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RESEARCH **REVIEW ARTICLE**

State of the Art Management of Acute Pulmonary Embolism

Eyadeh Mdanat MD[1] , Armita Kabirpour MD[2], Erick Sun MD[2], Sophia Alexis MD[2], John Puskas MD MSc[2] , Omar Lattouf MD PHD[3*]

- The incidence of venous thrombo-embolization including pulmonary embolism has increased rapidly over the past few years particularly after the COVID-19 pandemic, drawing more attention to pathophysiology and optimal management of VTE and PE.

- Acute PE disrupts the cardiopulmonary system by obstructing RV outflow resulting in passive congestion, reducing pulmonary gas exchange, and decreasing left ventricular filling volume resulting in poor perfusion.

- Management of RV failure is critical in patients with acute PE; therefore cardiologists should be driving the primary management of PE patients.

[1] Cayuga Medical Center, Ithaca, New York

[2] Icahn School of Medicine, New York, NY, USA

[3] Emory University School of Medicine

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Corresponding Author:
Omar M Lattouf MD PHD

Professor of Surgery
Emory University School of Medicine
GA, USA

Email: Omar.m.lattouf@emory.edu

ABSTRACT

Surgical management of pulmonary embolism was a trigger point for the development of cardiopulmonary bypass, a new era in the history of cardiac surgery, cardiology, and medicine. Systemic thrombolysis and eventually catheter-directed therapy overtook the interest in surgical management of pulmonary embolism. Surgical pulmonary embolectomy is limited to patients in critical condition with high mortality after other interventions have failed. The value and suitability of surgical intervention were questioned and discouraged clinicians from surgical pulmonary embolectomy promptly before patients became too critically ill with irreversible end-organ dysfunction. The Achilles heel of the management of PE patients is decompression of RV afterload by relieving RVOT obstruction to improve RV function and VL filling. Understanding the pathophysiology of RVOT obstruction and management of RV failure is key with the multidisciplinary heart team being in the driver's seat medically and surgically managing patients with PE.

HISTORICAL BACKGROUND

In 1908, Friedrich Trendelenburg first described the phenomenon of substernal pain and rapid collapse associated with sudden pulmonary embolism (PE) (1). Over the last century surgical management of PE has continued to evolve and has been intricately linked to the development of cardiopulmonary bypass and the beginning of cardiac surgical operations.

Although most early attempts at surgical pulmonary embolectomy (SPE) were unsuccessful, one of Trendelenburg's students, Dr. Martin Kirschner, reported a successful SPE on March 18, 1924, before the cardiopulmonary bypass era in a 38-year-old woman who was found to have three large emboli in her pulmonary artery three days after an inguinal hernia repair (2). In the United States, the first successful embolectomy by the Trendelenburg method was first reported by R. W. Steenburg, MD, and Richard Warren, MD, at the Peter Bent Brigham Hospital, Boston in 1958. The Trendelenburg procedure was based on occlusion of the proximal pulmonary artery (PA) and aorta by traction on an encircling band through the transverse sinus and extraction of clots through a small pulmonary arteriotomy (3). As a pioneer surgeon, John Gibbon reported his series of 142 patients undergoing the Trendelenburg procedure in which there were only nine survivors. One could say, with great confidence, that the usually fatal challenges of the Trendelenburg Procedure led to the design and building of the first heart-lung machine, heralding a new era in cardiac surgery, cardiology, and medicine (4). Following the introduction of cardiopulmonary bypass in 1953, Dr. Edward Sharp was the first to perform and publish a pump-supported SPE in 1962, followed by Dr. Denton A. Cooley and associates (5,6,7).

Ironically, in the following decades, interest in the use of fibrinolytic therapy such as the plasminogen activators urokinase and tissue-type plasminogen activator (t-PA) grew and the practice of SPE became restricted to critically ill patients (6). This shift in patient selection resulted in surgical mortality rates in the middle-to-late 20th century of more than 30%, naturally creating significant apprehension towards the surgical approach. (8)

This "no-win" situation, in which surgeons and institutions limited SPE primarily to extremely high-risk patients, led to many surgeons losing interest in the field (9).

Despite the abandonment of this technique at most hospitals in the 1980s to 1990s, new data started to emerge demonstrating the safety and efficacy of SPE in carefully selected patients. A study by Gulba et al, showed a rate of survival of 77% with surgical pulmonary embolectomy in patients with PE and shock, compared to a 67% survival rate with fibrinolytic therapy (10). In another study, Takahashi et al described a 5-year survival rate of 87.5% in a cohort of 24 patients presenting with circulatory collapse, including almost 50% of whom were resuscitated after cardiac arrest. Furthermore, the authors reported outstanding long-term cardiac recovery as demonstrated by a reduction in mean pulmonary artery systolic pressure from 66.9 mmHg to 28.5 mmHg (11).

These reports provided evidence of favorable outcomes with SPE in massive PE and led to a resurgence of interest in the use of SPE as a first-line treatment option earlier in the course of pulmonary embolic disease rather than as a delayed and high-risk rescue therapy (12).

CLASSIFICATION OF PULMONARY EMBOLI

The American Heart Association (AHA) divides pulmonary embolism into three classifications: massive/high risk, sub-massive/intermediate risk, and low risk. Massive PE is defined by hypotension with systolic blood pressure (SBP) less than 90 mmHg for over 15 minutes, inotropic support needed to keep SBP over 90 mmHg, or a greater than 40 mmHg drop in SBP for greater than or equal to15 minutes (14, 15, 16, 17). Sub-massive PE is defined by SBP over 90 mmHg with evidence of right heart dysfunction by dilated right ventricle (RV) on echocardiography, a right ventricle-to-left ventricle size ratio over 0.9 on 4-chamber computed tomography angiogram (CTA), or increased brain natriuretic peptide (BNP) or troponin biomarkers (16, 17). Low-risk PE is defined as occurring in normotensive patients with no evidence of RV strain on echocardiogram, normal RV-LV ratio on CTA, and normal cardiac biomarkers (18).

