Deep Venous Thrombosis and Pulmonary Thromboembolism

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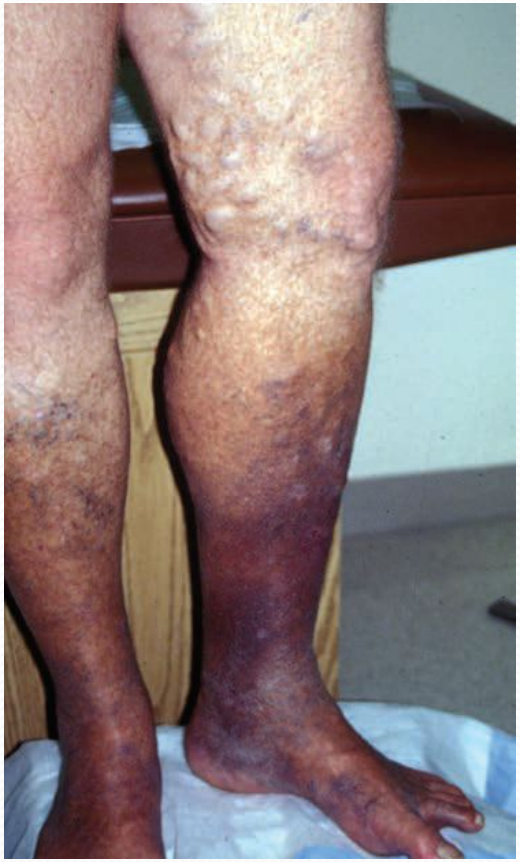
EPIDEMIOLOGY

- Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death and disability as well as psychological illness and emotional distress. In the United States, the Surgeon General estimates that there are 100,000 to 180,000 deaths annually from PE and hasdeclared thatPE is the most common preventable cause of death among hospitalizedpatients. Survivors may suffer the complications ofchronic thromboembolic pulmonary hypertension or postthrombotic syndrome.

Postthrombotic syndrome (also known as *chronic venous insufficiency) damages the venous valves* of the leg and worsens the quality of life by causing ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes skin ulceration.



PATHOPHYSIOLOGY

Virchow's triad of venous stasis, hypercoagulability, and endothelial injury leads to recruitment of activated platelets, which release microparticles.

Prothrombotic States

The two most common autosomal dominant genetic mutations are factor V Leiden, which causes resistance to the endogenous anticoagulant, activated protein C (which inactivates clotting factors V and VIII), and the prothrombin gene mutation, which increases the plasma prothrombin concentration. Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated with VTEbut are rare.

■PATHOPHYSIOLOGY

Antiphospholipid antibody syndrome is the most common acquired cause of thrombophilia and is associated with venous or arterial thrombosis. Other common predisposing factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, blood transfusion, long-haul air travel, air pollution, estrogen-containing contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma. Inflammation predisposes to thrombosis, and conditions such as psoriasis and inflammatory bowel disease have become recognized risk factors of VTE. Sedentary lifestyle is an increasingly prevalent etiology of fatal PE. A Japanese study found that each 2 h per day increment of television watching is associated with a 40% increased likelihood of fatal PE.

PATHOPHYSIOLOGY

When deep venous thrombitheir site of formation, they embolize to the vena cava, right atrium, and right ventricle, and lodge in the pulmonary arterial circulation, thereby causing acute PE. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect. Many patients with PE have no evidence of DVT because the clot has already embolized to the lungs.

Physiology

The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O2 tension gradient, which represents the inefficiency of O2 transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries. Other pathophysiologic abnormalities include: 1. *Increased pulmonary vascular resistance due to vascular obstruction* or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O2 gradient.

Physiology

2. *Impaired gas exchange due to increased alveolar dead space from* vascular obstruction, hypoxemia from alveolar hypoventilation relativeto perfusion in the nonobstructed lung, right-to-left shunting,or impaired carbon monoxide transfer due to loss of gas exchangesurface.
3. *Alveolar hyperventilation due to reflex stimulation of irritant receptors.*
4. *Increased airway resistance due to constriction of airways distal to the* bronchi.
5. *Decreased pulmonary compliance due to lung edema, lung hemorrhage,* or loss of surfactant.

- **Pulmonary Hypertension, Right Ventricular (RV) Dysfunction, and RV Microinfarction**

Pulmonary artery obstruction and neurohumoral mediators cause a rise in pulmonary artery pressure and in pulmonary vascular resistance. When RV wall tension rises, RV dilation and dysfunction ensue, with release of the cardiac biomarker, brain natriuretic peptide, due to abnormal RV stretch. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction

reduces LV distensibility and impairs LV filling. Increased RV wall

tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death.

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

Pulmonary Embolism Massive PE accounts for 5–10% of cases, and is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure.**Submassive PE accounts for 20–25% of patients, and is characterized** by RV dysfunction despite normal systemic arterial pressure. Thecombination of right heart failure and release of cardiac biomarkersindicates a high risk of clinical deterioration. **Low-risk PE constitutes**about 65–75% of cases. These patients have an excellent prognosis.

TABLE 2

Classification of pulmonary embolism

Massive

Sustained hypotension: systolic blood pressure < 90 mm Hg for at least 15 minutes OR requiring inotropes (cannot be due to another cause)

Pulseless

Persistent bradycardia (≤ 40 beats per minute with signs or symptoms of shock)

Submassive

Systolic blood pressure ≥ 90 mm Hg

Right ventricular dysfunction or myocardial necrosis

Low risk

Normal blood pressure

Normal biomarker levels

No right ventricular dysfunction

Adapted from information in reference 3.

Deep Venous Thrombosis

Lower extremity DVT usually begins in the calf and propagates proximally to the popliteal vein, femoral vein, and iliac veins. Leg DVT is about 10 times more common than **upper extremity DVT, which is often precipitated by placement** of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase. **Superficial venous thrombosis usually presents with erythema, tenderness, and a**"palpable cord." Patients are at risk for extension of the thrombosis to the deep-venous system.

DIAGNOSIS

Clinical Evaluation PE is known as "the Great Masquerader."Diagnosis is difficult because symptoms and signs are nonspecific.The most common symptom is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to ensue despite standard medical treatment of the concomitant illness. This scenario presents a clinical clue to the possible coexistence of PE.

Hospitalization for syncope was associated with a 17% rate of newly diagnosed PE in an Italian multicenter study of 560 patients. Among those patients who had no alternative explanation for syncope, 25% had PE. Even when there was an alternative explanation for syncope, 13% had PE. When clinical suspicion was high according to the Wells Score or when the plasma d-dimer level was elevated, 42% had PE. PE in these patients was anatomically extensive, and 42% had thrombus in the main pulmonary artery.

DVT, the most common symptom is a cramp or "charley horse" in the lower calf that persists and intensifies over several days.

