hemodynamic improvement, including a decreased mean right ventricular to left ventricular (RV/LV) diameter and decreased mean pulmonary artery systolic pressure (PASP) in patients who received USAT. However, only ULTIMA compared USAT to anticoagulation alone, while PERFECT allowed the use of any infusion catheters with no difference identified between USAT and infusion catheters without ultrasound.[6,8] Bleeding rates were favorable with a cumulative three major bleeding events in the studies and one intracranial hemorrhage in the OPTALYSE PE high dose thrombolytic cohort.[9]

Favorable outcomes as well as important complications have been reported independently with both systemic and catheter-based thrombolytic interventions. Therefore, it is of the utmost importance that we begin to try and understand direct comparisons of these interventions to better inform clinical decision making in the acutely ill PE patient. Hemodynamic markers such as a decrease in mean pulmonary artery pressure and increase in cardiac output have been used as markers of clinical improvement with thrombolysis in the acute setting.[10] These parameters require invasive measurement with a right heart catheter which is not practical in clinical practice. Multiple echocardiographic parameters including RV/LV ratio, reduction in RV end-diastolic diameter, and increase in tricuspid annular plane systolic excursion (TAPSE) have also been assessed as markers of clinical improvement.[11,12] However, the complex geometry of the right ventricle can make reproducible measurements of RV size parameters and functionality challenging, a problem compounded in the acutely ill patient. The driver of mortality in submassive and massive PE patients is a compromise of cardiac output due to obstructive shock. Left ventricular outflow tract velocity time integral (LVOT VTI), an echocardiographic measurement of stroke volume (SV), a component of cardiac output, has been demonstrated to be a predictor of outcomes in acute PE, including death, cardiac arrest, shock or need for reperfusion.[13]

The objective of this study was to compare the effects of systemic thrombolytics versus catheter-directed thrombolytics versus anticoagulation alone on LVOT VTI as well as weighing composite bleeding outcomes in patients with submassive and massive PE.

Methods

This was a retrospective cohort study conducted at a large academic medical center using electronic health record data. Patients were included in the study if they were greater than 18 years of age with a diagnosis of acute submassive or massive PE according to American Heart Association guideline definitions.[14] Patients were excluded if they were pregnant, had a history of ICH, were actively bleeding, had a known coagulation disorder, or had a history of stroke or transient ischemic attack, head trauma, or other active intracranial disease within three months prior (see Appendix A for full inclusion and exclusion criteria).

Eligible patients were identified utilizing International Classification of Diseases 9 and 10 codes for acute PE. Further eligibility was determined by searching for specific drug orders such as "alteplase 24 mg/250 ml, alteplase 50–100 mg IV push, and heparin 25,000 units/250 ml." Patients were then chosen from this list utilizing an internet-based randomization tool. Once inclusion and exclusion criteria were assessed, data were obtained via manual chart review. Patients in the USAT group were treated with an intracatheter alteplase (tPA) bolus of 2–5 mg (per catheter if bilateral catheters were used) followed by an infusion at a rate of 0.5–1 mg/h/catheter for 6–24 h via the EKOS[TM] system per physician discretion based on patient's risk of bleeding and hemodynamic compromise. Patients in the systemic tPA group received 50–100 mg over 1–2 h if they had a pulse. Patients who were pulseless received a 50 mg bolus, followed by another 50 mg given over 1 h. All three groups received continuous infusion heparin, which was titrated to goal a PTT goal of 63–91 or anti-Xa goal of 0.3–0.7. Prior to discharge, patients in all groups were transitioned to a long-term anticoagulant choice consisting of rivaroxaban, apixaban, dabigatran, warfarin, or low-molecular weight heparin.

The primary clinical outcome was the percent change in LVOT VTI between pre- and post-treatment echocardiograms. LVOT VTI was calculated by placing the pulsed Doppler sample volume in the outflow tract below the

aortic valve and recording the velocity (cm/s). When the velocity signal is integrated with respect to time, the distance blood moves with each systole is calculated in cm/systole.[15] Secondary clinical outcomes included percent change in RV/LV end-diastolic ratios, TAPSE and PASP between pre- and post-treatment echocardiograms, as well as composite bleeding per GUSTO criteria (see Appendix A for a full list of outcomes). One investigator, in a blinded fashion, obtained end-diastolic RV/LV ratios from the echocardiographic apical four-chamber view. Subannular measurements were obtained 1 cm above and parallel to the tricuspid annular line, which was drawn at the septal insertion point of tricuspid valve, perpendicular to the interventricular septum line.