The European Society of Cardiology (ESC) further subdivided the intermediate-risk group into intermediate-low risk, defined by only one of either imaging-confirmed RV dysfunction or elevated biomarkers, and intermediate-high risk, in which both RV dysfunction and elevated cardiac biomarkers together are present concurrently (19).

A less common classification of PE based on the location of the pulmonary thrombus has also been

described by a group at Vanderbilt University. Type A PE involves the main PA trunk or either branch pulmonary arteries. Type B PE are those with peripheral emboli located beyond the main pulmonary arteries. In this classification, a type A PE meets the indication for surgical embolectomy regardless of hemodynamic status (20).

EPIDEMIOLOGY

Studies conducted in Western Europe, North America, Australia, and Latin America point to an annual incidence of venous thromboembolism (VTE) between 75 and 269 cases per 100,000 persons. Subjects who are 70 years of age or older have an incidence of up to 700 per 100,000 persons (13). VTE is the third most common cause of acute cardiovascular disease after myocardial infarction and stroke. In the United States, the annual cost of VTE is projected to be between $7-10 billion for the treatment of about 900,000 patients with VTE, with PE accounting for about 150,000-250,000 hospitalizations, and about 60,000-100,000 deaths annually. VTE has become recognized as a huge financial and clinical burden to the US healthcare system and thus is gaining more attention as the US looks to reign in growing healthcare costs (21, 22).

Deep Vein Thrombosis (DVT), particularly in proximal deep lower extremity veins, if left untreated, is reported to result in a 40% incidence of pulmonary emboli, hence the importance of surveillance and early therapy once DVT is suspected or diagnosed. (23, 24)

In addition to its acute morbidity and mortality, PE is estimated to result in chronic thromboembolic pulmonary hypertension (CTEPH) in 1.3-3% of patients (25, 26).

PREDISPOSING FACTORS

The classic triad of risk factors for the development of thromboembolic disease as proposed in 1856 by Virchow includes: stasis, vessel wall injury, and hyper-coagulable state. (27)

Risk factors can be further subdivided into; Strong, moderate, and weak risk factors.

Strong risk factors include; Lower limb fracture, Knee/hip replacement, Hospital admission for heart failure or atrial fibrillation/flutter, or recent myocardial infarction within the past 3 months, major trauma, spinal cord injury, or past VTE.

Moderate risk factors include knee arthroscopy, blood transfusions, venous central lines, chemotherapy, oral contraceptives and hormone replacement therapy, post-partum, cancer, stroke, thrombophilia, inflammatory bowel disease, and infections.

Weak risk factors include more than 3 days of bed rest, immobility due to prolonged sitting (car/airplane), obesity, laparoscopic surgeries, pregnancy, and varicose veins. (19).

TRAVEL- Long-distance travel is associated with an increased risk of VTE due to prolonged immobility, especially when combined with additional comorbidities, at which the risk increases substantially. (28)

OBESITY-The risk of VTE for obese patients is directly proportional to Body Mass Index (BMI). A prospective study identified a BMI of 29kg/m2 and above to confer a 3.2 times greater relative risk for the development of VTE compared with lower BMI (29). Obesity is likely to contribute to a hypercoagulable state via increased circulating levels of pro-inflammatory cytokines. (30).

ESTROGEN-Estrogen-containing oral contraceptives, hormone replacement therapy in post-menopausal women, along with raloxifene and tamoxifen in breast cancer patients were found to increase the risk of VTE through actions related to the coagulation cascade causing pro-thrombosis. Pregnancy and the peripartum period are associated with an increased level of circulating estrogen, a pro-thrombotic state, and an increased risk of VTE (31-34).

CANCER - Pancreatic, hematological, lung, gastric, and brain malignancies are most associated with the development of VTE (19). Many oncologists treating cancer patients may initiate aggressive DVT prophylaxis (27). Diagnosis of cancer is increased in post-VTE patients, leading clinicians to screen their patients with VTE for undiagnosed occult malignancy (35-37).

TRAUMA/SURGERY-Patients undergoing surgical procedures, particularly of the spine, pelvis, hip, thigh, knees, and ankle are at increased risk of VTE. The post-operative state confers all three risk factors of Virchow's triad. The combination of vein injury from trauma or surgery, immobility causing venous flow stasis, and the pro-inflammatory postoperative condition led to an increased rate of VTE. The risk is highest in the first month after trauma or surgery (38).

THROMBOPHILIA- One should suspect genetic predisposition in the following conditions: family history of thromboembolic disease, thrombus development in unusual anatomic locations, recurrent idiopathic thrombus formation

in young patients, and resistance to commonly used anticoagulants. Deficiencies in protein C, protein S, and antithrombin III are associated with a high risk of thromboembolic disease but are less prevalent than the Factor V Leiden (FVL) mutation. (39).

Factor V Leiden includes a point mutation (adenine for guanine) leading to glutamine for arginine substitution at location 506 on factor V. This substitution results in Protein C resistance. It is estimated that 5% of Caucasians in Europe and North America have heterozygous genetic defects. The heterozygous state has a three- to fivefold increased lifetime VTE risk, and the homozygous state carries a significantly higher risk. (39)

Of note, the use of oral contraceptives in patients with FVL deficiency increases the likelihood of VTE by 35 times (39-41). Other pro-thrombotic conditions include lupus anticoagulant syndrome and hyperhomocysteinemia (42-43).

