# APPLIED
# PHARMACOLOGY

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# Alteplase for the Treatment of Pulmonary Embolism
## A Review

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**ABSTRACT**
Pulmonary embolism can present with a wide range of symptoms, from asymptomatic to cardiac arrest, making diagnosis challenging. Alteplase is a fibrinolytic that is indicated for the treatment of pulmonary embolism in intermediate- and high-risk patients. Controversy exists as to the patient population that will benefit most from fibrinolytic therapy, as well as the proper dose and administration technique. The patient's risk of bleeding should be weighed against the potential benefits of treatment in light of the clinical presentation because of the high mortality rate associated with pulmonary embolism. Nurses at the bedside must monitor for signs of bleeding when alteplase is administered. Fibrinolytic therapy will frequently be started in the emergency department, and the nurse must ensure that alteplase is administered in a safe and effective manner. This review discusses the clinical evidence for alteplase in pulmonary embolism and its specific role in treatment. **Key words:** *alteplase, bleeding, hemodynamics, pulmonary embolism*

VENOUS THROMBOEMBOLISM (VTE) is a disorder in which blood clots inappropriately, causing a deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE). Acute PE is a life-

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threatening complication that occurs in more than 200,000 people in the United States per year (Stein & Matta, 2012). In Europe, epidemiological data estimate that VTE causes 317,000 deaths per year, with 59% of these being from PE (Konstantinides et al., 2014). Venous thromboembolism has been previously identified as the leading cause of preventable hospital mortality (Martino et al., 2006). Untreated DVT can result in PE in 50%–79% of patients (Kearon, 2003; Sandler & Martin, 1989). Pulmonary embolism is the third leading cause of mortality in hospitalized patients, with 90-day rates reaching 8.7%–17.6% (Goldhaber & Elliott, 2003; Goldhaber, Visani, & De Rosa, 1999; Laporte et al.,

2008). Because of the spectrum of clinical presentation, the European guidelines for the treatment of PE suggest replacing the commonly used terms "massive," "submassive," and "nonmassive" with the risk of death due to PE: high-risk, intermediate-risk, and low-risk, respectively (see Table 1; Jaff et al., 2011; Konstantinides et al., 2014). Replacing the vague, ambiguous terms with objective terms to help stratify patients based on risk factors could lead to earlier identification and treatment. There are a multitude of risk factors (see Table 2) that increase the risk of VTE and subsequently the risk of PE (Aujesky et al., 2006; Darze et al., 2005; Heit et al., 2002; Laporte et al., 2008; Rogers et al., 2012; Sorensen et al., 2011).

The intent of this review article is to discuss the use of alteplase (rt-PA) for treating PE and specific considerations of this therapy for emergency department (ED) patients. There are many differences in the administration of rt-PA based on the indication, and this review

**Table 2.** Risk factors for thromboembolism

| |
|---|
| Immobilization |
| Cancer |
| Age 70 years or more |
| Atrial fibrillation |
| Heart failure |
| Acute myocardial infarction |
| Infection |
| Erythropoiesis-stimulating agents |
| Blood transfusion |
| Major surgical procedures |
| Previous VTE |
| Trauma |
| Placement of a central venous catheter |
| Smoking |
| Obesity |
| Pregnancy |
| Hormone replacement therapy |

*Note.* From Aujesky et al. (2006); Darze et al. (2005); Heit et al. (2002); Laporte et al. (2008); Rogers et al. (2012); Sorensen et al. (2011)). VTE = venous thromboembolism.

**Table 1.** Pulmonary embolism risk stratification

| Mortality risk | Historic classification | Risk parameters |
|---|---|---|
| High-risk PE | Massive PE | Sustained hypotension (SBP less than 90 mmHg) for at least 15 min |
| | | Persistent profound bradycardia (HR less than 40 bpm) |
| | | Requirement for inotropic support not due to other causes such as: |
| | | RV dysfunction[a] |
| | | Elevated cardiac biomarkers[b] |
| Intermediate-risk PE | Submassive PE | Normotensive (SBP greater than 90 mmHg) |
| | | RV dysfunction[a] |
| | | Elevated cardiac biomarkers[b] |
| Low-risk PE | Nonmassive PE | Normotensive (SBP greater than 90 mmHg) |
| | | Normal cardiac biomarkers |
| | | No RV dysfunction |

*Note.* From Jaff et al. (2011); Konstantinides et al. (2014). BNP = brain-type natriuretic peptide; bpm = beats per minute; HR = heart rate; PE = pulmonary embolism; SBP = systolic blood pressure; RV = right ventricular.
[a]RV dysfunction defined as the presence of at least one of the following: RV dilation or RV systolic dysfunction on echocardiography; RV dilation on computed tomographic scan; elevation of BNP greater than 90 pg/ml; elevation of N-terminal pro-BNP greater than 500 pg/ml; electrocardiographic changes.
[b]Elevated cardiac markers defined as: elevation of troponin I greater than 0.4 ng/ml; elevation of troponin T greater than 0.1 ng/ml.

helps distinguish the differences when using rt-PA for PE compared with ischemic stroke or myocardial infarction. This article discusses patient presentation and a brief review of clinical evidence and provides the bedside nurse with clinical pearls when administering rt-PA for PE.

