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Catheter-Directed Therapy for Acute Submassive Pulmonary Embolism: Summary of Current Evidence and Protocols

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Treatment of acute submassive pulmonary embolism (PE) with thrombolytic therapy remains an area of controversy. For patients who fail or who have contraindications to systemic thrombolysis, catheter-directed therapy (CDT) may be offered depending on the patient's condition and the available institutional resources to perform CDT. Although various CDT techniques and protocols exist, the most studied method is low-dose catheter-directed thrombolytic infusion without mechanical thrombectomy. This article reviews current protocols and data on the use of CDT for acute submassive pulmonary embolism.

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Background and Pathophysiology

The clinical diagnosis of acute submassive pulmonary embolism (PE) is acute PE resulting in right heart strain in the absence of systemic hypotension.[1] The pathophysiology of PE consists of direct physical obstruction of the pulmonary arteries resulting in hypoxemic vasoconstriction and release of potent pulmonary arterial vasoconstrictors, further increasing pulmonary vascular resistance and right ventricular (RV) afterload. Acute RV pressure overload may result in RV hypokinesis and dilation, tricuspid regurgitation, and ultimately RV failure. RV pressure overload may also result in increased wall stress and ischemia by increasing myocardial oxygen demand while simultaneously limiting its supply. If left untreated, severe RV failure leads to impaired left ventricular (LV) output, systemic arterial hypotension, and life-threatening hemodynamic shock.[2]

The appropriate diagnosis of submassive PE relies on early detection of right heart strain. Prompt identification of heart strain allows subsequent risk stratification to identify candidates for possible treatment escalation beyond anticoagulation. Echocardiography is an important modality that may detect RV dysfunction in the setting of acute PE. Important echo findings in patients with submassive PE include RV dilation, hypokinesis, interventricular septal flattening, and paradoxical motion toward the LV. RV-to-LV ratio can be determined in the left parasternal long-axis view or subcostal view and ratio of 0.9 or greater has been identified as an independent predictor of hospital mortality.[2-4]

Computed tomography imaging can also help identify patients with right heart strain in the context of simultaneous acute PE diagnosis. Similar to echocardiography, computed tomography angiography can be used to detect RV enlargement, flattening of the interventricular septum, and RV-to-LV diameter ratio. In addition to imaging findings, assessment of cardiac biomarkers and electrocardiographic abnormalities may also be used to help diagnose submassive PE. Classically, incomplete or complete right bundle-branch block, T-wave inversions in leads V1 through V4, and the combination of S wave in lead I, Q wave in lead III, and T-wave inversion in lead III (S1Q3T3) signify RV strain. Elevations in cardiac biomarkers including troponin, brain natriuretic peptide, and heart-type fatty acid–binding protein are associated with RV dysfunction and can help characterize the severity of submassive PE.[1-5] Various prognostic models based on these clinical and laboratory values, in particular the pulmonary embolism severity index score (PESI), have been used in the early risk stratification of PE to estimate the risk of adverse events[6,7] and to help identify appropriate candidates for treatment escalation.[8]

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Among all patients with acute PE, as many as 25% may be diagnosed with submassive PE; however, the optimal treatment strategy for these patients with submassive PE remains unclear.[9] Prior observational real-world studies have demonstrated up to 20% mortality risk within 3 months and a higher risk of rapid clinical deterioration among patients with submassive PE treated with anticoagulation alone.[5,10] In a randomized trial,[11] escalative therapy with systemic thrombolysis was associated with lower rates of hemodynamic compromise or collapse, and a recent meta-analysis of randomized controlled trials enrolling patients with submassive PE demonstrated a significant survival benefit with the use of systemic thrombolytic therapy; however, there was a higher risk of bleeding complications compared to anticoagulation alone.[12]

Endovascular Protocol for Submassive PE

Although the optimal protocol for treatment of acute submassive PE is still in evolution, the most common regimen for catheter-directed therapy (CDT) is local low-dose thrombolytic infusion without mechanical intervention.[2,13–16] The use of a low-dose thrombolytic infusion may mitigate the risk of major bleeding complications compared to full-dose systemic thrombolysis.[2] CDT infusion can be performed with either standard infusion catheters or with an ultrasound-assisted thrombolysis (USAT) catheter.[4,16–22] Depending on PE distribution, unilateral or bilateral pulmonary arterial catheters may be placed. Typical infusion rates consist of 1 mg/h through a single infusion catheter, 0.5-1 mg/h each through bilateral catheters, or a weight-based total dose of 0.01 mg/kg/h tPA. Regardless, some believe the rate should rarely exceed 1 mg/h. The need for concomitant full-dose anticoagulation is controversial as it may increase bleeding risk. At our institution, we rarely exceed 500 U of heparin during CDT infusions. Image-guided access and careful catheter placement are important to minimize the risk of procedure-related complications. Ideally, the catheters should be placed in the largest thrombosed vessel[13] for optimal effect.

Although mechanical CDT is indicated for acute massive PE, there are no large-scale studies to support routine use of catheter-directed mechanical thrombectomy for submassive PE, and doing so may be associated with risk of major complications.[23,24] However, for patients with submassive PE with contraindications to local pharmacologic thrombolysis, mechanical CDT alone with concomitant full-dose anticoagulation may be considered if treatment escalation is desired. This application is still considered experimental,[9] and the risk of complications from using mechanical devices in this subgroup remains unknown. Therefore, further prospective studies are needed to establish safety.

Current Literature

Patel et al recognized paucity in contemporary real-world data regarding use and outcomes comparing systemic thrombolysis with catheter-directed thrombolysis for PE and designed an observational study using National Inpatient Sample data from 2010-2012. The authors identified 110,731 patients hospitalized with PE and 1521 patients treated with thrombolysis. Using propensity score analysis, they compared outcomes between systemic thrombolysis and catheter-directed thrombolysis. They concluded that catheter-directed thrombolysis was associated with lower combined in-hospital mortality and intracerebral hemorrhage (1.37% vs 0.28%, $P = 0.09$). Interestingly, the authors found that among patients aged 75 or older, in-hospital mortality was significantly reduced in the catheter-directed thrombolysis group (26.05% vs 13.85%, $P = 0.04$),[15] suggesting that CDT may be beneficial in this patient population.

Table Recent Trials Focusing on Catheter-Directed Therapy for Submassive PE

Study	Year	Design	Massive (n)	Submassive (n)	Females (%)	Mean Age (y)	Technical Success (%)	Major Bleeds (%)	ICH (%)
Kuo et al[14] (PERFECT)	2015	Prospective	28	73	48	60	100	0	0
Piazza et al[3] (SEATTLE II)	2015	Prospective	31	119	51	59	98	10	0
Kucher et al[4] (ULTIMA)	2014	Prospective, RCT	0	30	63	64	100	0	0
Fuller et al[24]	2017	Retrospective	0	27	59	54	100	0	0
Liang et al[23]	2016	Retrospective	8	55	57	59	100	3	0
Bagla et al[22]	2015	Retrospective	0	45	44	57	100	4	0
Engelberger and Kucher[17]	2015	Retrospective	14	38	37	65	100	4	0
Dumantepe et al[18]	2014	Retrospective	6	16	41	54	100	0	0
Kennedy et al[19]	2013	Retrospective	12	48	42	61	100	0	0
Total			99	451					

ICH, intracerebral hemorrhage; RCT, randomized controlled trial.