Antiphospholipid syndrome (APS) is an autoimmune condition associated with antiphospholipid autoantibodies (aPL) in addition to a hyper-coagulability state that can affect any blood vessel; small or large. When larger vessels are involved, such as arteries or veins, it results in thrombosis or embolism, whereas small vessel involvement, including capillaries, arterioles, and venules, results in thrombotic microangiopathy. (42). APS is diagnosed based on clinical and lab criteria; the patient should have a minimum of 1 of 2 clinical criteria (vascular thrombosis or pregnancy loss) and at least 1 of 3 laboratory criteria (LAs, aCLs, and/or anti-β2GPI). Laboratory criteria should be positive on two or more occasions, preferably 12 weeks apart. (42).

Anticoagulation is important after being diagnosed with APLA syndrome. Studies have shown an increased rate of recurrence a few years after stopping AC in patients with APLA syndrome. (42).

Level of anticoagulation also plays a role in treatment, with intermediate intensity (INR 2-2.9) and high intensity (>=3 INR) warfarin treatment reduced recurrence significantly, however, the low intensity (INR=<1.9) showed no effect. (42).

PATHOPHYSIOLOGY

Acute PE disturbs the cardiopulmonary system by obstructing RV outflow, reducing pulmonary gas exchange, and decreasing left ventricular (LV) filling volume (preload). Together, these factors result in decreased cardiac output and diminished volume of oxygenated blood available to perfuse the body, most notably the brain, heart, and kidneys. Furthermore, the reduced forward flow of blood out of the RV (RV failure) leads to passive venous congestion, manifested by peripheral edema, as well as hepatic and renal congestion. (19)

Typically such patients have a rise in pulmonary artery (PA) and RV pressures. This is in part due to mechanical obstruction of the pulmonary arteries as well as the release of thromboxane A2 and serotonin, which cause vasoconstriction in the pulmonary vascular bed (44).

At a cellular level, the increased RV filling (preload) leads to increased wall tension and oxygen consumption. Therefore, the energy requirement of the RV myocytes increases in the setting of decreased perfusion of coronary arteries with oxygenated blood. This imbalance in supply and demand causes ischemic changes in the already strained RV, which may result in cardiac enzyme leakage, RV myocardial infarction, and further deterioration in the RV function, causing a downward spiral into acute RV failure (19).

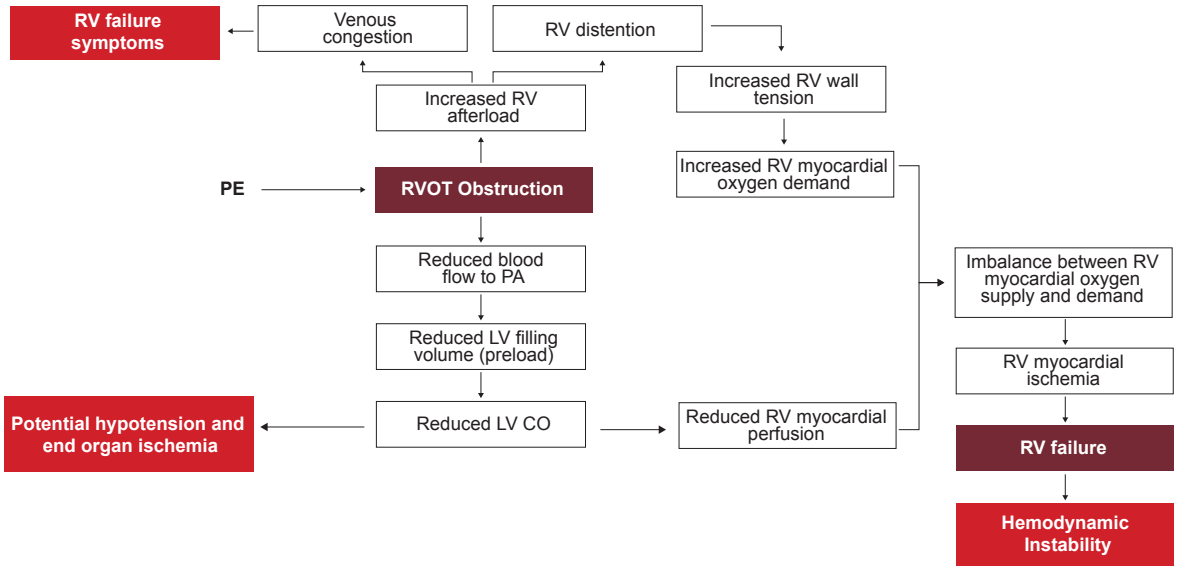
The abrupt rise in right heart pressure caused by mechanical factors and release of vasoactive agents may push the RV beyond the limits of the Frank-Starling mechanism, causing deterioration in hemodynamics with tachycardia, and in more severe cases leading instead to bradycardia, declining blood pressure, and hemodynamic collapse. Echocardiography will reveal a distended RV, interventricular septum deviation towards the LV, and poorly filled LV. The effective cardiac output in such a situation is greatly reduced, leading to further end-organ ischemia, acidosis, and rise in serum lactate; all predictive of poor clinical outcomes unless timely and successful intervention is provided (19).

Angiographic studies have shown that markedly elevated pulmonary artery pressure and severe right ventricular strain start to manifest when thrombo-embolic clot burden occludes more than 30–50% of the total cross-sectional area of the pulmonary arterial bed (45,46).