## PATHOPHYSIOLOGY

Pulmonary embolism is the obstruction of a pulmonary artery by a thrombus. Virchow's triad of blood stasis, endothelial dysfunction, and hypercoagulability contributes to thrombus formation (Kiyomura, Katayama, Kusanagi, & Ito, 2006; Mustard, Murphy, Rowsell, & Downie, 1962). Thrombi typically originate in the deep veins located in the legs, most commonly the iliofemoral vein in the calf (Galanaud et al., 2009; Girard et al., 2001; Tapson, 2008). The emboli travel through the venous system into the right side of the heart and then to the lungs and pulmonary arteries. After traveling through the heart, the emboli most commonly block the bifurcation of the pulmonary artery or lobar branches (Smithburger, Campbell, & Kane-Gill, 2013). Pulmonary emboli can lead to significant impairment in oxygenation and ventilation, leading to life-threatening hypoxia. Increased right ventricular (RV) afterload due to increased clot burden and flow obstruction causes a decrease in RV output, leading to RV dilation and dysfunction manifesting as hypoxia, hypotension, shortness of breath, and even cardiac arrest (Galanaud et al., 2009; Tapson, 2008). Death from PE does not result from respiratory failure but rather RV failure (Stein et al., 2007). Patients with PE are risk-stratified on the basis of their level of hemodynamic and cardiac dysfunction at presentation. Acute PE, the focus of this article, is characterized by a sudden onset of symptoms compared with chronic PE where the symptoms are persistent or recurrent. Untreated or misdiagnosed acute PE can lead to chronic thromboembolic pulmonary hypertension, a leading cause of pulmonary hypertension, and death (Kim et al., 2013).

## CLINICAL PRESENTATION

Presentation of PE varies significantly from asymptomatic to sudden cardiac arrest, making diagnosis challenging. The hemodynamic response to the embolism depends on the size and location of clots, which contribute significantly to the variability in patient presentation (Goldhaber & Elliott, 2003). The most common signs and symptoms (see Table 3) are nonspecific and include dyspnea, chest pain, hemoptysis, and cough (Goldhaber et al., 1999; Pollack et al., 2011; Tapson, 2008). Hypotension, shock, and elevated pulmonary arterial pressure are rare but important clinical presentations to recognize because these patients have the highest risk of mortality (Goldhaber & Elliott, 2003; Konstantinides et al., 2014).

## DIAGNOSIS

If there is a clinical suspicion of PE, the diagnostic workup should include a physical examination, laboratory testing, and imaging. Commonly elevated laboratory markers include D-dimer, brain natriuretic peptide, and cardiac troponin I and/or T. Patients who are hemodynamically unstable may have a bedside echocardiography performed to identify RV dysfunction, which correlates to increased mortality (Stein et al., 2006). The gold standard for diagnosis of acute PE is computed tomography–pulmonary angiography (Estrada-Y Martin & Oldham, 2011; Huisman & Klok, 2013). Other lesser used options for

**Table 3.** Signs and symptoms of pulmonary embolism

| | |
|---|---|
| Dyspnea | Tachypnea |
| Chest pain | Wheezing |
| Hemoptysis | Syncope |
| Palpitations | Fever |
| Cough | Hypotension (SBP less than |
| Tachycardia | 90 mmHg) |
| | Shock |

*Note.* From Goldhaber et al. (1999); Pollack et al. (2011); Tapson (2008)). SBP = systolic blood pressure.

diagnosis include a ventilation–perfusion scan or pulmonary angiography.