- Wells Point Score criteria help estimate the clinical likelihood of DVT and PE**. Patients with a low-to-moderate likelihood of** DVT or PE should undergo initial diagnostic evaluation with d-dimertesting alone (see "Blood Tests") without obligatory imaging tests**. However, patients with a high clinical likelihood of VTE** should skip d-dimer testing and **undergo imaging** as the next step inthe diagnostic algorithm. **Clinical Pearls Not all leg pain is due to DVT, and not all dyspnea** is due to PE**. Sudden, severe calf discomfort suggests a** ruptured Baker's cyst. Fever and chills usually herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. Recurrent left thigh edema especially in young women raises the possibility of May-Thurner Syndrome, with right proximal iliac artery compression of the left proximal iliac vein. However, if a leg is diffusely edematous, DVT is unlikely. More probable is an acute

TABLE 273-1 Clinical Decision Rules

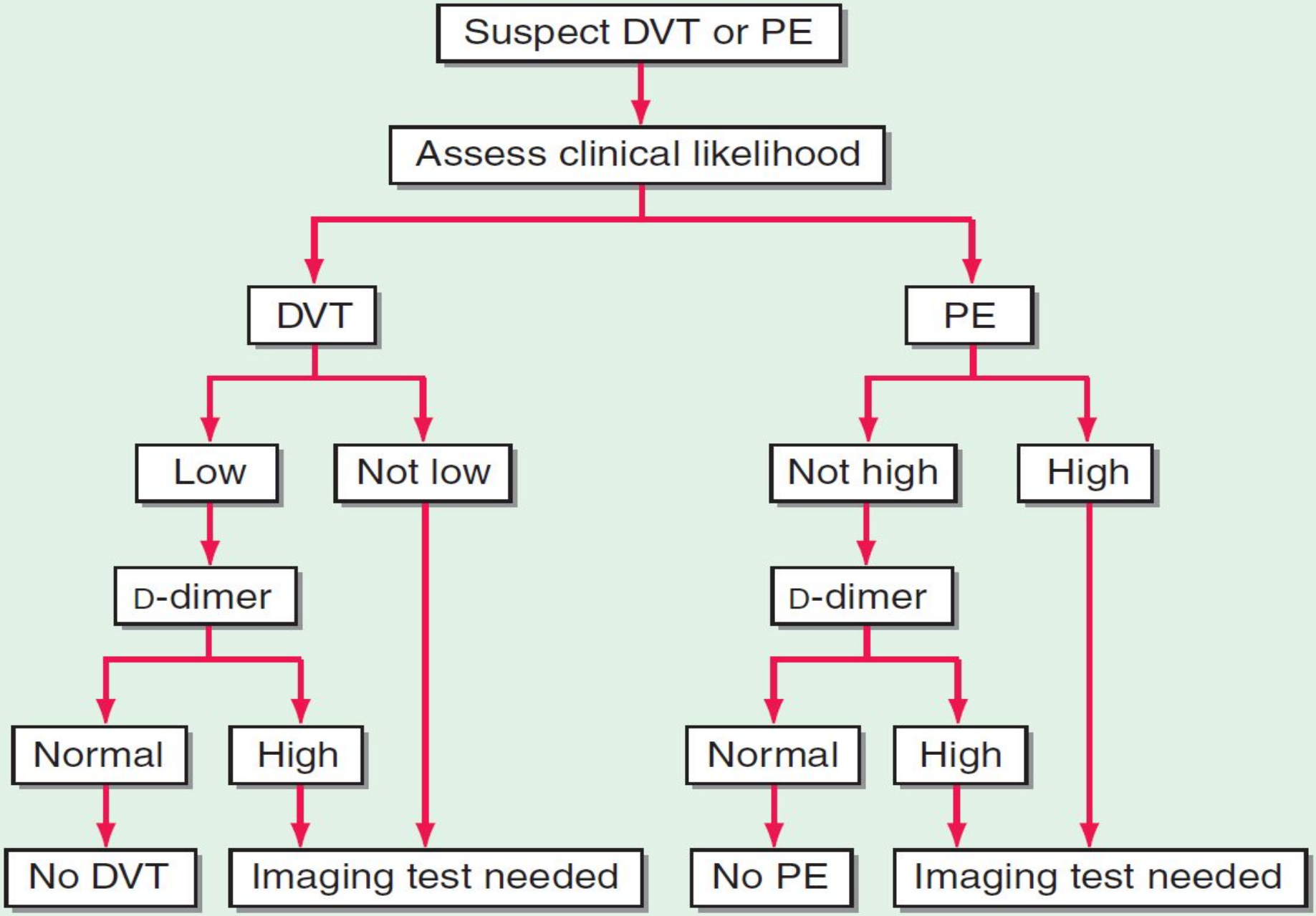
Low Clinical Likelihood of Deep Venous Thrombosis (DVT) If Point Score Is Zero or Less; Moderate Likelihood If Score Is 1 to 2; High Likelihood If Score Is 3 or Greater

CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	–2

High Clinical Likelihood of Pulmonary Embolism (PE) if Point Score Exceeds 4

CLINICAL VARIABLE	PE SCORE
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Algorithm for Diagnostic Imaging



- Patient selection is important when considering beta blockers for STEMI. Oral beta blocker therapy should be initiated in the first 24 h for patients who do not have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk for cardiogenic shock, or (4) other relative contraindications to beta blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease).

Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

exacerbation of venous insufficiency due to post thrombotic syndrome. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms. *Pulmonary infarction usually indicates a small PE. This condition is* exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. *Non thrombotic PE etiologies include fat* embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize, such as hair, talc, and cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin.

Nonimaging Diagnostic Modalities

BLOOD TESTS The quantitative *plasma d-dimer enzyme-linked immunosorbent assay (ELISA)*rises in the presence of DVT or PE because of the breakdown of fibrinby plasmin. Elevation of d-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the d-dimer is>80% for DVT (including isolated calf DVT) and >95% for PE. The d-dimer is less sensitive for DVT than for PE because the DVT thrombussize is smaller. A normal d-dimer is a useful "rule out" test. However,the d-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperativestate and those in the second or third trimester of pregnancy. Therefore,d-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

ELEVATED CARDIAC BIOMARKERS **Serum troponin and** plasma heart-type fatty acid–binding protein levels increase because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

ELECTROCARDIOGRAM **The most frequently cited abnormality,** in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III**. This finding is relatively** specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V1 to V4.

Noninvasive Imaging Modalities • VENOUS ULTRASONOGRAPHY

Ultrasonography of the deep-venous system relies on loss of vein compressibility as the primary diagnostic criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure on the ultrasound transducer. This creates the illusion of a "wink." With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity mildly dilated, and collateral channels may be absent. Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, one should consider alternative imaging modalities for DVT, such as computed tomography (CT) and magnetic resonance imaging.