Table 1. Characteristics of the patients at baseline.

Characteristic	USAT ($N = 20$)	Systemic tPA ($N = 16$)	Anticoagulation alone ($N = 15$)	P
Age	60.6 ± 17.9	58.8 ± 16.2	63.3 ± 15.0	0.74
Gender, n (%)				0.64
Male	10 (50)	6 (37.5)	8 (53.3)	
Race, n (%)				0.986
African American	5 (25)	5 (31.3)	6 (40)	
Caucasian	14 (70)	9 (56.2)	5 (33.3)	
Hispanic	0 (0)	0 (0)	0 (0)	
Other	0 (0)	2 (12.5)	2 (13.3)	
Unknown	1 (5)	0 (0)	2 (13.3)	
HFrEF, n (%)	1 (5.3)	2 (13.3)	2 (13.3)	0.661
Atrial fibrillation, n (%)	0 (0)	1 (6.7)	3 (20)	0.103
Mitral valve regurgitation, n (%)				0.132
Trivial/none	17 (94.4)	12 (85.7)	9 (64.3)	
Mild	1 (5.6)	1 (7.1)	3 (21.4)	
Moderate	0 (0)	1 (7.1)	0 (0)	
Severe	0 (0)	0 (0)	2 (14.3)	
Tricuspid valve regurgitation, n (%)				0.595
Trivial/none	4 (22.2)	6 (46.2)	6 (42.9)	
Mild	8 (44.4)	3 (23.1)	3 (21.4)	
Moderate	5 (27.8)	3 (23.1)	5 (35.7)	
Severe	1 (5.6)	1 (7.7)	0 (0)	
Prior DVT, n (%)	4 (21.1)	4 (26.7)	4 (26.7)	0.906
Prior PE, n (%)	1 (5.3)	4 (26.7)	7 (46.7)	0.020
History of cancer, n (%)	5 (26.3)	1 (6.7)	5 (33.3)	0.189
Pulmonary embolism				<0.001
Submassive	17 (85)	3 (18.8)	10 (66.6)	
Massive	3 (15)	13 (81.2)	5 (33.3)	
Cardiac arrest, n (%)	1 (5)	7 (43.4)	1 (6.7)	0.004
LVOT VTI on admit (cm)	14.26 ± 4.11	13.51 ± 3.72	15.50 ± 3.28	0.341
TAPSE on admit (cm)	1.53 ± 0.41	1.34 ± 0.78	1.69 ± 0.54	0.572
PASP on admit (mmHg)	48.69 ± 18.59	59.38 ± 18.84	51.10 ± 15.44	0.406
RV/LV ratio, initial	1.09 ± 0.23	1.22 ± 0.25	1.00 ± 0.35	0.210
Troponin I, initial (ng/ml)	0.65 ± 1.09	0.49 ± 0.54	0.27 ± 0.38	0.401
Troponin I, repeat (ng/ml)	0.99 ± 1.14	1.18 ± 1.27	0.35 ± 0.61	0.114
BNP on admit (ng/l), n (%)				0.445
<100	4 (26.7)	2 (13.3)	1 (9.1)	
>100	11 (73.3)	13 (86.7)	10 (90.9)	

BNP: brain natriuretic peptide; DVT: deep vein thrombosis; HFrEF: heart failure with reduced ejection fraction; LVOT VTI: left ventricular outflow tract velocity time integral; PASP: pulmonary artery systolic pressure; PE: pulmonary embolism; RV/LV: right ventricular to left ventricular; TAPSE: tricuspid annular plane systolic excursion; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.
Plus-minus values are means ±SD. N (%) may not correlate with sum of each group due to missing data.

Continuous data were analyzed using one-way ANOVA, categorical data were analyzed using Kruskal–Wallis ANOVA, and nominal data were analyzed using Chi-squared test with Bonferroni adjustment. A p-value of <0.05 was considered statistically significant. A sample size of convenience was utilized. All analyses were done using SPSS Version 23.