## TREATMENT OPTIONS

Treatment of acute PE starts with supportive care and hemodynamic stabilization (Jaff et al., 2011; Konstantinides et al., 2014). When the diagnosis of PE is confirmed or highly suspected, parenteral anticoagulant therapy with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux (Arixtra) is recommended as first-line therapy (Jaff et al., 2011; Kearon et al., 2012; Konstantinides et al., 2014). Subcutaneous LMWH or fondaparinux is preferred over treatment with intravenous UFH due to a reduced risk of major bleeding and heparin-induced thrombocytopenia. However, in patients with renal impairment, concerns about subcutaneous absorption, or planned administration of fibrinolytics such as rt-PA, intravenous UFH is preferred. Anticoagulants work on the clotting cascade and inhibit the formation of thrombin but do not break down thrombi that are already present. Treatment guidelines and scientific statements for the treatment of PE (see Table 4) recommend the use of fibrinolytic therapy in intermediate-risk or high-risk patients with signs of RV dysfunction or hemodynamic instability (Jaff et al., 2011; Kearon et al., 2012; Konstantinides et al., 2014). Treatment and long-term management can be challenging due to the number of anticoagulants available, multiple guidelines with different recommendations and grades of evidence, and an abundance of new evidence not reflected in the most recent treatment guidelines. Providers must use clinical judgment and weigh the risks and benefits of specific therapies including thrombolysis. The potential benefits of preventing hemodynamic instability and even death are weighed against the serious adverse effects including major bleeding and intracranial hemorrhage. There are other options for treatment including surgical embolectomy, endovascular clot retrieval, and catheter-directed thrombolysis (CDT). Surgi-cal embolectomy, excision of the thrombi, is recommended in high-risk patients who have failed previous treatment or have contraindications to thrombolysis or anticoagulants (Jaff et al., 2011; Kearon et al., 2012; Konstantinides et al., 2014). The AngioVac Cannula (AngioDynamics, Latham, NY) is Food and Drug Administration (FDA) approved for removal of undesired vascular debris during extracorporeal bypass up to 6 hr (Sobieszczyk, 2012). Suction is created via bypass initiation, which removes debris and allows blood to recirculate into the body. This is an option for acute PE (clots present for less than 3 months) and is considered an alternative to surgery. Catheter-directed thrombolysis is discussed in more detail later in this review. Food and Drug Administration-approved oral options for long-term treatment of PE include warfarin (Coumadin), a vitamin K antagonist, and the newer direct oral anticoagulants (DOACs), including dabigatran etexilate (Pradaxa), apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto). The use of DOACs has reduced hospital admissions and hospital length of stay (LOS; Merli et al., 2015). The lack of required monitoring and convenient initiation prevents admission from the site of diagnosis, which is frequently the ED. Rivaroxaban and apixaban work within a few hours, whereas dabigatran etexilate, edoxaban, and warfarin require concomitant parenteral anticoagulant therapy for a minimum of 5 days. Rivaroxaban and apixaban do not require concomitant parenteral therapy, which reduces hospital LOS. The newer DOAC agents require dose adjustments for patients with renal impairment and lack a reliable reversal agent.

## ALTEPLASE

Alteplase (Activase) is a second-generation fibrinolytic and the most commonly used agent today (Nordt & Bode, 2003). Tissue-type plasminogen activator (t-PA) occurs naturally in the body, released from endothelial cells (Levin, Marzec, Anderson, & Harker, 1984). Alteplase is a recombinant form of

**Table 4.** Treatment recommendations for fibrinolytic therapy

| | |
|---|---|
| 2014 European Society of Cardiology Guidelines on the Management of Acute Pulmonary Embolism | "Therapy is recommended in high risk patients." (Class I; LOE B)<br><br>"Therapy should be considered for patients with intermediate- to high-risk PE and clinical signs of hemodynamic decompensation." (Class IIa; LOE B)<br><br>"Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension." (Class III; LOE B) |
| 2011 American Heart Association Management of Massive and Submassive Pulmonary Embolism | "Thrombolysis is reasonable for patients with massive acute PE and acceptable risk of bleeding complications." (Class IIa; LOE B)<br><br>"Therapy may be considered for patients with submassive PE judged to have clinical evidence of adverse prognosis and low risk of bleeding complications." (Class IIb; LOE C)<br><br>"Therapy is not recommended for patients with low-risk PE or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening." (Class III; LOE B) |
| 2012 American College of Chest Physicians Antithrombotic Therapy for Venous Thromboembolism Disease | "In patients with acute PE associated with hypotension (SBP less than 90 mmHg) who do not have a high risk of bleeding, we suggest systemically administered thrombolytic therapy over no such therapy." (Grade 2C)<br><br>"In selected patients with acute PE not associated with hypotension and a low risk of bleeding whose initial clinical presentation or clinical course suggests a high risk of developing hypotension (SBP less than 90 mmHg), we suggest administration of thrombolytic therapy." (Grade 2C)<br><br>"In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy." (Grade 1C) |

*Note*. From Jaff et al. (2011); Kearon et al. (2012); Konstantinides et al. (2014). LOE = level of evidence; PE = pulmonary embolism; RV = right ventricular; SBP = systolic blood pressure.

t-PA that binds to fibrin in a clot and converts plasminogen to plasmin, inducing fibrinolysis. The end result of this action is dissolution of a clot. Beneficial effects on hemodynamics and pulmonary blood flow from rt-PA are seen 2–24 hr after the infusion is started. An advantage of rt-PA compared with previous fibrinolytics is that it selectively activates plasminogen in the presence of fibrin, limiting its systemic effects (Genetech, 2015). Other less commonly used fibrinolytics include streptokinase, tenecteplase, and urokinase (Ouriel, 2002; Stringer, 1996). This review article focuses on the use of rt-PA. Alteplase was originally FDA approved in 1987 for the treatment of ST-elevation myocardial ischemia (STEMI), but it was not until 2002 that it gained approval to treat acute PE (Genetech, 2015). Alteplase is hepatically metabolized and cleared from the plasma within 5 min (Ouriel, 2002). Dissolution of the thrombus ultimately leads to improved hemodynamics, oxygenation, and ventilation due to reduced clot burden.