Other studies utilizing computerized tomographic angiography (CTA), however, have reported that clot burden was only moderately correlated with right ventricular dilation or pulmonary hypertension but did not correlate with all-cause death or clinical deterioration. (47-49)

In a subset of patients, with increased right-sided pressures, right-to-left shunting may occur in a previously “dormant” patent foramen ovale

Figure 1. The effect of Pulmonary Embolism on the right ventricle, myocardium, and circulation



(PFO) further exacerbating hypoxemia. Additionally, paradoxical embolization through a PFO is a grave concern for stroke and other organ injury (19).

CLINICAL PRESENTATION

Acute PE manifests clinically in various ways and can be confused with myocardial infarction or aortic dissection. Commonly patients with PE present with non-specific cardiopulmonary symptoms such as dyspnea, tachypnea, chest pain, and cough. Hemoptysis may be present in some cases. (19, 50-53) Syncope or near-syncope, hypotension, extreme hypoxemia, electromechanical dissociation, or cardiac arrest, would each be suggestive of a massive or "high-risk" PE (52). Patients with isolated subsegmental PE may present with mild dyspnea and chest discomfort, with normal vital signs and cardiac function (54).

On physical examination, the clinician should look for tachypnea, tachycardia, signs of altered mental status, poor distal perfusion, evidence of hypoxia, left parasternal heave, distended jugular veins, and a systolic murmur caused by tricuspid regurgitation that increases with inspiration. The electrocardiogram occasionally reveals a new right bundle branch block or inverted T waves in leads V1–V4 (19, 55). The S1Q3T3 pattern is an uncommon EKG finding but can indicate right ventricular strain. Milder cases can only present with sinus tachycardia. Atrial abnormalities; like atrial fibrillation, can also be associated with PE. (19).

PRE-TEST PROBABILITY

The lack of specific initial diagnostic criteria before obtaining an echocardiogram or a CTA has prompted many to devise various PE scoring systems such as the Wells' Score, simplified Wells score, the Geneva score, and the Pulmonary Embolism Rule-out Criteria to attempt to identify the pre-test probability of VTE and the likelihood of PE. (19, 55-58). These tests rely on various initial patient history and physical findings such as age, dyspnea, tachycardia, BP, unilateral leg swelling, and history of prior PE (59). Simplified Pulmonary Embolism Severity Index (sPESI) is another risk stratification tool that provides a 30-day mortality risk. special considers age, pertinent medical history (cancer or cardiopulmonary disease), and vital signs (heart rate, SBP, and oxygen saturation) (18).

Pre-test probability categories depend on patient symptoms and presentation in addition to risk factors for VTE, which match with increasing actual prevalence of confirmed PE. This pre-test assessment can be done either by implicit (empirical) clinical judgment or by using prediction rules. The pre-test probability step is an important one in diagnosing PE cases, as the probability after doing imaging studies depends on both imaging results and pretest probability. (19)

Since PE cases can present as chest pain, shortness of breath, and even syncope, investigating these patients for PE may lead it increased costs and complications of unnecessary testing. Hence

it is recommended to use The Pulmonary Embolism Rule-out Criteria (PERC) for emergency department patients to determine patients whose likelihood of having PE is so low that diagnostic workup should not even be initiated. It has eight clinical variables related to PE absence: age < 50 years; pulse < 100 beats per minute; SaO2 >94%; no unilateral leg swelling; no hemoptysis; no recent trauma or surgery; no history of VTE; and no oral hormone use.(19)

Studies have shown the safe exclusion of PE in patients with low clinical probability who, in addition, met the PERC rule-out criteria. However, the low PE prevalence in these studies does not back up the generalizability of the results. (19)

LABORATORY TESTS

In patients with a high likelihood of PE, the following laboratory tests should be obtained: complete blood count, blood chemistry including liver enzymes, coagulation profile, troponin level, BNP, D-Dimer, and arterial blood gas (ABG) with blood lactate level if oxygen saturation is subnormal via pulse oximetry. Hypoxemia on ABG is a sensitive sign of massive/sub-massive PE (19, 50). Elevated lactate is evidence of poor systemic perfusion, another indicator of high-risk PE (60). Normal D-Dimer level effectively rules out PE, while a positive D-Dimer is non-specific and by itself does not necessarily confirm PE. Therefore, D-Dimer has a high negative predictive value and a low positive predictive value (19). Elevated troponin is an evidence of myocardial cell necrosis and requires further action in patients suspected to have PE. Elevated BNP or its precursor (pro-BNP), a highly sensitive marker of RV dysfunction, is further evidence of hemodynamic compromise. Both troponin and BNP are not specific for PE but are associated with an increased risk of in-hospital mortality and indicate a potentially unstable cardiopulmonary situation that deserves intensive management (19, 61,62).

IMAGING STUDIES

COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CTA) FOR PE

CTA is the most efficient and definitive test to establish the presence or absence of massive PE. Importantly, CTA can readily and reliably distinguish between acute aortic dissection versus PE in patients whose clinical presentation may be similar (57, 63).

PE CTA has a specific protocol using multi-detector CT scanners after intravenous contrast injection into a suitable size vein that allows injection of 50 to 100 ml of intravenous contrast dye at an injection rate of 4 – 5 ml/s followed by a saline chaser at the same injection rate (64). If the patient is on extra-corporal membrane oxygenation (ECMO), it is essential to stop the ECMO flow for the few seconds the contrast is being injected to allow the contrast to reach pulmonary circulation instead of the ECMO circuit. A study reported increased diagnosis of PE with the use of PE CTA from 62.1 to 112.3 per 100,000 (81% rise) from 1998 to 2006 as compared to 1993 to 1998 based on the U.S. nationwide inpatient sample cohort and the multiple cause-of-death database. PE case fatality rate also decreased from 12.1% to 7.8%, possibly due to increased and more timely diagnosis as well as improved clinical management associated with the growing interest in VTE (65).