Results

A total of 225 patients were screened from January of 2010 through January of 2019. Of these patients that met inclusion criteria, 20 were treated with USAT, 16 with systemic tPA
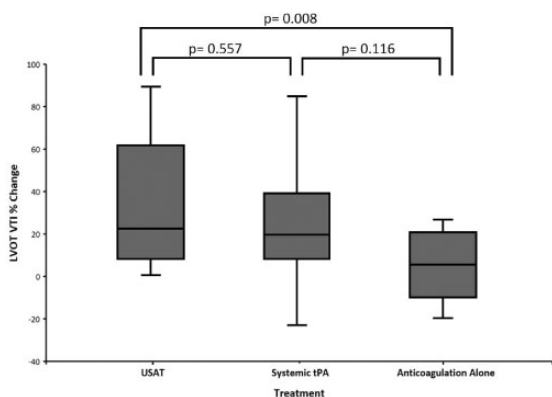

Fig. 1. The box represents the interquartile range, while the whiskers represent minimum and maximum data. LVOT VTI: left ventricular outflow tract velocity time integral; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.

therapy, and 15 with anticoagulation alone. The remaining 174 patients were excluded due to missing LVOT VTI values on pre- or post-echocardiograms and intracranial or intraspinal disease within three months prior to study treatment (Fig S1 of Appendix B). The mean age of the study population was 61 years old. The anticoagulation alone group had a higher rate of previous PE compared to the other two groups. There were significantly more patients with massive PE in the systemic tPA group compared to the other two groups. The median time until post-treatment echocardiogram was two days in both the USAT and systemic tPA groups and six days in the anticoagulation (AC) group (p = 0.032). LVOT VTI and other baseline hemodynamic parameters did not statistically differ between the three groups (Table 1 and S1 in Appendix B). However, the systemic tPA group had a lower TAPSE at baseline. In addition, this group appeared to have a larger distribution of patients with moderate to severe RV dilation at baseline.

When comparing the primary outcome between USAT and anticoagulation alone, the percent change in LVOT VTI was significantly higher in the USAT group (37.3 versus 3.7%, p = 0.008). Likewise, there was improvement in LVOT VTI favoring systemic tPA compared to anticoagulation alone, but it did not reach statistical significance. There was no difference in the primary outcome when comparing USAT to systemic tPA (Fig. 1 and Table 2). Although the changes did not reach statistical significance, percent change in left ventricular (LV) Doppler-measured SV and cardiac index (CI) mirrored LVOT VTI findings (Table 2).

With regard to echocardiographic measures of RV dysfunction, there were contrasting findings. Improvements in

Table 2. Echocardiographic hemodynamic outcomes.

Characteristic	USAT (N = 20)	Systemic tPA (N = 16)	Anticoagulation alone (N = 15)	P
LVOT VTI pre-echo	14.26 ± 4.11	13.51 ± 3.72	15.50 ± 3.94	0.341
LVOT VTI post-echo	18.49 ± 3.19	16.65 ± 4.87	16.29 ± 5.20	0.281
LVOT VTI % change	37.35 ± 39.91	26.46 ± 29.13	3.67 ± 16.80	0.010
RVOT VTI pre-echo	8.20 ± 3.23	6.98 ± 2.06	10.32 ± 5.17	0.147
RVOT VTI post-echo	12.77 ± 3.82	10.15 ± 3.81	9.80 ± 3.71	0.122
RVOT VTI % change	87.24 ± 9.19	16.12 ± 3.80	28.33 ± 6.38	0.167
LV Doppler-measured SV pre-echo	55.70 ± 20.61	42.77 ± 15.57	54.64 ± 19.80	0.124
LV Doppler-measured SV post-echo	67.90 ± 17.45	50.57 ± 22.56	54.69 ± 22.74	0.045
LV Doppler-measured SV % change	37.31 ± 5.92	18.46 ± 3.17	1.51 ± 3.04	0.109
Cardiac index pre-echo	2.50 ± 1.06	1.8 ± 0.70	2.80 ± 1.02	0.034
Cardiac index post-echo	2.84 ± 1.00	2.1 ± 0.67	2.67 ± 1.71	0.196
Cardiac index % change	36.29 ± 9.02	35.01 ± 10.01	− 1.79 ± 5.61	0.412
Heart rate pre-echo	96 ± 15	94 ± 29	102 ± 23	0.543
Heart rate post-echo	85 ± 16	86 ± 17	88 ± 19	0.856

echo: echocardiogram; LV: left ventricle; LVOT VTI: left ventricular outflow tract velocity time integral; RVOT VTI: right ventricular outflow tract velocity time integral; SV: stroke volume; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.
Plus-minus values are means ±SD.

PASP paralleled the LVOT VTI findings (Fig. 2). There were no differences in percent change in TAPSE nor RVOT VTI among the three groups (Fig. 3 and Table 2). Compared to pre-intervention, RV/LV ratios in the systemic tPA group were significantly improved post intervention (1.23 versus 0.92, p = 0.002). The percent change of RV/LV ratios was also improved when systemic tPA was compared to both the USAT group (24.8% versus 1.5%, p = 0.025) and anticoagulation alone group (24.8% versus 6.6%, p = 0.023) (Fig. 4).