## CONTRAINDICATIONS AND ADVERSE EFFECTS

There are distinct differences for contraindications with rt-PA based on the indication. Patients presenting with ischemic stroke must

receive rt-PA within 3 hr, or 4.5 hr in certain populations, of onset of stroke symptoms (Jauch et al., 2013). When used for PE, there is no specified time frame; it should be given as soon as possible. Table 5 describes absolute and relative contraindications, which predispose patients to bleeding or increase their bleeding risk (Genetech, 2015; Nordt & Bode, 2003).

A recent meta-analysis suggests the rate of major bleeding from fibrinolytics to be 9.2%, similar to a previous estimated risk of 9.1% (Chatterjee et al., 2014; Wan, Quinlan, Agnelli, & Eikelboom, 2004). The most devastating adverse event from fibrinolytic therapy is intracranial hemorrhage, which occurs in 1.5% of patients receiving fibrinolytics (Chatterjee et al., 2014). Before, during, and after administration, patients should be closely monitored for bleeding, specifically at the infusion site, as well as for signs of gastrointestinal, intracranial, and genitourinary hemorrhage. Anaphylaxis has been reported with rt-PA.

Concomitant administration of antiplatelet agents (aspirin, ticlopidine [Ticlid], clopidogrel [Plavix], prasugrel [Effient], or ticagrelor [Brilinta]) and anticoagulants (including but not limited to warfarin, UFH, LMWH, and fondaparinux) compounds the risk of bleeding. When using rt-PA to treat acute PE, intravenous UFH at therapeutic doses is the preferred anticoagulant in all patients. Intravenous UFH is used because the infusion can be stopped and restarted. Oral and subcutaneous medications have an erratic onset (subcutaneous) and prolonged duration of action. The risk of bleeding is prolonged in patients receiving anticoagulants or antiplatelet agents and can last as long as 5–7 days (Genetech, 2015).

Despite the bleeding risk associated with rt-PA, restart the intravenous UFH infusion after rt-PA administration when the activated partial thromboplastin time (aPTT) is 80 s or less. Fibrinolytic therapy is an adjunct therapy with systemic anticoagulation, not a replacement for full anticoagulation. Preventing

**Table 5.** Contraindications for alteplase administration

| Major contraindications | Relative contraindications |
|---|---|
| Structural intracranial disease[a] | Systolic BP greater than 180 mmHg |
| Previous intracranial hemorrhage | Diastolic BP greater than 110 mmHg |
| Ischemic stroke within 3 months | Recent internal bleeding (nonintracranial) |
| Recent brain or spinal surgery | Recent surgery |
| Recent head trauma with fracture or brain injury | Recent invasive procedure |
| Bleeding diathesis | Ischemic stroke more than 3 months ago |
| Malignant intracranial neoplasm | Current anticoagulation therapy |
| Suspected aortic dissection | Traumatic or prolonged (greater than 10 min) cardiopulmonary resuscitation |
| | Pericarditis or pericardial fluid |
| | Diabetic retinopathy |
| | Pregnancy |
| | Age greater than 75 years |
| | Body weight less than 60 kg |
| | Female sex |
| | Black race |
| | Noncompressible vascular punctures |
| | Dementia |

*Note*. From Jaff et al. (2011); Kearon et al. (2012). BP = blood pressure.
[a]Neoplasms, arteriovenous malformations, aneurysm.

the serious bleeding risks from rt-PA requires weighing the risks and benefits and taking a thorough medical, surgical, and medication history.

## CLINICAL STUDIES

The first use of fibrinolytic therapy in acute PE was reported in a 1964 paper by Browse and James (1964) describing the successful use of streptokinase in three patients. Alteplase was not described until 1985 when a case report was published describing its successful use in a 63-year-old man with a massive pulmonary embolus (Bounameaux, Vermylen, & Collen, 1985). The current FDA-approved dose for the treatment of acute PE is 100 mg administered over 2 hr (Genetech, 2015). The intravenous UFH continuous infusion should be stopped when rt-PA administration begins and the restarted when the aPTT is 80 s or less. Older meta-analyses have compared the efficacy and safety of intravenous UFH versus fibrinolytics for the treatment of acute PE, with no difference in mortality, recurrent PE, or major bleeding events (Agnelli, Becattini, & Kirschstein, 2002; Wan et al., 2004).