ECHOCARDIOGRAPHY

In patients suspected of having PE, particularly those with cardio-pulmonary instability, immediate echocardiography is indicated with specific attention to RV size, filling volume, and contractility, as well as interventricular shifting toward the LV, intracardiac masses, and flow across a PFO. Echocardiography is also useful in ruling out other cardiac issues such as pericardial effusion or valvular heart disease (57). Often, we rely on a qualitative assessment of RV function particularly when urgent initiation of treatment is critical. If time allows, one should use quantitative assessment to document RV function. The following parameters are used to indicate echocardiographic evidence of significant PE with elevated risk of death: 1) a right to left ventricular end-diastolic diameter ratio >1 in the apical four-chamber view; 2) RV end-diastolic diameter >30 mm; and 3) paradoxical septal systolic motion of RV (66).

The McConnell sign, depressed RV free wall contractility compared to preserved apical contractility, is another finding that would point to serious PE (57, 67).
Additional echocardiographic findings indicative of significant RV dysfunction include gradient across tricuspid valve (TV) >30 mm Hg and a regurgitant jet velocity of the TV >2.7 m/sec (68, 69).

OTHER STUDIES

Ventilation perfusion (VQ) scans and pulmonary angiography used to be the primary imaging studies for PE until CTA became readily available. VQ scanning remains an option for patients with contrast allergy (70,71). Pulmonary angiography is more invasive and requires right heart catheterization performed by expert operators; it is therefore less commonly used in diagnos-

ing acute PE. It remains of value in diagnostic work-up of CTEPH to measure pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) along with fluoroscopic imaging of the PA branches (70-72). Magnetic resonance imaging (MRI) is much less commonly used. It is considered in patients with contrast dye allergy or in pregnant women. The experience using MRI for PE is limited and its diagnostic accuracy is narrow; these factors further limit its use. (73-77).

PULMONARY EMBOLISM RESPONSE TEAM (PERT)

VTE is a critical public health issue and PE is a common cause of death that has not received its due attention over the last several decades. Therefore pulmonary embolism response teams (PERTs) were introduced as a multidisciplinary collaboration of representatives from medicine, interventional radiology, critical care, cardiology, vascular, and cardiac surgery (78-81).

When a patient with high suspicion for PE is identified, the PERT team is activated by sending a message to a pager system or mobile phone network to notify and share clinical data with participants from various clinical services. All members of the multidisciplinary team are notified of the patient's clinical status at the same time (82). The participating providers eventually reach a consensus to proceed with the chosen treatment modality that is best suited for the patient's condition promptly (57, 79, 80).

THERAPEUTIC STRATEGIES

ANTI-COAGULATION

Unless contraindicated, upon serious suspicion of sub-massive or massive PE, intravenous heparin infusion should be initiated, even while a definitive work-up is pending (17). Once the diagnosis of sub-massive or massive PE is confirmed on imaging, further therapy should be diligently considered.

If clinical findings point toward a possible stroke, then a head CT scan should be obtained to look for the presence, type, and size of the stroke before initiation of anticoagulation. When a stroke and PE are diagnosed in the same patient, a neurology consult is warranted to assess the risk of transformation of ischemic to hemorrhagic stroke with therapeutic anticoagulation. The risk versus benefit of anticoagulation should be carefully considered for the individual patient with a non-hemorrhagic massive or sub-massive stroke. The AHA guidelines do not recommend initiating anticoagulation in patients with moderate to severe stroke. (83,84). It is not unreasonable to place an inferior vena cava (IVC) filter and delay anticoagulation if the concern for hemorrhagic transformation remains high (85).

OUTPATIENT ANTICOAGULATION THERAPY

For patients with low-risk PE with no hemodynamic compromise and no evidence of RV dysfunction, treatment is conservative with anticoagulation therapy alone. Outpatient therapy with close follow-up is sufficient unless other comorbid conditions exist that could complicate outpatient care (18).

Direct Oral Anticoagulants (DOACs) are commonly used for patients requiring anticoagulation for non-valvular heart disease, including VTE. DOACs are becoming the agent of choice to treat DVT and PE. Unlike anti-vitamin K agents, DOACs are administered at fixed doses and do not require monitoring. Two classes of DOACs are currently available, anti-factor Xa (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitor (dabigatran). These agents are selective and reversible inhibitors of a specific step in the coagulation pathway. DOACs have a short half-life and can be reversed promptly if needed (86-92).

Four randomized prospective trials (AMPLIFY, EINSTEIN, RECOVER, and HOKUSAI) have shown non-inferiority of DOACs to conventional treatment with heparin and vitamin K antagonists (93-97). Thus DOACs have replaced Vitamin K antagonists as the preferred intermediate and long-term treatment for VTE (98).

SYSTEMIC THROMBOLYSIS

In the acute phase, after intravenous heparin is infused, the question of how best to further manage sub-massive or massive PE can be challenging. Anticoagulation alone does not dissolve the thrombus. Thrombolytic agents, on the other hand, do cause thrombo-emboli to break down and dissolve, at least in part, if not fully. Systemic thrombolysis (ST) is the process of infusing a fibrinolytic agent through an intravenous access catheter inserted at a distance from the target vessel. It reduces the clot burden and may enhance blood flow through the target vessel. However, an increased risk of major bleeding, notably intracranial bleeding and stroke, is a very serious concern when using ST (16, 99). Risk factors associated with increased risk of bleeding caused by thrombolytic therapy infusion

include old age, recent brain or spine surgery or trauma, GI bleeding history, recent surgery, current intracranial tumors, and ischemic stroke in the past 3 or 6 months (85).