Baseline heart rate was significantly lower in the systemic tPA group. Heart rate appears to normalize faster, in about 12 hours, in the USAT and systemic tPA groups compared to anticoagulation alone (Fig S4 of Appendix B). However, there was no difference in heart rate at the time of both pre- and post-echocardiogram between all groups. The mean SBP and SpO$_2$ were significantly lower at baseline in the systemic tPA group (Fig S2 and S3 of Appendix B). The

systemic tPA group required more vasopressors and mechanical ventilation at every time interval except at 48 hours. There was no difference among all three groups in the number of patients completely weaned off vasopressors beyond 48 hours (Tables S2 and S3 of Appendix B).

There was no difference in composite bleeding between all three groups. However, the systemic tPA group had a larger distribution of patients with moderate–severe bleeding, which may be clinically relevant (Table 3). The systemic tPA group had a larger hospital mortality rate and longer ICU length of stay (LOS) compared to the other two groups. Hospital LOS was shorter in the USAT group compared to both systemic tPA and anticoagulation alone. USAT had a longer time until treatment initiation, but a shorter time until long-term anticoagulation transition (Table 3).

Discussion

Due to the adverse effects of thrombolytic therapy and an unproven benefit on mortality in certain populations, if the clinical decision is made to pursue thrombolysis of acute PE, it is essential that the PE community knows how to best optimize drug delivery and reduce systemic adverse outcomes in order to provide the best possible care for PE patients. This trial demonstrates that when directly comparing USAT with systemic thrombolysis, there are similar effects on the restoration of the echocardiographic measurement of SV. Furthermore, when comparing the effect of thrombolysis on LVOT VTI to the control group, anticoagulation only, USAT appears to have a more favorable response than systemic tPA. This improvement in LVOT VTI correlates with the improvements in PASP, LV Doppler-measured SV, and CI, but not with other markers of echocardiographic RV dysfunction such as TAPSE, RVOT VTI, or RV/LV ratios. These discrepancies may be due to differences in the underlying population that cannot be fully controlled. One could postulate the improved percent change in LVOT VTI with USAT to be a direct result
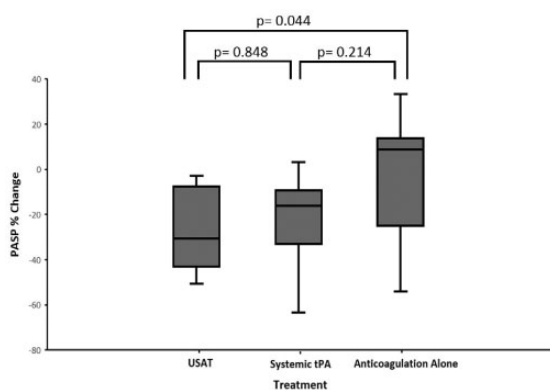

Fig. 2. The box represents the interquartile range, while the whiskers represent minimum and maximum data. PASP: pulmonary artery systolic pressure; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.
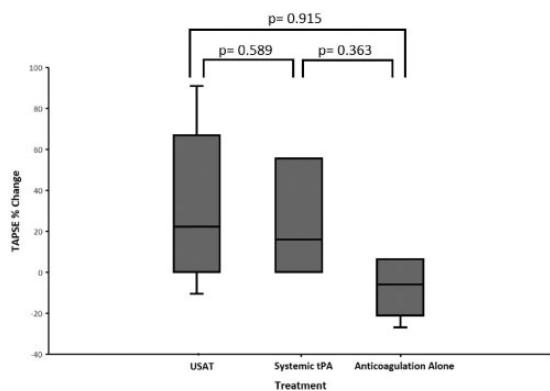

Fig. 3. The box represents the interquartile range, while the whiskers represent minimum and maximum data. TAPSE: tricuspid annular plane systolic excursion; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.
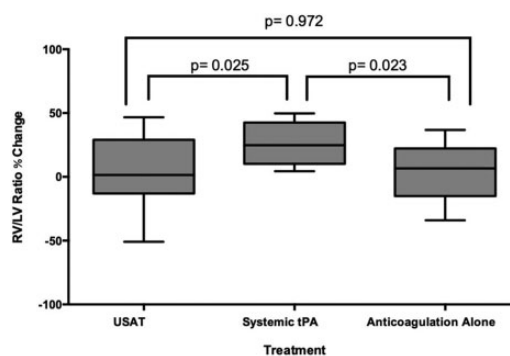

Fig. 4. The box represents the interquartile range, while the whiskers represent minimum and maximum data. RV/LV: right ventricular to left ventricular; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.