## HIGH-RISK PATIENTS

Many of the studies included in these meta-analyses did not include high-risk patients, in whom a benefit has been seen in other randomized controlled trials. The earliest studies included small numbers of patients and excluded high-risk patients and those hypotensive on admission (Bounameaux et al., 1985; Goldhaber et al., 1986, 1987). The first study to look at the FDA-approved dosing strategy randomized 101 hemodynamically stable patients to receive 100 mg of rt-PA administered over 2 hr compared with intravenous UFH by continuous infusion alone (Goldhaber et al., 1993). Patients treated with rt-PA had improved hemodynamics with a reduction in recurrent and fatal PE, and other studies showed similar results in high-risk patients (Konstantinides et al., 1998; Meneveau

et al., 1997). A review of randomized controlled trials for rt-PA in PE showed a lack of high-risk patients included in these studies, with only 1.3% being high-risk patients (Chatterjee et al., 2014). A 2010 study compared 50 mg of rt-PA compared with 100 mg of rt-PA when used in 103 high-risk patients, 32 of whom were hemodynamically unstable (Wang et al., 2010). The overall 3.9% mortality rate and the 2.9% recurrence rate demonstrate the efficacy of rt-PA in high-risk patients. A 2012 retrospective study looking at 72,230 patients demonstrated that fibrinolytic therapy in hemodynamically unstable patients improved mortality (8.4% vs. 42%; $p < 0.0001$; Stein & Matta, 2012). Although these retrospective data show a large benefit, high-risk hemodynamically unstable patients are not well represented in the published randomized controlled trials. Even with the lack of high-quality prospective evidence, fibrinolytic therapy is still recommended in high-risk patients who have no contraindications. This is likely due to the high mortality rate associated with acute PE and the improvement in embolic clot burden, recurrence, and mortality with systemic fibrinolytic therapy (Chatterjee et al., 2014; Stein & Matta, 2012; Wang et al., 2010).

## INTERMEDIATE-RISK PATIENTS

The use of rt-PA in intermediate-risk PE was first studied in 2002 comparing rt-PA in addition to intravenous UFH versus intravenous UFH alone (Konstantinides, Geibel, Heusel, Heinrich, & Kasper, 2002). Patients included in this study were hemodynamically stable with RV dysfunction, pulmonary artery hypertension, or new electrocardiographic signs of RV strain. This study and subsequent studies showed improved 30-day survival, hemodynamic, and oxygenation parameters and reduced hospital stay and recurrent PE (Konstantinides et al., 2002; Sharifi, Bay, Skrocki, Rahimi, & Mehdipour, 2013; Wang et al., 2010). The aforementioned studies did not show a difference in mortality. The 2002 study used 100 mg of rt-PA for all patients;

a 10-mg intravenous bolus was administered and then 90 mg was administered over 2 hr. The use of reduced dose rt-PA for intermediate-risk patients was first studied in a randomized clinical trial comparing 50 and 100 mg of rt-PA, both administered over 2 hr. The use of 50 mg of rt-PA (2-hr intravenous continuous infusion) resulted in less bleeding with similar efficacy compared with 100 mg of rt-PA (Wang et al., 2010). One hundred twenty-one patients with intermediate-risk PE were randomized to receive 50 mg of rt-PA (10-mg intravenous bolus and then 40-mg intravenous continuous infusion over 2 hr) in addition to intravenous UFH compared with intravenous UFH alone. Those randomized to rt-PA in addition to intravenous UFH had reduced hospital LOS and reduced pulmonary pressures (Sharifi et al., 2013). Of note, there were no documented occurrences of intracranial hemorrhage in any group receiving fibrinolytic therapy. Reduced dose rt-PA was used in 98 patients who were then transitioned to rivaroxaban therapy 24 hr after rt-PA administration, and no increase in bleeding and reductions in pulmonary pressures were found (Sharifi, Bay, Schwartz, & Skrocki, 2014). With the increased use of DOACs, this study suggests that administering rt-PA and then transitioning to a DOAC are safe. The use of rt-PA in intermediate-risk PE is not FDA approved and the dose varies from 50 to 100 mg given over 2 hr. In the authors' opinion, patients with intermediate-risk PE should receive 50 mg of rt-PA in addition to intravenous UFH due to similar efficacy and improved safety if no contraindications exist. In intermediate-risk patients with PE, the risk of bleeding from administering rt-PA is not warranted in every patient due to the reduced PE mortality risk.