In a prospective trial among 265 patients with sub-massive PE randomly selected to receive alteplase plus heparin or heparin infusion alone, Konstantinides S, et al, reported no difference in mortality benefit between the two groups (100). In a larger follow-up randomized prospective trial (PEITHO) on 1005 patients with sub-massive PE, Konstantinides et al, reported that systemic thrombolysis with tenecteplase versus anticoagulation had no mortality benefit during the index hospitalization, and worse all-cause mortality at 3-year follow up, concluding that ST has no advantage over anticoagulation alone in patients with sub-massive PE. Two meta-analyses of previously published studies by Stavros Konstantinides, MD, also showed minimal or no mortality benefit of ST in patients with sub-massive PE. Any small mortality benefit was counterbalanced by an increased risk of major bleeding, intracranial hemorrhage, and stroke. (100, 101). Therefore AHA clinical practice guidelines recommend against the use of full-dose systemic fibrinolytic therapy for acute sub-massive PE (101-104). Another meta-analysis of 16 randomized controlled trials that compared systemic thrombolysis to anticoagulation in the management of acute PE, did not show a statistically significant difference in in-hospital survival and did report an increased risk of major bleeding and intracranial hemorrhage with ST (102-105). Systemic thrombolytic therapy in hemodynamically stable patients was associated with an increased risk of mortality based on data from a large national survey (106).

The international PEITHO (Pulmonary Embolism Thrombolysis), the largest (1003 patients) multi-national randomized clinical trial comparing systemic thrombolytic therapy versus intravenous heparin failed to show the benefit of thrombolysis over intravenous heparin in patients with sub-massive PE (57, 101). In certain situations, where patients may have both paradoxical stroke and PE, therapeutic options are limited and it is better to avoid using thrombolytic therapy due to the increased risk for intracranial hemorrhage associated with thrombolytic therapy (107,108).

These findings have significantly reduced the interest in ST for PE patients. ST is no longer recommended as primary therapy for patients with intermediate-risk or sub-massive PE, even if signs of both right ventricular dysfunction and myocardial injury are initially present (57). ST has been reserved for patients who are at risk of immediate death with intravenous lytic therapy being the only option available (51).
On the other hand, when followed up over a long period (28±5 months), patients who underwent systemic thrombolysis and survived without major bleeding events or strokes had a lower incidence of pulmonary hypertension, better New York Heart Association (NYHA) status, and performed better on 6-minute walk test (109, 110).

It has also been noted that at long-term follow-up, some patients remain at risk for long-term cardio-pulmonary dysfunction manifesting with easy fatigue, dyspnea, and compromised quality of life. A prospective study that has examined 109 previously healthy patients with documented sub-massive PE treated with anti-coagulation only revealed that at 6 months follow-up, 41% of them had cardiopulmonary abnormalities, manifesting with RV abnormalities (dilatation or hypokinesis), limitation of exercise ability, heart failure, and limitation of 6 minutes-walk distance <330 meters. Furthermore, 20% of patients indicated that their quality of life was diminished, reported an inability to carry mild duties such as shopping, or required home oxygen supplementation (111). Additionally, 4% of post-PE patients developed CTEPH 2-year follow-up reported by Pengo et.al (112).

These trials suggest that systemic thrombolysis most likely reduces mortality and prevents hemodynamic compromise in patients with massive PEd, but was associated with an increased risk of major and intracranial bleeding at the time of initial therapy. As for the sub-massive PE patients, it is uncertain if systemic thrombolysis lowers mortality, but it increases major bleeding by 3-fold and intracranial bleeding about by 5-fold. These concerning risks have reduced enthusiasm for the use of systemic thrombolysis use in patients with sub-massive PE (110).

In summary, AHA guidelines do not support ST for sub-massive PE. In the case of massive and life-threatening PE, AHA guidelines support aggressive reperfusion therapy including ST, catheter-directed thrombolysis (CDT), and/or surgical pulmonary embolectomy (SPE). When considering ST, the risk of bleeding versus the benefit of thrombolytics must be weighed (16, 113).

The ESC suggests giving ST to high-risk PE patients and anticoagulation alone to intermediate-low-risk patients. For intermediate- high-risk patients, clinical judgment is warranted particularly if clinical deterioration is seriously suspected (111).

"Half-dose" systemic fibrinolytic treatment, 50 mg of alteplase instead of 100 mg intravenous dose has gained interest among many physicians despite the absence of definitive safety and efficacy evidence. It is usually infused over 2 hours, however, in life-threatening situations it can be given over a matter of minutes. (109, 114, 115). At this stage, authorities in the field recommend against its use and consider its use to be off-label, except in life-threatening situations (101).

INTERVENTIONAL AND CATHETER DIRECTED THERAPY (CDT)

The risk of major bleeding, ICH, and stroke in patients receiving ST has led to the use of CDT. CDT is also intended to eliminate or reduce the thrombus burden and relieve pulmonary arterial obstruction in a timely manner. This improves cardiopulmonary performance and hemodynamics (16, 80). Patients suffering from acute PE with evidence of compromised hemodynamics and right heart strain, confirmed by echocardiography or CTA, are considered for such therapy. Data point towards improved early hemodynamic status in patients with sub-massive acute PTE treated with CDT (116).

CDT includes delivery of a reduced dose of clot-targeted lytic infusion, clot fragmentation, and clot aspiration. CDT utilizes endovascular techniques under radiographic imaging guidance to position specially designed catheters with side holes across a pulmonary artery thrombus to achieve clot lysis by infusing lytic agents such as tissue plasminogen activator (tPA) (117).

There are multiple types of catheters with different regimens and as the interest in this area grows, different device manufacturers are testing various devices to relieve thromboembolic PA obstruction. The two basic types of catheters are debulking and lytic delivery catheters. Debulking catheters utilize mechanical means for prompt reduction of the obstruction, best for more urgent situations. Lytic delivery catheters require more time to allow the pharmacologic lytic agents to gradually cause thrombolysis and they are thus more commonly used in hemodynamically stable patients (118).