Table 3. Secondary outcomes.

Characteristic	USAT (N = 20)	Systemic tPA (N = 16)	Anticoagulation alone (N = 15)	P
Composite bleeding, n (%)				0.179
Mild	4 (20)	2 (12.5)	1 (6.7)	
Moderate	0 (0)	1 (6.3)	0 (0)	
Severe	0 (0)	2 (12.5)	0 (0)	
Hemodynamic collapse within seven days of treatment, n (%)	2 (10)	1 (6.3)	1 (6.7)	0.899
Hospital mortality, n (%)	1 (5)	5 (31.3)	0 (0)	0.013
ICU LOS (days), (mean ± std)	4.10 ± 1.68	7.50 ± 6.27	5.87 ± 3.07	0.050
Hospital LOS (days), (mean ± std)	8.20 ± 4.05	15.13 ± 13.03	14.73 ± 4.10	0.019
Time until post-treatment echo (days), (median, IQR)	2 (1.5–3)	2 (1–3)	6 (3–9)	0.032
Time until treatment initiation (hours), (mean ± std)	21.40 ± 21.42	7.98 ± 8.97	8.83 ± 12.33	0.023
Time until transition to long-term AC (hours), (mean ± std)	65.26 ± 38.98	94.10 ± 57.48	137.73 ± 84.41	0.006
Six-minute walk test at follow-up (m), (mean ± std)	472.00 ± 84.92	290.67 ± 158.48	354.00 ± 59.40	0.250

AC: anticoagulation; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; tPA: alteplase; USAT: ultrasound-accelerated thrombolysis.
N (%) may not correlate with sum of each group due to missing data.

of the local administration of drug therapy in combination with ultrasound thrombus disruption and propagation of drug distribution into fibrin clots.

This trial was not powered to detect a statistical difference in composite bleeding outcomes, but did find a higher distribution of patients who had moderate–severe bleeding in the group treated with systemic thrombolytic therapy. There were significantly more patients with massive PE, including cardiac arrest, in the systemic tPA group compared to the other two groups. As expected, there was a higher mortality rate, greater need for vasopressors and mechanical ventilation, and longer ICU and hospital LOS in the systemic tPA group, congruent with this patient populations severity of illness at baseline. Time until treatment initiation was significantly longer in the USAT group, likely due to catheterization lab preparation and patient transportation. In contrast, patients who received USAT were transitioned to long-term anticoagulant choices sooner, potentially hastening disposition. The long hospital LOS and delayed transition to long-term anticoagulation choice in the control group could potentially be contributed to comorbid conditions.

There are several limitations to this study. First, the retrospective nature of the study limits the availability of data, particularly follow-up data, and there is significant patient heterogeneity at baseline between the groups despite not meeting statistical significance. Second, a sample size of convenience was chosen, which does not allow for power calculations. Thus, the trend toward statistical significance of LVOT VTI percent change in the systemic tPA group when compared to AC may have crossed significance with an increasing population sample. Third, due to the retrospective nature of the study, the median time until post-treatment echocardiogram was two days in both the USAT and systemic tPA groups and six days in the AC

group. This difference in timing may allow for improvement in echocardiogram parameters in the AC group. In addition, it was difficult to control for disease severity, as the majority of patients who received systemic thrombolytics were more likely to be hemodynamically unstable at baseline. The increased use of vasopressors in the systemic tPA group likely confounds the interpretation of their baseline echocardiogram parameters. Finally, a significant number of patients were excluded due to missing echocardiogram data, potentially contributing to selection bias.

Conclusion

In conclusion, this retrospective study of acute submassive or massive PE demonstrated greater improvement in LVOT VTI in patients treated with USAT as compared to AC alone. However, this difference was not seen when comparing systemic tPA to AC alone. This change parallels trends seen in PASP, but not other markers of echocardiographic RV dysfunction (TAPSE and RV/LV ratios). As such, LVOT VTI, rather than echocardiographic markers of RV dysfunction, may be considered a more useful prognostic marker of both dysfunction and improvement after reperfusion therapy.

Contributorship

DA provided substantial contribution to conception and design of the work; acquisition, analysis, and interpretation of data; and drafting and revision of the final manuscript. TC, MC, and DSJ provided substantial contribution to conception and design of the

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Supplemental material

Supplemental material for this article is available online.

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