## CARDIAC ARREST

Cardiac arrest secondary to a PE event is a serious adverse effect associated with a high mortality rate (Bailen, Cuadra, & Aguayo De Hoyos, 2001). The current American Heart Association (AHA) guidelines for the treatment of PE in cardiac arrest do not recommend the use of fibrinolytic therapy due to published studies showing a lack of efficacy (Vanden Hoek et al., 2010). However, the 2012 American College of Chest Physician (ACCP) guidelines recommend bolus fibrinolytic therapy in patients with imminent or actual cardiac arrest (Kearon et al., 2012). In this setting, a 2-hr infusion is unrealistic. However, a 0.6 mg/kg (maximum 50 mg) rt-PA intravenous bolus given over 15 min has been compared with 100 mg intravenous bolus infused over 2 hr with no difference in efficacy or bleeding (Sors et al., 1994). This was the fastest published administration of rt-PA for PE, although these patients were not in cardiac arrest. Various dosing and infusion times have been studied, but there is a lack of clinical head-to-head studies to definitively say which regimen is best (Prom, Dull, & Delk, 2013). When administering rt-PA for cardiac arrest, it requires prolongation of cardiopulmonary resuscitation (CPR). Once the decision is made to administer rt-PA, it has to be reconstituted, administered, and then CPR must be continued for at least 30 min after the rt-PA bolus to see the effects of fibrinolysis. The published evidence is primarily observational focusing on case reports and case series with a high likelihood of publication bias. These authors conclude that administering rt-PA in cardiac arrest with a known or high clinical suspicion of PE is reasonable with the understanding that CPR will need to be prolonged up to 30 min post-rt-PA administration at a minimum. We recommend a rapid intravenous push dose of 0.6 mg/kg (maximum of 50 mg) to swiftly attempt to improve cardiac perfusion at a dose studied in a randomized clinical trial.

## CATHETER-DIRECTED THROMBOLYSIS

The most common method of administering rt-PA is systemically via a peripheral or central vein. A unique method of administration is via CDT in patients who have failed systemic therapy, have RV dysfunction, or who are not candidates for systemic fibrinolytic administration (Meneveau et al., 2006). The majority of systems administer rt-PA directly into

the pulmonary artery at the site of the visible clot via a specialized pulmonary artery catheter (Engelberger et al., 2015; Uflacker, 2001). Anticoagulant therapy is started and the patient is taken to the catheterization laboratory to visualize the thrombus and measure the pulmonary artery pressure. The catheter is then inserted and the fibrinolytic is administered directly into the pulmonary artery. There are a wide variety of systems with various administration techniques based on the system being used. For example, the EKOS EndoWave (EKOS Corporation, Bothell, WA) system is a unique ultrasound-assisted, catheter-directed, low-dose fibrinolytic endovascular system. The Intelligent drug delivery catheter (EKOS Corporation, Bothell, WA) is inserted; the inner lumen exerts ultrasonic waves, which separate the fibrin strands and make the thrombus more permeable to fibrinolytic therapy while the outer lumen infuses rt-PA (Chamsuddin et al., 2008). The CDT dosing strategy for rt-PA is 0.5–1 mg/hr given with a mean total dose of 10–24 mg in addition to systemic anticoagulant administration (Kucher et al., 2014; Kuo et al., 2009; Piazza, Bhalla, & Kuo, 2014). The overall clinical success rate is high ranging from 76% to 100% clot resolution (Chamsuddin et al., 2008; De Gregorio et al., 2002; Kucher et al., 2014; Kuo et al., 2008, 2009; Meneveau et al., 2006; Piazza et al., 2014). The most common adverse effects are groin hematomas and bradyarrhythmias (Kuo et al., 2009). Although rt-PA is not currently FDA approved for CDT, the EKOS EndoWave system is FDA approved for the treatment of PE.

## TREATMENT RECOMMENDATIONS

Systemic fibrinolytic therapy is not indicated for every patient who has PE (see Figure 1 as a guide for administering rt-PA in PE). Treatment recommendations for systemic fibrinolysis in PE are listed in Table 4. Fibrinolytic therapy is recommended for high-risk patients with acute PE who are hemodynamically unstable. In patients with intermediate-risk acute PE, it is reasonable to administer fibrinolytic therapy if patients are at low risk of bleeding. There have been four meta-analyses that have compared the use of fibrinolytics with anticoagulants alone individually (Agnelli et al., 2002; Chatterjee et al., 2014; Dong, Hao, Yue, Wu, & Liu, 2009; Wan et al., 2004). The most recent meta-analysis (Chatterjee et al., 2014) showed a reduction in all-cause mortality when fibrinolytics were used. There was also a benefit seen in high-risk patients with a concomitant increased rate of bleeding, similar to the previous analyses. In the authors' opinion, fibrinolytic therapy should be given to high- or intermediate-risk patients who are hemodynamically unstable or have evidence of RV dysfunction.