Ekos (EKOS Corporation, Bothell, WA, USA), an ultrasound-based catheter, transmits ultrasound waves and infuses lytic agents simultaneously. It uses the benefit of mechanical softening of the thrombus to allow better diffusion of the lytic agent, enhancing the lysis of the targeted thrombus. This technique requires a lower dose of lytic agent and entails a lower risk of bleeding and ICH (119, 120).

Complications of CDT include access difficulty, access point bleeding requiring transfusion, PA injury, fatal PA perforation, distal embolization, reperfusion injury, "no-reflow" phenomena, hemodynamic deterioration, and death (118).

COMMONLY USED CDT DEVICES

The AngioVac (AngioDynamics, Latham, NY, USA) is a catheter system composed of a balloon or self-expandible funnel-tipped catheter advanced via a 26F sheath inserted into femoral or internal jugular veins, connected to an external circuit of pump, filter, and tubes that aspirates, filters and re-infuses the filtered venous blood back into the venous system, most often into the contralateral femoral vein. Its circulation is similar to veno-venous (V-V) ECMO but lacks the reservoir and oxygenator. The AnioVac system requires systemic anticoagulation, usually with heparin, with a target activating clotting time (ACT) of 300 seconds. The device in its current format is better suited for extraction of clots and masses from the inferior vena cava (IVC), superior vena cava (SVC), right atrium (RA), and RV. It uses a stiff catheter for extraction of PA clots, which is somewhat cumbersome and difficult to maneuver through the RV and PA. The risk of PA and cardiac injury by the stiff catheter has led to the use of alternative devices to access PA thrombi (121).

The **FlowTriever System** (Inari Medical Inc, CA, USA) has a 22F venous sheath and 3 self-expanding nitinol disks delivered to a target location(s) over a wire under radiographic guidance. Once in place the disks are deployed and expanded, causing fragmentation and capture of fragmented clots. The disks are then retrieved into the delivery system along with the captured fragments and externalized. This system does not require additional devices such as pumps. However, it does require specialized training because its large size sheath makes manipulation into the PA challenging.

Penumbra Indigo thrombectomy system (Penumbra, Alameda, CA, USA) has an 8F catheter system that is introduced via femoral vein inserted sheath over wire under radiographic guidance. Once placed proximal to the clot, the thrombectomy catheter is advanced while applying suction using the integrated pump system. Its small diameter makes it easier to introduce into the pulmonary circulation. This system is FDA-approved for the extraction of clots from the arterial and venous circulation.

Additional percutaneous techniques have combined clot fragmentation and aspiration to facilitate the breakdown and removal of thrombi fragments. Frequently a small dose of fibrino-

lytic agents (4 to 10 mg of tPA) is delivered at the target site for clot disruption. This process of fragmentation has been done using pigtail catheters and inflation/deflation angioplasty balloons (122).

Rotational Thrombectomy Devices, such as Arrow-Trerotola percutaneous thrombolytic device (Teleflex Inc., Morrisville, NC, USA), the Cleaner (Argon Medical Devices, Plano, TX, USA), and the Aspirex Catheter (Straub Medical, Wangs, Switzerland) are much less commonly used. They have the common features of fragmenting the thrombus by rotating different-shaped basket-like device tips and aspirating the fragmented clots (123-125). There are no randomized trials to validate the safety and efficacy of these devices.

MECHANICAL CIRCULATORY SUPPORT (MCS)

Extracorporeal membrane oxygenation (ECMO) and RV Assist Devices (RVADs) have been used since the 1970s for supportive management of patients with massive PE by providing oxygenation and un-loading the RV to allow RV recovery. ECMO is a supportive measure using a mechanical extra-corporal circuit that provides oxygenation and carbon dioxide removal from blood while supporting the cardiopulmonary system in failure situations and facilitating pulmonary recovery by avoiding barotrauma and allowing pulmonary rest (126).

There are two major types of ECMO, V-V, and veno-arterial (V-A) and, both support oxygenation and carbon dioxide removal, but V-A ECMO also provides hemodynamic support in the setting of cardiogenic shock.

In Patients with massive PE, ECMO provides hemodynamic stability before surgical embolectomy (127). The use of V-A ECMO was also found to be beneficial in reserving end-organ function and is often considered a bridge to recovery or surgical intervention. Therefore it helps providers to triage massive PE patients and determine the suitable management approach based on their clinical condition (128).

SURGICAL PULMONARY EMBOLECTOMY (SPE)

Surgical embolectomy is the last option of management, especially in those with a poor prognosis due to hemodynamic or respiratory instability. Recent reports with a focus on improved surgical approaches showed that embolectomy has similar long-term mortality rates to thrombolysis. Importantly, SPE has a lower rate of bleeding complications, ICH, and strokes. (129, 130).

In a retrospective study by Winters et al., among 126 patients treated for life-threatening PE, 60 patients underwent SPE and 66 were treated with CDL, while 10 in each group had pre-procedural hypotension, 6 in the SPE and 4 in the CDL group had pre-procedural cardiac arrest. The in-hospital mortality was 3.3% for the SPE group and 3% for the CDL group. On midterm follow-up, both groups showed marked improvement in RV function, even though 76.9% of the SPE group had moderate to severe pre-procedural RV dysfunction while 56.9% of the CDL had moderate to severe pre-procedural RV dysfunction. The authors concluded that both treatment approaches could be applied to selected high-risk PE patients with acceptable morbidity and mortality risks (131).