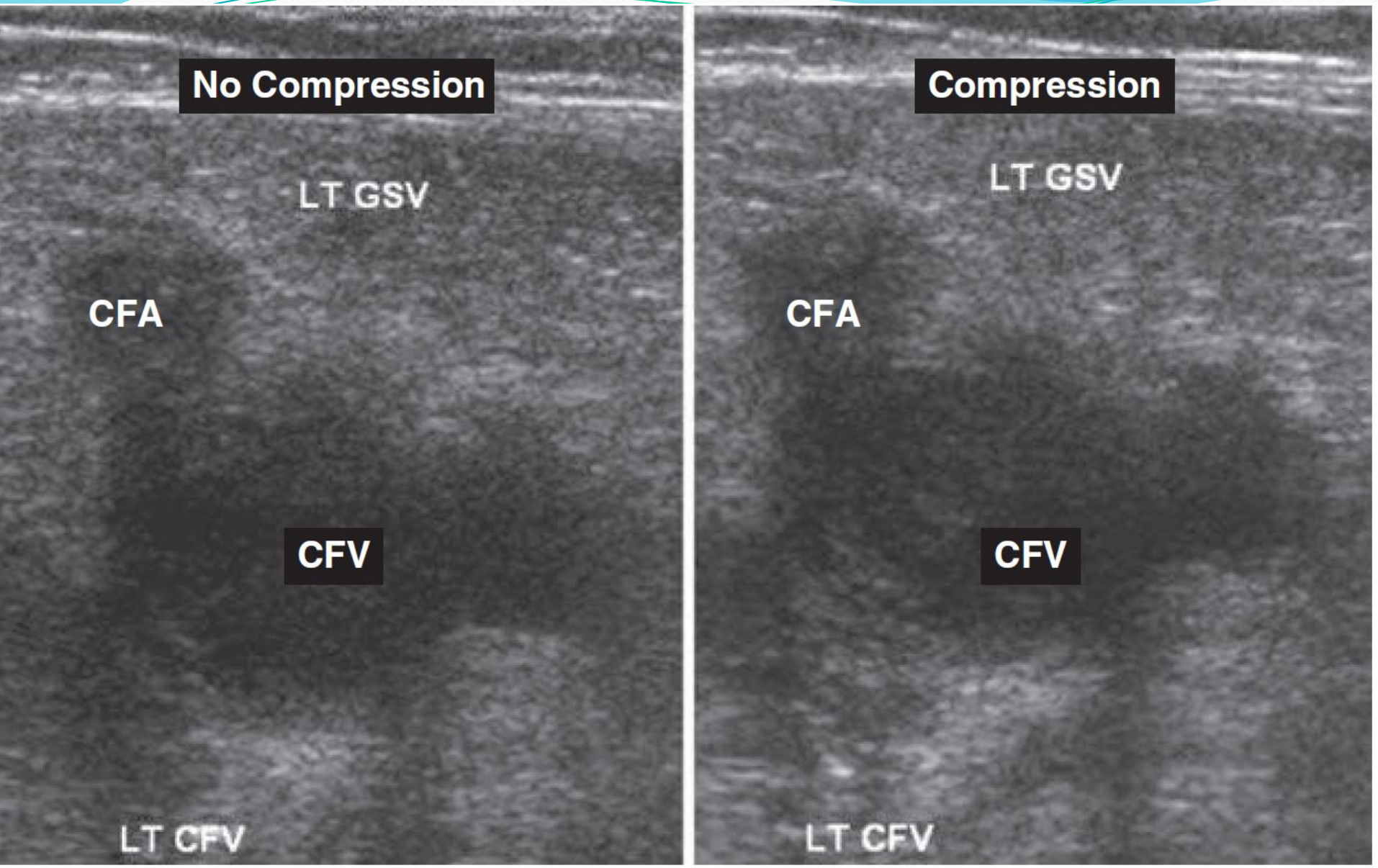
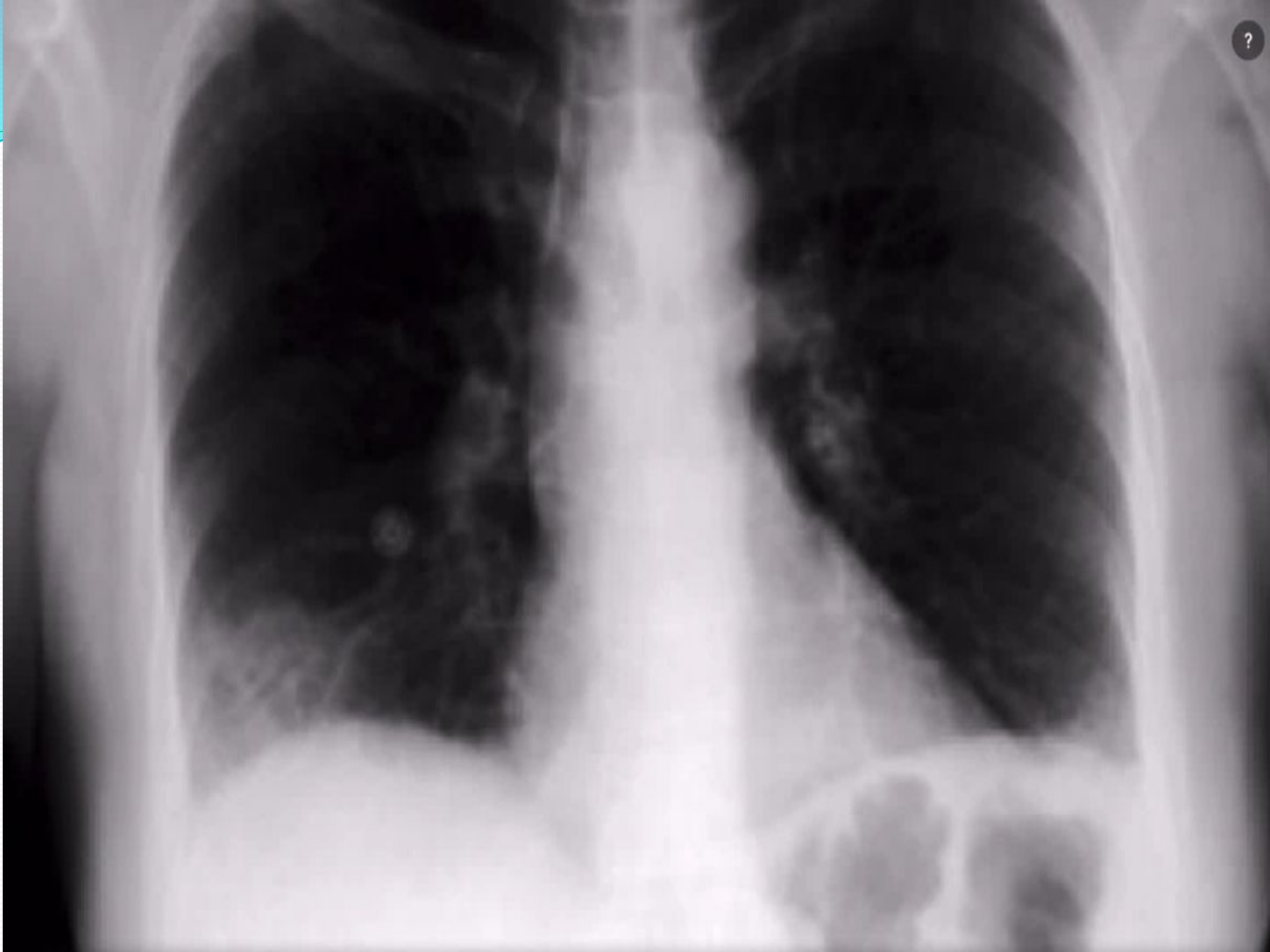