Two of the three treatment recommendations discuss the use of CDT therapy, and the European guidelines discuss the need to further define its place in therapy for PE (Jaff et al., 2011; Konstantinides et al., 2014). The European guidelines state that CDT therapy may be considered in intermediate- to high-risk patients who are at high risk of bleeding from systemic fibrinolytic therapy (Class IIb, LOE B). The AHA states that depending on local expertise, CDT is indicated in high-risk patients, those who remain unstable after systemic fibrinolytic administration (Class IIa, LOE C), or in intermediate-risk patients who are hemodynamically unstable (Class IIb, LOE B). As discussed previously, there is controversy regarding the use of rt-PA in patients with cardiac arrest. The AHA guidelines recommend against fibrinolytic therapy in cardiac arrest secondary to PE (Class III, LOE A), and the ACCP guidelines recommend the use of bolus fibrinolytic therapy if the cardiac arrest is secondary to PE (Kearon et al., 2012; Vanden Hoek et al., 2010). Administering rt-PA in cardiac arrest should be a patient-specific decision by the provider and the code leader due to the paucity of available evidence and the time CPR must be extended for treatment success. Determining the patient-specific bleeding risk is a subjective assessment and one that depends on a provider evaluation and clinical judgment.
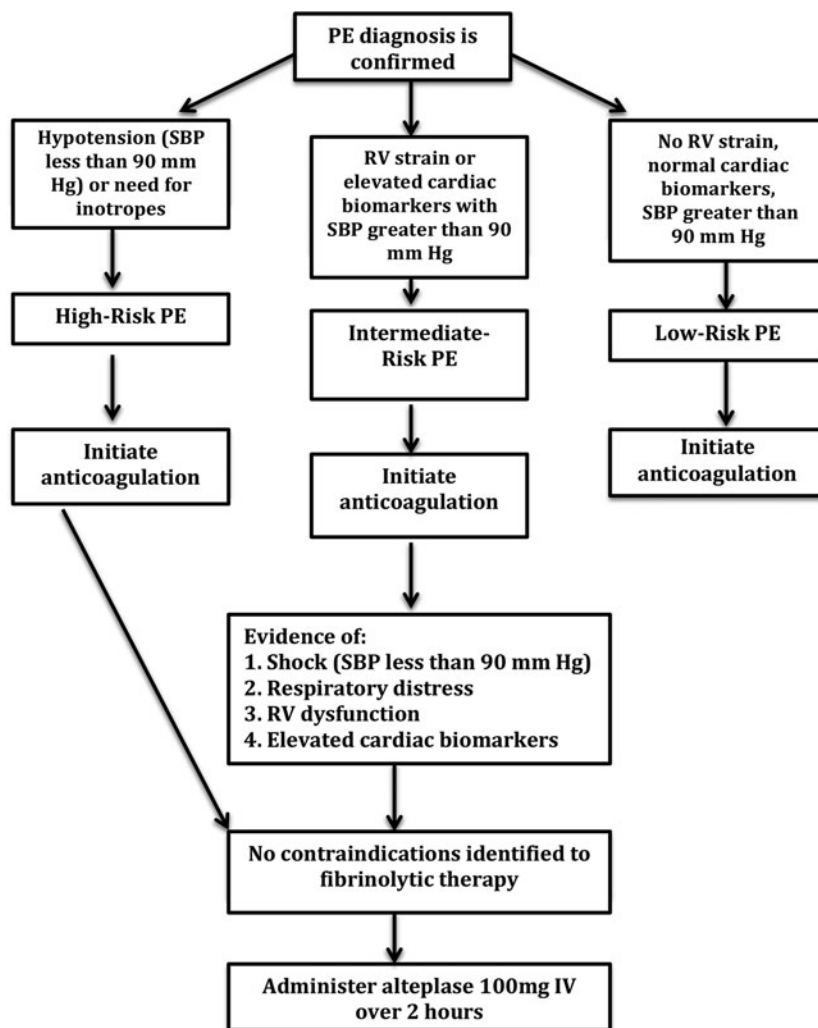
SBP = systolic blood pressure; RV = right ventricular; PE = pulmonary embolism; IV = intravenous

**Figure 1.** Acute PE treatment algorithm. IV = intravenous; PE = pulmonary embolism; RV = right ventricular; SBP = systolic blood pressure.