In another study of 44 patients who underwent SPE between 1998-2014, with 35 sub-massive and 9 massive PEs, only one patient died during hospitalization. At midterm follow-up on 12 patients, only one patient had moderate RV dysfunction and none had any more than mild tricuspid regurgitation and mild PA hypertension; these clinical outcomes lead the authors to conclude that SPE in selected patients provides favorable survival data and RV function (132).

In a study by Lattouf et al on 27 consecutive patients treated with SPE for isolated massive or submissive PE over 12 years (1998-2010), there was zero operative and hospital mortality and 79% ten-year actuarial survival, leading the authors to conclude that SPE offers excellent short and long term survival benefits (133).

In a multi-institutional study, Keeling et al reported the outcome of 216 SPEs performed at four high-volume institutions between 1998-2014. 17.8% had massive PEs and 82.2% had submassive PEs. The hospital mortality was 11.7%, skewed perhaps by a high mortality of 32% among those patients who had experienced pre-operative cardiac arrest (134).

Surgical embolectomy is usually indicated for patients with tPA contraindications, unsuccessful attempts with tPA and CDT, or patients with massive PE and shock with a high probability of death while waiting for systemic thrombolysis to be effective, or no response to thrombolysis and medical treatment, provided that good surgical expertise and resources are present (57, 135-137).

Technique: Median sternotomy is followed by anticoagulation with heparin and initiation of cardiopulmonary bypass. For optimal venous drainage and full RV access, dual venous cannulation is used. The main PA is opened longitudi-

nally, for a length of approximately 5 cm, safely distal to the pulmonic valve. Visible clots are grasped with sponge forceps. Small clot fragments can be removed with gentle suction. The aorta can be gently retracted for better visualization of the PA. A secondary incision can be made in the right PA, distal to the initial incision, between the superior vena cava and the ascending aorta for better access to distal clots in the distal right PA branches (122).

SPE can also be done via a less invasive approach. This can be achieved by femoral cannulation for CPB to provide hemodynamic support and thoracoscopic aided removal of clots via a 1.5-inch left para-sternal incision. This more technically challenging procedure avoids sternotomy while accomplishing the removal of life-threatening pulmonary emboli (138).

IVC FILTER

An IVC filter is indicated for patients with DVT/PE who have contraindications to anticoagulation or for patients with recurrent PE on adequate anticoagulation (16, 57). It is preferred to use retrievable IVC filters as these have lower complication rates (139). Retrievable IVC filters are also used in the perioperative situation for patients undergoing SPE to reduce the incidence of recurrent post-op PE. A retrospective analysis of unstable PE patients who underwent SPE showed lower mortality in those who received IVF filter (140, 141).

The American, European, and PREPIC2 (prevention of recurrent pulmonary embolism by vena cava interruption) studies have suggested not to use IVC filters in intermediate and low-risk PE patients. On the other hand, 3 large studies, from the US and Japan, reported that using IVC filters resulted in better outcomes in massive and intermediate-high-risk PE patients (142-144)

Complications associated with IVC filters are common sometimes serious. A serious side effect presented in a systematic review is venous wall penetration, which happened in 19% of the cases in that study, 5% of the patients required surgical removal of the IVC filter. Other complications include fracture of the filter and/or embolization, and DVT occasionally extending up to the IVC. (19)

The post-thrombotic syndrome (PTS), is an important DVT chronic complication, Manifestations of PTS vary from mild to severe clinical symptoms or signs limiting activity and workability. (145) It occurs in 20% to 50% of patients within 2 years of DVT diagnosis and would be severe in around 5% to 10% of cases. (145)

Typical symptoms include leg pain; leg heaviness sensation and limb swelling. Symptoms can be persistent or intermittent and are usually made worse by ambulation and improve with rest and leg elevation. (146)

Typical signs may include leg edema, redness, cyanosis when the leg is in a dependent position, perimalleolar telangiectasias, new varicose veins, stasis hyperpigmentation, skin and subcutaneous tissue thickening of the lower limb, also known as lipodermatosclerosis, and in more severe cases, leg ulcers, that can be precipitated by minor injuries. (146)

PTS RISK FACTORS AT THE TIME OF DVT DIAGNOSIS:

- DVT location: Risk is higher with proximal (iliac or common femoral vein) than distal (calf) DVT, History of ipsilateral DVT, History of primary venous insufficiency, High body mass index (BMI), and Older age. (146)

RISK FACTORS RELATED TO DVT MANAGEMENT;

- Quality of oral anticoagulation: Increase the risk with inadequate anticoagulation (Defined as sub-therapeutic international normalized ratio [INR] more than 50% of the time) especially the first 3 months with vitamin K antagonists.
- Choice of anticoagulant to treat DVT: A meta-analysis data suggested that the use of LMWH monotherapy for DVT management may lead to lower rates of PTS than giving LMWH for 5 to 7 days followed by vitamin K antagonists. (146) The use of direct anticoagulants (DOAC) can be associated with a lower risk of PTS due to their rapid onset and they're easier to administer. (147,148)

RISK FACTORS DURING DVT FOLLOW-UP;

- Recurrent Ipsilateral DVT, Persistent venous signs and symptoms 1 month post-acute DVT, in addition to Residual thrombosis on follow-up ultrasound after 3-6 months post-acute DVT) (146)

CONCLUSION

Management of RV failure in PE patients is critical and highlights the role of cardiologists and cardiac surgeons as vital members of PERT. SPE is usually indicated for patients with tPA contraindications, unsuccessful attempts with tPA and CDT, or patients with massive PE and shock with a high probability of death while waiting for other therapeutic modalities to be effective. Recent studies have shown favorable outcomes after SPE, provided that good surgical expertise and resources are present.

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