FIGURE 273-4 Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left

CXR

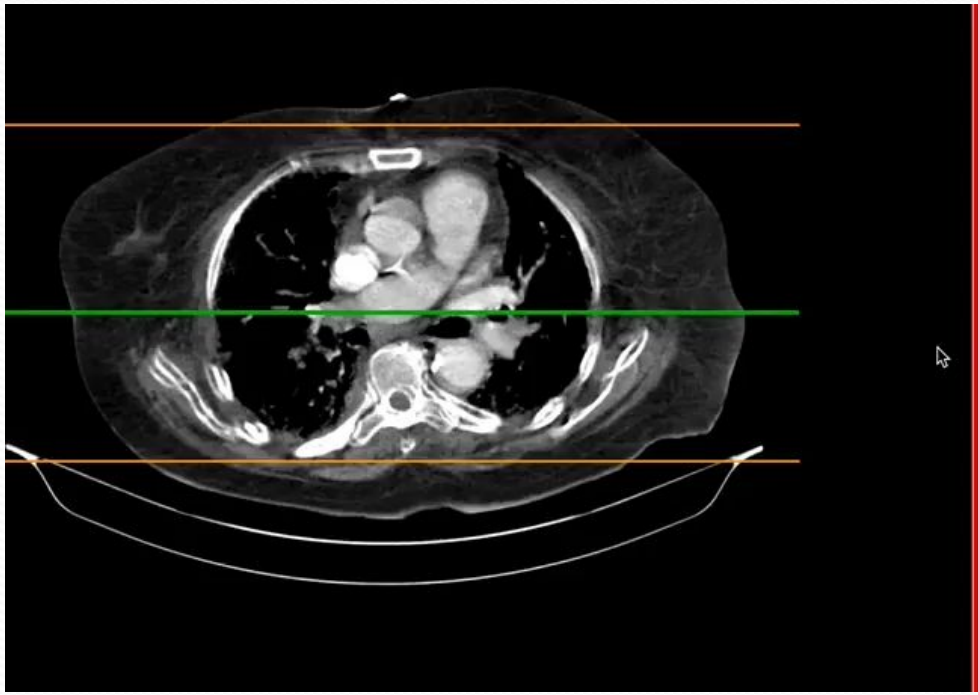
A normal or nearly normal chest x-ray

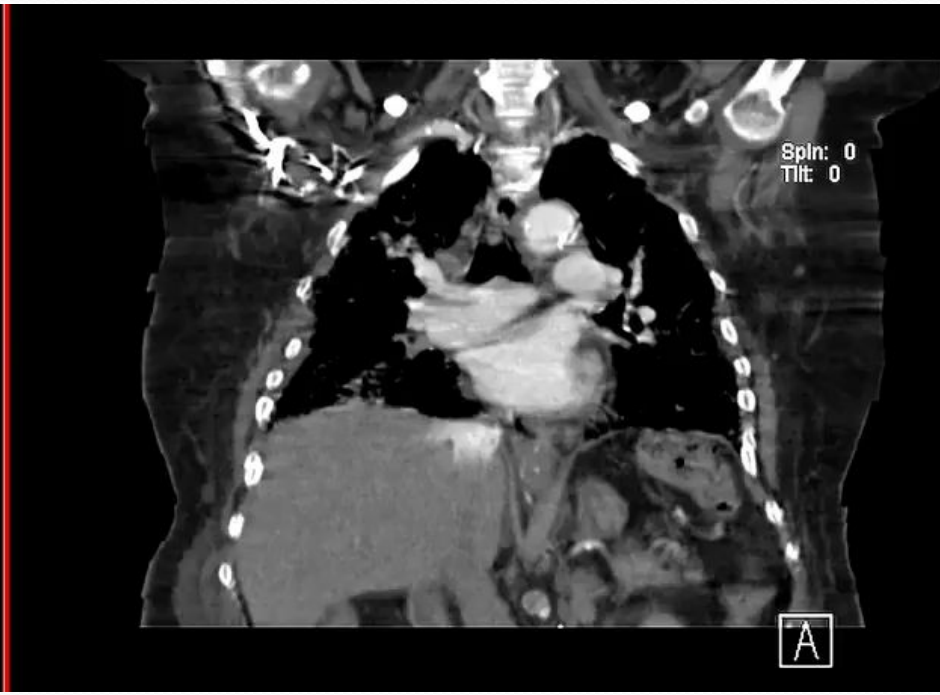
often occurs in PE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedged-shaped density usually located at the pleural base (Hampton's hump), and an enlarged right descending pulmonary artery (Palla's sign).



CHEST CT

CT of the chest with intravenous contrast is the principal imaging test for the diagnosis of PE**. "Thin-cut chest CT** images" can provide exquisite detail, with ≤1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. The CT scan also provides an excellent four-chamber view of the heart. RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE patients who have normal RV size. When imaging is extended distally below the chest to the knee, pelvic and proximal leg DVT also can be diagnosed by CT scanning. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs, such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology. Sometimes, asymptomatic early-stage lung cancer is diagnosed incidentally. Major efforts are underway to reduce radiation and contrast material requirements for chest CT. "Triple rule-out CT" utilizes ECG-synchronized acquisition, adjusts contrast material timing, and opacifies both the thoracic aorta and pulmonary artery circulation to exclude the three major causes of acute chest pain: PE, acute aortic syndrome, and acute coronary syndrome.

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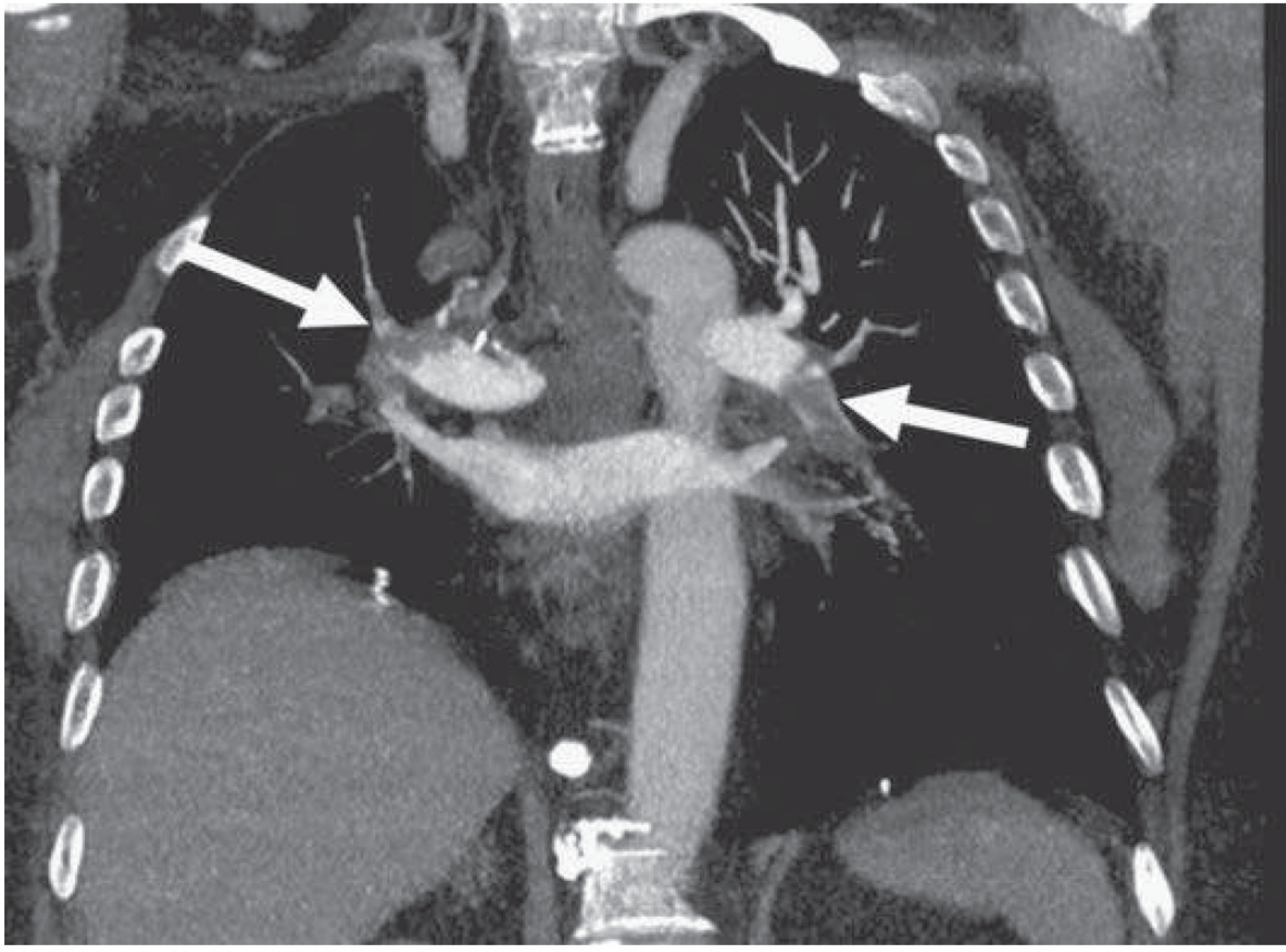
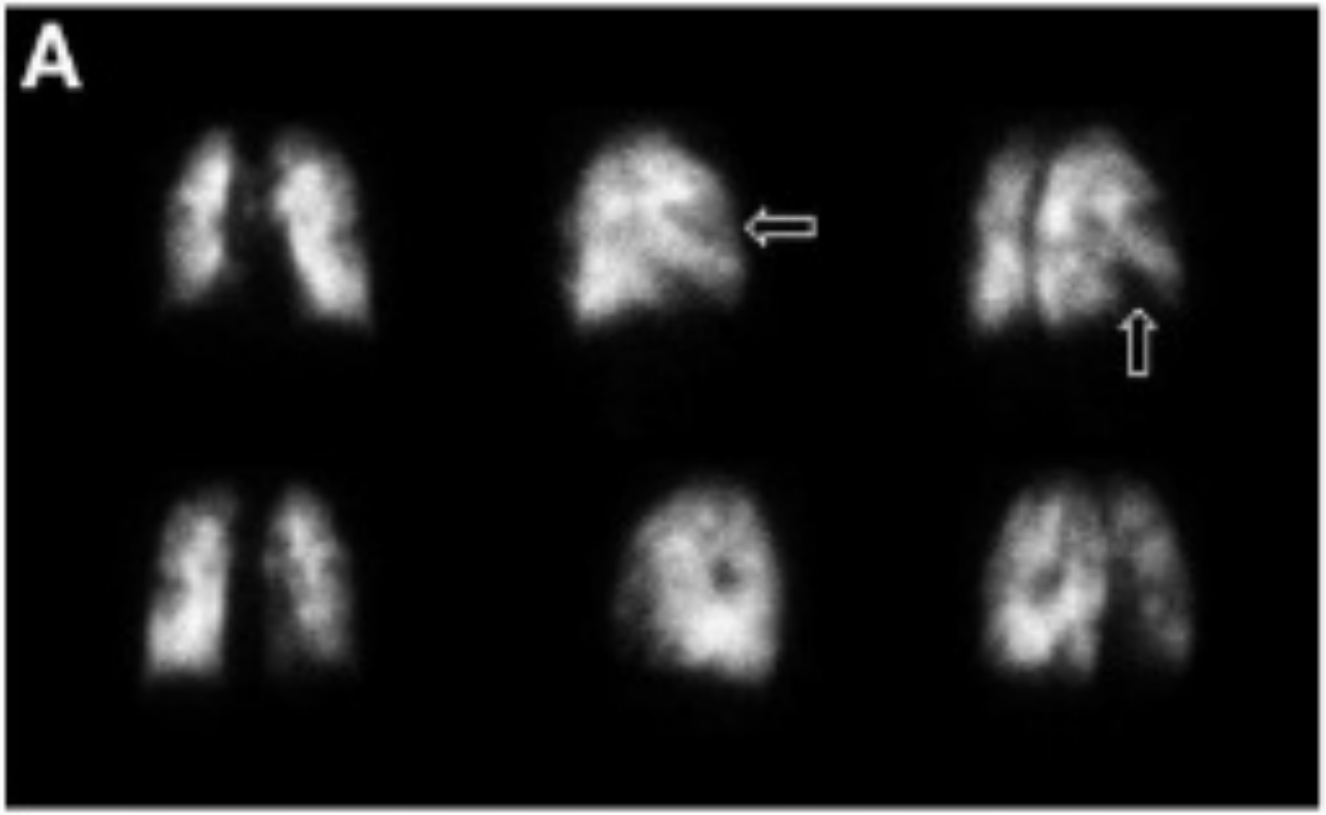