## ADMINISTRATION AND MONITORING

Recently, there has been a great deal of controversy as to the appropriate rt-PA dose to administer for PE due to various dosing and administration methods studied in clinical trials. The dosing regimen for rt-PA for acute PE varies significantly, from a weight-based 0.6-mg/kg regimen for cardiac arrest to full-dose 100 mg of rt-PA given over 2 hr for high-risk patients and 50–100 mg of rt-PA for intermediate-risk patients. When used for intermediate-risk patients, rt-PA may be administered with a 10-mg bolus and the remaining 40 mg given over 2 hr or the entire 50-mg dose may be given over 2 hr. Alteplase administration for PE differs from its use in the treatment of acute ischemic stroke and STEMI. Be aware that different providers may use different regimens when rt-PA is used for

PE. The two most common rt-PA doses for PE are 50 and 100 mg, and outside of a cardiac arrest it should be administered over 2 hr. There is no time window for rt-PA when treating PE, and therapy should start immediately once the diagnosis is confirmed or highly suspected. Patients need close monitoring, ideally in an intensive care unit setting, for at least 24 hr. Alteplase is reconstituted with sterile water for injection to form a 1-mg/1-ml infusion that can be safely administered via a peripheral or central catheter (Genetech, 2015). Although reconstitution in a pharmacy in a sterile hood is preferred, many hospitals have nurses or pharmacists reconstitute rt-PA at the bedside. Reconstitution of rt-PA should occur immediately before planned administration because it is stable at room temperature for only 8 hr (Genetech, 2015). Once reconstituted via manufacturer recommendations, caution should be excised not to shake the solution. Foaming may occur and is common. Alteplase should not be mixed with any other intravenous medications and is incompatible with dextrose-containing fluids (Genetech, 2015).

Monitor closely for adverse effects, by performing neurological assessments every 15 min during rt-PA administration, every 30 min for 6 hr after administration, and every hour for 24 hr after the infusion (Genetech, 2015). Patient complaints of headache, blurred vision, or sensory changes should be taken very seriously because they can be indicative of serious adverse effects including intracranial hemorrhage. The head of the bed should remain at 30° to help prevent adverse neurological events. Blood pressure should be checked every 15 min for 2 hr, every 30 min for 6 hr, and every hour for 24 hr, and hypertension should be aggressively treated (Genetech, 2015). These patients should be on continuous cardiac monitoring in case there is in advertent lysis of a coexisting coronary thrombus resulting in dysrhythmias.

Monitoring of the infusion site is also recommended because superficial bleeding can occur from the site and may herald a more serious bleeding event. Efforts should be made to avoid insertion of urinary catheters and gastric tubes in addition to arterial and venous punctures during the rt-PA infusion. If blood needs to be drawn, ensure that pressure is held on the site for 15–30 min for venipunctures and at least 30 min for arterial punctures, with pressure dressing application if necessary. Continue monitoring respiratory symptoms even after rt-PA is administered because an acute decompensation could signify treatment failure. Bleeding risk is still high for up to 24–48 hr after rt-PA administration. Placement of urinary catheters, gastric tubes, or additional intravenous catheters or nasogastric tubes should be delayed for 24 hr if possible.

Catheter-directed thrombolysis administration of rt-PA consists of a smaller amount of rt-PA (0.5–1 mg/hr) given over a longer period of time (15–24 hr). Monitoring for bleeding should be just as rigorous as when rt-PA is systemically administered. Similar to systemic rt-PA administration, placement of urinary catheters, gastric tubes, or additional intravenous catheters should be delayed for 24 hr if possible.

Although the risk of bleeding is the main adverse effect, for acute PE treatment, fibrinolytic therapy should be given in addition to systemic anticoagulation. Currently, the ACCP guidelines recommend suspension of intravenous UFH while rt-PA is being administered. After the continuous rt-PA infusion is complete, an aPTT level should be checked. If the aPTT level is 80 s or less, then the intravenous UFH infusion should be restarted at the same rate it was infusing before rt-PA was started without a bolus dose.

If patients have received other anticoagulants either parenterally or orally, the guidelines consider it a relative contraindication to rt-PA administration. Patients should have a thorough medication history completed by the nurse, pharmacist, or provider. The provider will need to make the patient-specific decision on the risks of bleeding and benefits of treatment with systemic fibrinolytic therapy. Coagulation studies may be drawn including anti-Xa, aPTT, thrombin time, ecarin clotting time, or prothrombin

time, based on what agent the patient was receiving.

## CONCLUSION

Acute PE is a life-threatening condition with varying presentations from asymptomatic to cardiac arrest. The gold standard for treatment is systemic anticoagulation when PE is confirmed or highly suspected. Fibrinolytic treatment with rt-PA should be considered for high- or intermediate-risk patients with evidence of hemodynamic instability or RV dysfunction. Studies have shown this to be an effective treatment option, although it carries a risk of life-threatening bleeding. Although there is sufficient evidence for the use of rt-PA in PE, there is still significant debate on what dose patients should receive, how it should be administered, and which patient population benefits most from fibrinolytic therapy. Clinicians need to weigh the patient-specific bleeding risk against the benefits when choosing to start an rt-PA infusion for PE. The ED nurse is an essential part of ensuring safe and effective management of patients experiencing an acute PE event. Recognition of different PE dosing regimens, as well as close monitoring for bleeding, anaphylaxis, worsening respiratory symptoms, and other adverse effects, ensures these critically ill patients receive the best care possible.

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