has become a second-line diagnostic

test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal non ventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such asasthma and chronic obstructive pulmonary disease. A high-probability scan for PE is defined **as two or more segmental perfusion defects** in the presence of normal ventilation. The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and, in contrast, is about 90% certain in patients with high-probability scans. Unfortunately, most patients have nondiagnostic scans, and fewer than one-half of patients with angiographically confirmed PE have a high probability scan. As many as 40% of patients with high clinical suspicion for PE but “low-probability” scans do, in fact, have PE at angiography.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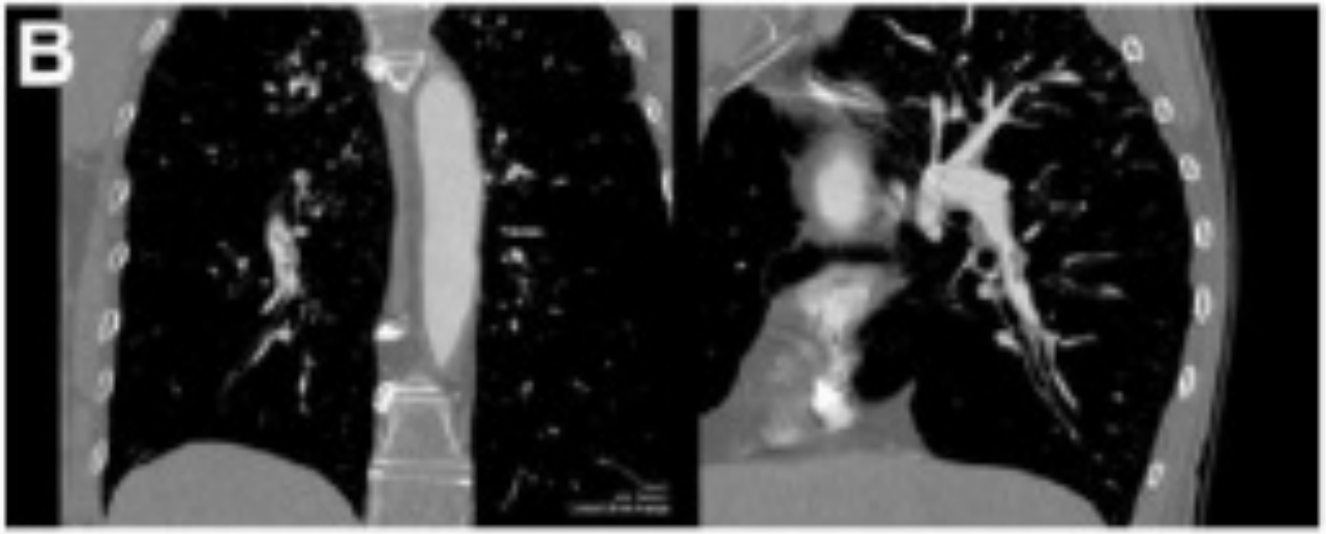
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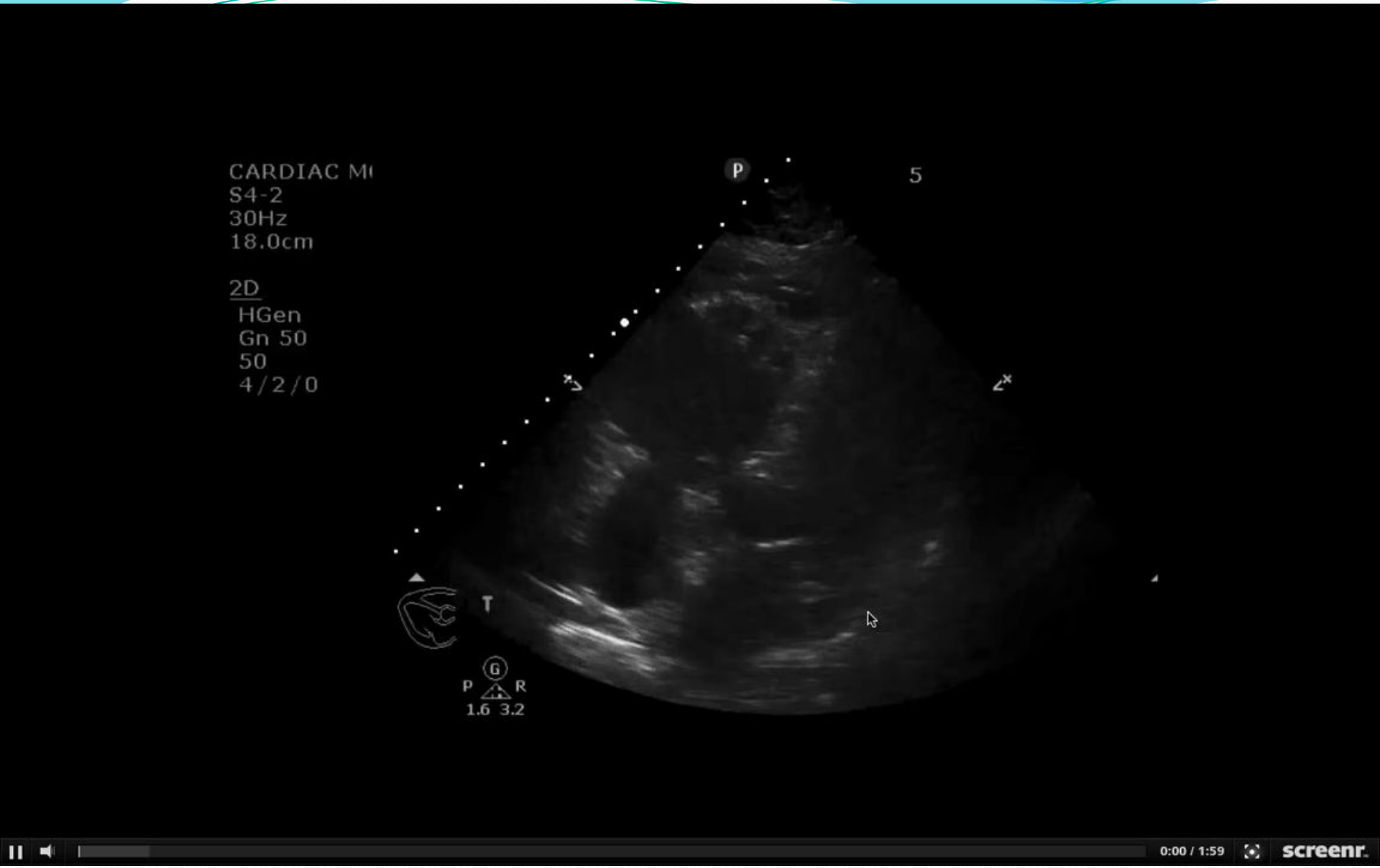
- **MAGNETIC RESONANCE (MR) (CONTRAST-ENHANCED) IMAGING When**

  ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE, but is not reliable for smaller segmental and subsegmental PE.

- **ECHOCARDIOGRAPHY**

Echocardiography is *not a reliable diagnostic* imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that may mimic PE, such as acute myocardial infarction, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or hyperkinetic motion Mof the RV apex. One should consider transesophageal echocardiographyMwhen CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast Ndespite premedication with high-dose steroids. This imaging modality can identify saddle, right main, or left main PE.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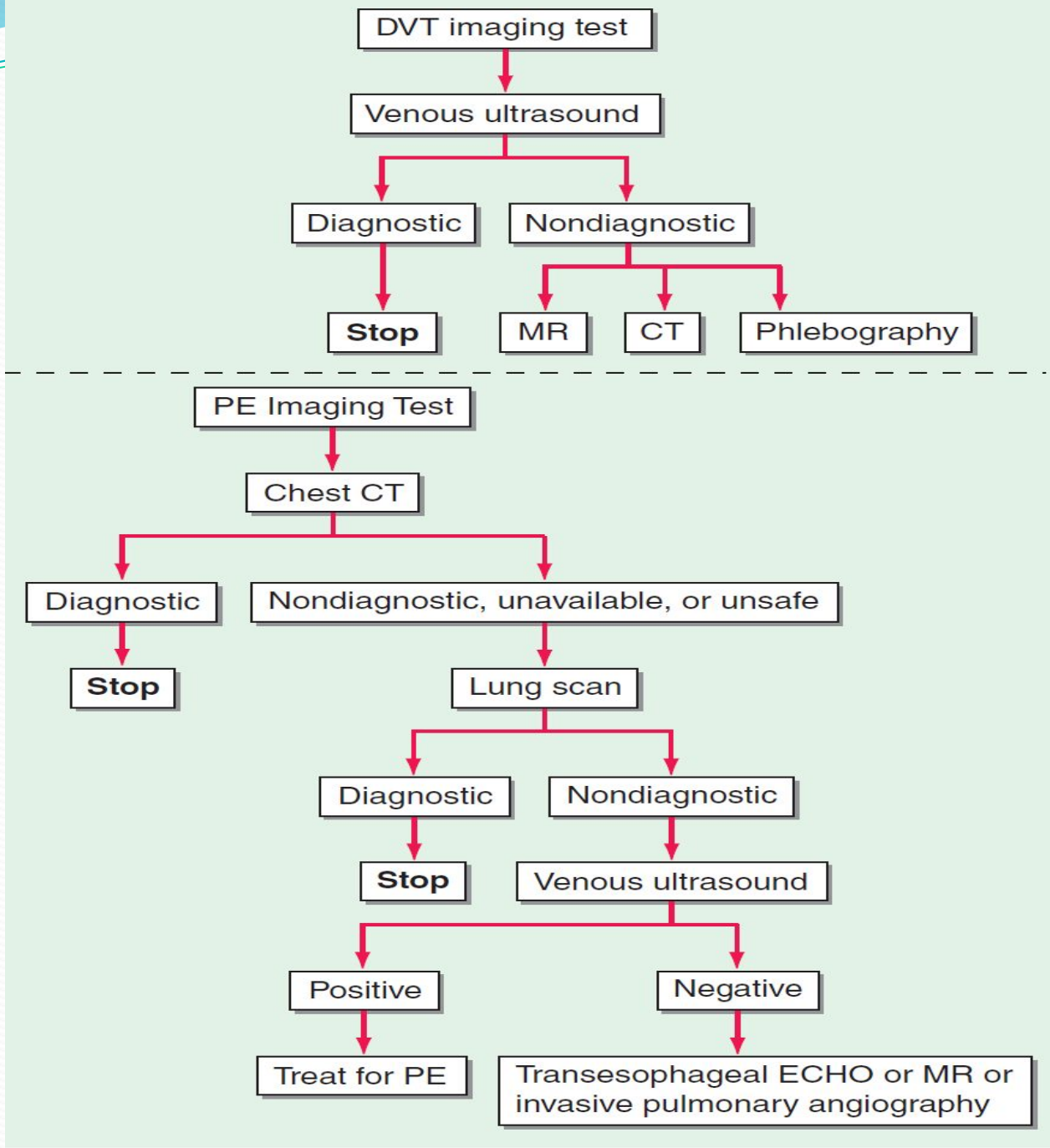
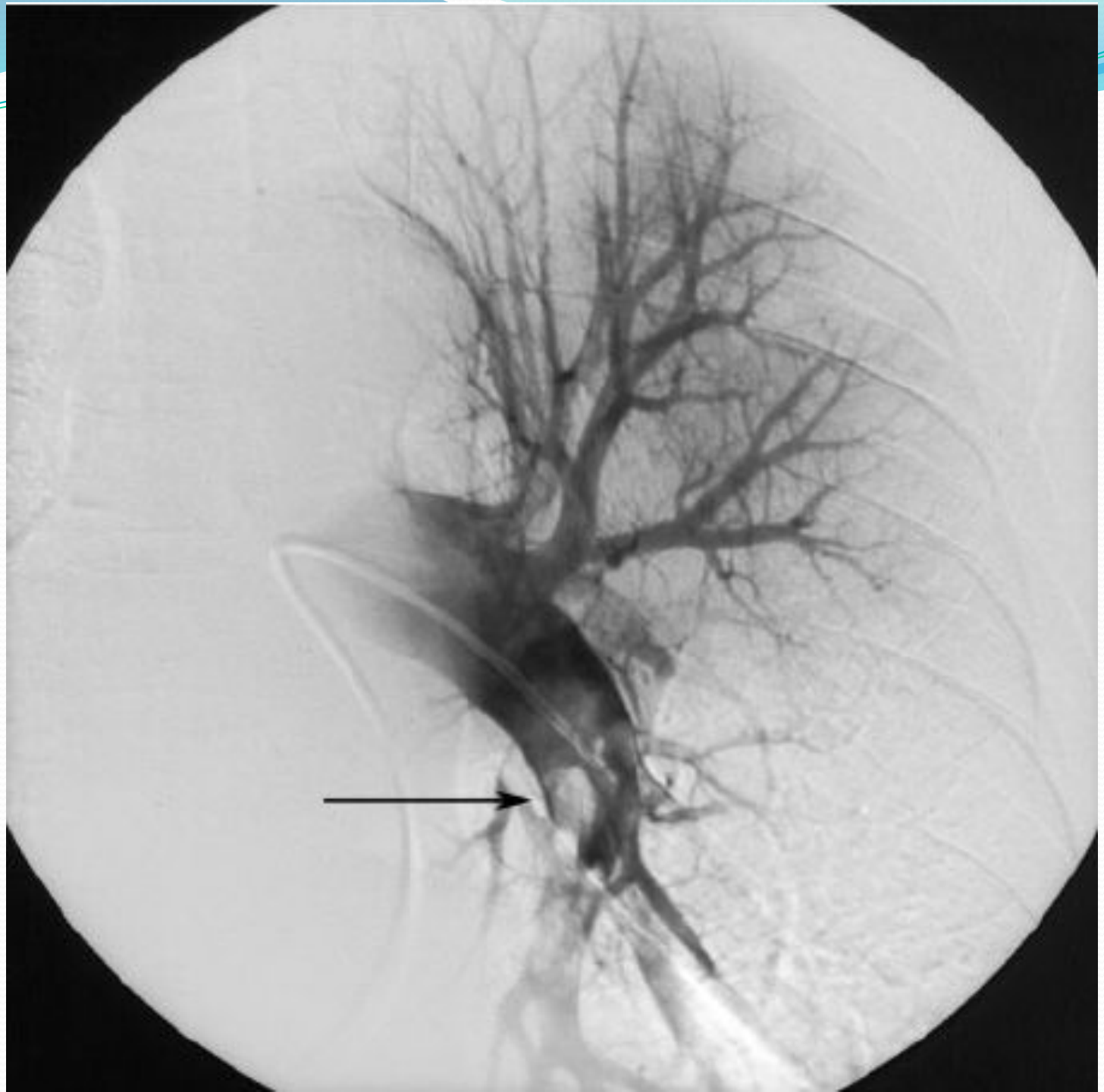
Invasive Diagnostic Modalities • PULMONARY ANGIOGRAPHY

Chest CT with contrast has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis is planned. A definitive diagnosis of PE requires visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion ("cut-off") of vessels, segmental oligemia or avascularity, and a prolonged arterial phase with slow filling, and tortuous, tapering peripheral vessels.

CONTRAST PHLEBOGRAPHY Venous ultrasonography has virtually replaced contrast phlebography as the principal diagnostic test for suspected DVT.

ALGORITHM FOR DVT AND PE DIAGNOSIS





TREATMENT

Deep Venous Thrombosis

PRIMARY THERAPY

Primary therapy consists of clot dissolution with pharmacomechanical therapy that usually includes low-dose catheter-directed thrombolysis. This approach is reserved for patients with extensive femoral, iliofemoral, or upper extremity DVT. The open vein hypothesis postulates that patients who receive primary therapy will sustain lesslong-term damage to venous valves, with consequent lower rates of postthrombotic syndrome.

SECONDARY PREVENTION

Anticoagulation or placement of an inferior vena caval (IVC) filter constitutes *secondary prevention of VTE*. *In 2016, the FDA approved* a new retrievable IVC filter that is inserted at the bedside withultrasound visualization of the femoral or internal jugular vein

(AngelR Filter) but without the need for any fluoroscopic or other radiological imaging.

For patients with swelling of the legs when acute DVT is diagnosed,

below-knee graduated compression stockings may be prescribed,

usually 30–40 mmHg, to lessen patient discomfort. They

should be replaced every 3 months because they lose their elasticity.

However, prescription of vascular compression stockings in asymptomatic

newly diagnosed acute DVT patients does not prevent the

development of postthrombotic syndrome.

TREATMENT

Pulmonary Embolism

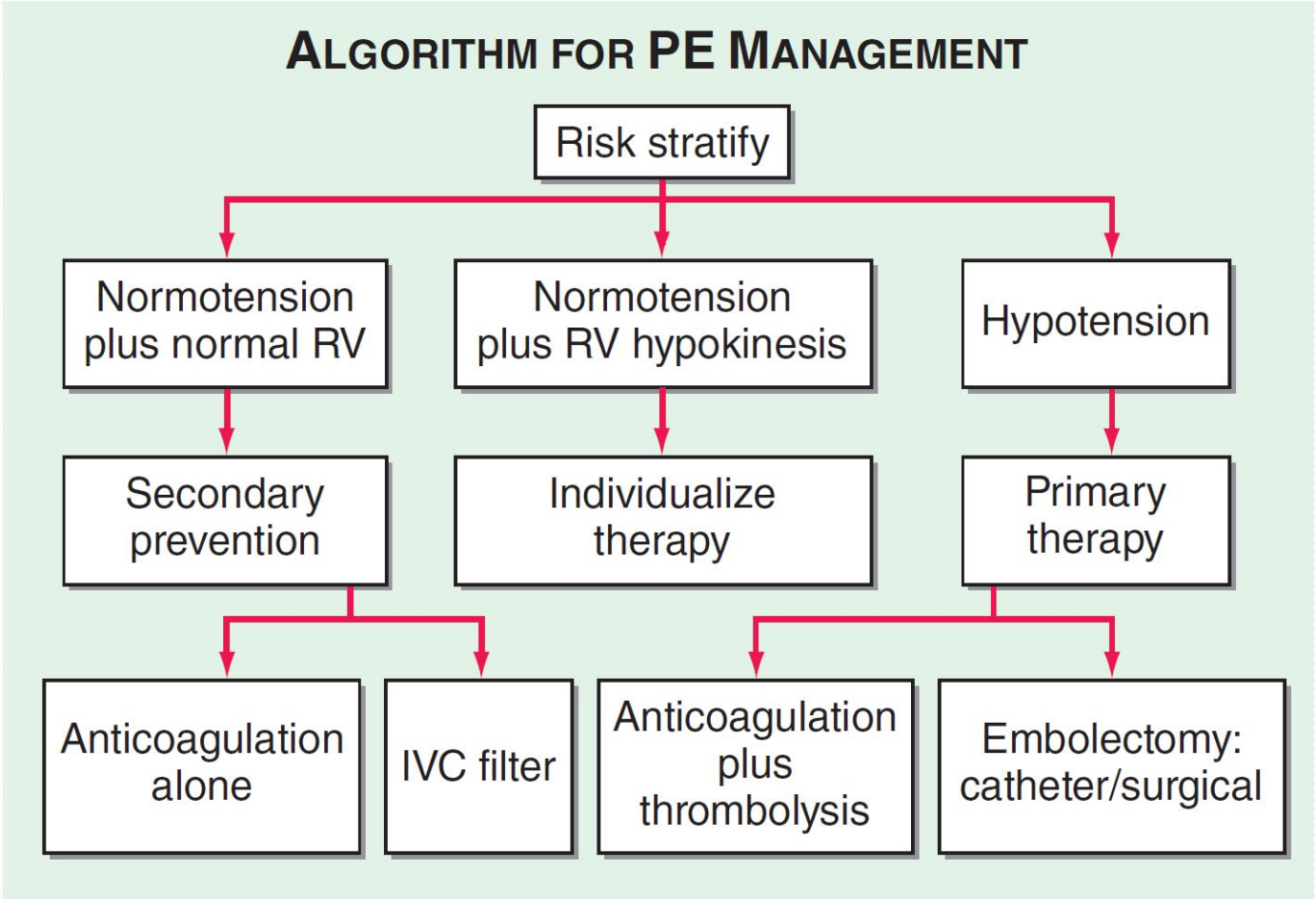


FIGURE 273-7 Acute management of pulmonary thromboembolism. RV, righ
ventricular; IVC, inferior vena cava.

ANTICOAGULATION

Effective anticoagulation is the foundation for successful treatment of DVT and PE. There are three major strategies: (1) the classical but waning strategy of parenteral anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux "bridged" to warfarin, (2) parenteral therapy switched after 5 days to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or (3) oral anticoagulation monotherapy with rivaroxaban or apixaban (both are anti-Xa agents) with a 3-week or 1-week loading dose, respectively, followed by a maintenance dose without parenteral anticoagulation. For patients with VTE in the setting of suspected or proven heparin-induced thrombocytopenia, one can choose between two parenteral direct thrombin inhibitors: argatroban and bivalirudin.

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h in patients with normal liver function. The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired. Heparin also has pleiotropic effects that may decrease systemic and local inflammation.

Low-Molecular-Weight Heparins These fragments of UFH *exhibit* less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux, an anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

Warfarin This vitamin K antagonist prevents carboxylation activation

- of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin. Warfarin dosing In an average-size adult, warfarin is often initiated in a dose of 5 mg. The prothrombin time is standardized by calculating the international normalized ratio (INR), which assesses the anticoagulant effect of warfarin **The target INR is usually** 2.5, with a range of 2.0–3.0. The warfarin dose is usually titrated empirically to achieve the target INR. Proper dosing is difficult because hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Increasing age and systemic illness reduce the required warfarin dose. Pharmacogenomics may provide more precise initial dosing of warfarin. *CYP2C9* variant alleles impair the hydroxylation of S-warfarin, thereby lowering the dose requirement. Variants in the gene encoding the vitamin K epoxide reductase complex 1 (*VKORC1) can predict whether patients* require low, moderate, or high warfarin doses.

However, genetic testing is not used clinically to dose patients with warfarin. Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Patients can self-monitor their INR with a home point-of-care fingerstick machine and can occasionally be taught to self-dose their warfarin. Warfarin can cause major hemorrhage, including intracranial hemorrhage, even when the INR remains within the desired therapeutic range. Warfarin can cause "off target" side effects such as alopecia or arterial vascular calcification. Some patients complain that warfarin makes them feel cold or fatigued.

Novel Oral Anticoagulants: Novel oral anticoagulants (NOACs) are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring, and have few of the drug-drug or drug-food interactions. Betrixaban, a direct factor Xa inhibitor, was approved by the FDA in 2017 for VTE prophylaxis in acutely ill medical patients during mhospitalization and continuing for a total duration of 5 to 6 weeks.Rivaroxaban and apixaban, direct factor Xa inhibitors, are approvedmas monotherapy for acute and extended treatment of DVT and PE, without a parenteral "bridging" anticoagulant. Dabigatran, andirect thrombin inhibitor, and edoxaban, a factor Xa inhibitor, arenapproved for treatment of VTE after an initial 5-day course of parenteral anticoagulation.

Complications of Anticoagulants

The most serious adverse effect of anticoagulation is hemorrhage. For life-threatening or intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered. There is no specific reversal agent for bleeding caused by fondaparinux or factor Xa inhibitors. However, the dabigatran antibody, idarucizumab, is an effective and rapidly acting antidote for dabigatran that is now licensed for use. Andexanet is a universal anti-Xa antidote for betrixaban, rivaroxaban, apixaban, and edoxaban that is undergoing review by the FDA. Major bleeding from warfarin is best managed with prothrombin complex concentrate. With less serious bleeding, fresh-frozen plasmanor intravenous vitamin K can be used. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absencenof bleeding.

Duration of Anticoagulation

For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, **3 months** of anticoagulation usually suffice.

For an initial episode of provoked proximal leg DVT or PE**, 3–6 months** of anticoagulation used to be the classic teaching. However, the EINSTEIN CHOICE study found that patients with provoked VTE derived as great a risk reduction in recurrent VTE with extended duration anticoagulation as patients with unprovoked VTE. For patients with cancer and VTE, **prescribe LMWH** as monotherapy without warfarin and continue anticoagulation indefinitely unless the patient is rendered cancer-free.

Among patients with idiopathic, unprovoked VTE, the recurrence rate is high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked. Unprovoked VTE may be caused by an exacerbation of an underlying inflammatory state and can be conceptualized as a chronic illness, with latent periods between flares of recurrent episodes. American College of Chest Physicians (ACCP) guidelines recommend considering anticoagulation for an indefinite duration with a target INR between 2 and 3 for patients with idiopathic VTE and a low bleeding risk. An alternative approach after the first 6 months of anticoagulation is to reduce the intensity of anticoagulation and to lower the target INR range to between 1.5 and 2. Another approach for patients at lower risk of recurrence, especially if there is an important reason to avoid long-term anticoagulation, is to consider low-dose aspirin after completing the initial period of standard anticoagulation

Counterintuitively, the presence of genetic mutations such as heterozygous factor V Leiden and prothrombin gene mutation does However, patients with antiphospholipid antibody syndrome may warrant indefinite duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

INFERIOR VENA CAVA FILTERS

- (1) active bleeding that precludes anticoagulation and
- (2) recurrent venous thrombosis despite intensive anticoagulation.
- (3)Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis
- (4) prophylaxis of extremely high-risk patients are

"softer" indications for filter placement.

The filter itself may fail by permitting the passage of small- to medium-size clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop.

MANAGEMENT OF MASSIVE PE

For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Dopamine and dobutamine are first-line inotropic agents for treatment of PE-related shock. Maintain a low threshold for initiating these pressors. Often, a "trial-and-error" approach works best; other agents that may be effective include norepinephrine, vasopressin, or phenylephrine.

FIBRINOLYSIS

Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by:

(1) dissolving much of the anatomically obstructing pulmonary arterial thrombus,

(2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension

(3) lysing much of the source of the thrombus in the pelvic or deep leg veins, there by decreasing the likelihood of recurrent PE.

The preferred systemically administered fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) prescribed as a continuous peripheral intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, this approach can be used for at least 14 days after the PE has occurred. A popular off-label dosing regimen is 50 mg of TPA administered over 2 h. This lower dose is widely perceived to be associated with fewer bleeding complications.

PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY

- PULMONARY EMBOLECTOMY
- PULMONARY THROMBO ENDARTERECTOMY 6 Month after PTE FOR treatment PHTN.

TABLE 273-4 Prevention of Venous Thromboembolism Among Hospitalized Patients

CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR 2.0–3.0) Enoxaparin 40 mg daily Enoxaparin 30 mg bid Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily, beginning 6-10 hours postoperatively Aspirin 81–325 mg daily Dabigatran 110 mg first day, then 220 mg daily Apixaban 2.5 mg bid, beginning 12–24 h postoperatively Intermittent pneumatic compression (with or without pharmacologic prophylaxis)
Medically ill patients, during hospitalization	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Medically ill patients, during and after hospitalization	Betrixaban 80 mg daily for 35–42 days
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients remains uncertain)