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Pulmonary Hypertension in the Critical Care Setting: Classification, Pathophysiology, Diagnosis, and Management

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Pulmonary hypertension (PH) is common in the critical care setting, and may be a target for specific therapy. Moderate degrees of PH are most often the consequence of acute or chronic heart failure, hypoxemia, or acute pulmonary embolism (PE), and may be relatively rapidly reversible. The consequences of more severe forms of PH, both acute and chronic, can include hypotension; low cardiac output; right heart failure with congestion of the liver, gut, and kidneys; and varying degrees of hypoxemia, each of which can lead to death or severe disability. We will review the physiology, definitions, classification, pathogenesis, diagnostic tools and algorithms for the diagnosis and specific treatments for the various causes of PH as seen in the critical care setting.

Physiology, definition, and classification

Normally the pulmonary artery pressure is about one fifth of systemic pressure. The pulmonary vasculature in adults and children has excellent vasodilator reserve and accommodates increases in flow. However, the pulmonary vasculature, like the systemic vasculature, can respond in varying degrees and pathologically to several triggers including pressure, flow, hypoxemia, toxins, and emboli, which can induce endothelial dysfunction, loss of elastance, smooth muscle vasoconstriction, and cellular hypertrophy resulting in decreased luminal diameter of the resistance vessels, the pulmonary arterioles.

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Significant PH is most commonly defined as an sPA or right ventricular systolic pressure (RVSP) >40 mm Hg or mean PA (mPA) >25 mm Hg at rest or $>$ 30 mm Hg during exercise. Additional criteria for PAH are a PCW $\leq$ 15 mm Hg, and pulmonary vascular resistance (PVR) $\geq$ 3 Wood units (also known as RU or resistance units) [2]. This definition has been used to characterize PAH for epidemiologic studies and new drug evaluation. Lesser degrees of PH with lower pulmonary vascular resistance can be found in mildly symptomatic persons with early PAH. With an increase in stroke volume from obesity, anemia, or sepsis, the sPA or right ventricular systolic pressure (RVSP) estimated from the echo-Doppler may exceed 40 mm Hg.

In the intensive care unit (ICU) patient, PH may be suspected due to characteristic signs and symptoms, discovered incidentally on an echo-Doppler, or its presence may be known at the time of ICU admission. Of course, multifactorial pulmonary hypertension is common and more often the rule in the ICU. The Venn diagram in Fig. 1 depicts the potential relationship between the various etiologies of PH. For example, pulmonary emboli, both acute and chronic, could result in PH from hypoxemia, pulmonary vasoconstriction, decrease in the pulmonary vascular volume, and often occurs in the setting of congestive heart failure (CHF). Chronic left heart failure or mitral valve disease can result in pulmonary congestion and interstitial lung disease, hypoxemia, hypertrophy of the pulmonary arterioles, and noncompliance of the major pulmonary arteries.

The determinants of the systolic pulmonary artery pressure (sPA) include the right ventricular stroke volume and compliance of the main pulmonary artery and its branches. The diastolic pulmonary artery pressure (dPA) determinants include the tone of the pulmonary arterioles, the size of the pulmonary vascular bed ($>100{,}000$ pulmonary arterioles), the pulmonary capillary wedge

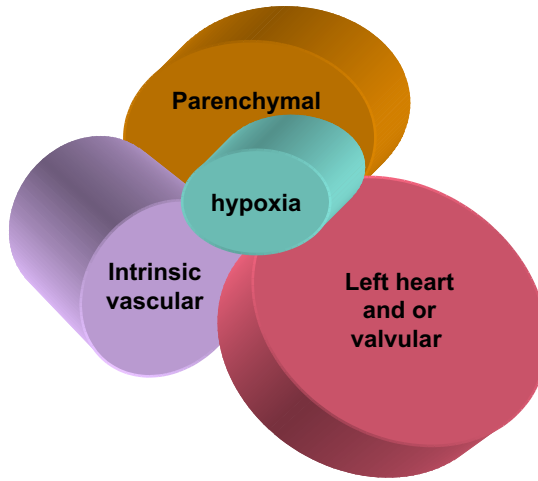

Fig. 1. Paradigm of multifactorial pulmonary hypertension.

Box 1. Classification of pulmonary hypertension (modified from Venice Classification 1)

Class I. Pulmonary arterial hypertension
Idiopathic (familial or sporadic)
Related to or associated with:
- Collagen vascular diseases (especially scleroderma and lupus)
- Portal hypertension
- HIV infection
- Congenital heart disease with right to left shunting (repaired, nonrepaired, small, large),
- Drugs and toxins such as anorexigens (fenfluramine derivatives), cocaine
- Other including Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, hemolytic anemia, splenectomy, myeloproliferative disorders

Persistent pulmonary hypertension of the newborn associated with significant venous or capillary involvement
- Pulmonary veno-occlusive disease (idiopathic or associated with scleroderma/lupus)
- Pulmonary capillary hemangiomatosis

Class II. Pulmonary venous hypertension
Left-sided atrial, ventricular, or valvular diseases or disorders
Secondary to veno-occlusive diseases due to fibrosing mediastinitis, compression by adenopathy/tumors, fibrosis by drugs, ie, bleomycin, mitomycin C, cyclophosphamide, etoposide)

Class III. Pulmonary hypertension secondary to disorders of respiratory system and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing, obstructive sleep apnea
Alveolar hypoventilation disorders
Chronic exposure to high altitude,
Alveolar capillary dysplasia, neonatal lung disease

Class IV. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal and/or distal arteries
In situ thrombotic disease, sickle cell disease
Nonthrombotic pulmonary embolism (parasites [schistosomiasis], foreign body, tumors)

Class V. Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, Other

pressure (PCW) or pulmonary artery occlusive pressure (PAOP), which is a reflection of the pulmonary venous pressure, left atrial pressure, mitral valve function, and left ventricular diastolic pressure.

The World Health Organization (WHO) classification of PH (Box 1) [1], most recently updated in 2003 at the Third World Symposium of Pulmonary Hypertension in Venice, Italy, provides a comprehensive scheme that groups disorders according to similarities in pathophysiology and treatment. The terms "primary pulmonary hypertension" and "secondary pulmonary hypertension" have been abandoned due to marked heterogeneity in the conditions to which the later term applied. Idiopathic pulmonary arterial hypertension (IPAH), formerly called primary pulmonary hypertension, is the prototype of pulmonary arterial hypertension (PAH). It is useful to first consider the mechanism/etiology of PH from an anatomic perspective as precapillary, postcapillary, or both.

Pathogenesis

The pathogenesis of diseases associated with acute and chronic PH as listed in Box 1 share much in common. PH associated with chronic thromboembolism (CTEPH) is unique in that it results from an occluding thrombus of major and secondary branches that become a fibrotic mass with occlusion or significant stenosis following varying degrees of lysis. Additionally, in a significant percentage there is further development of down-stream resistance vessel disease that is similar to that found in other causes of precapillary PH, including PAH and hypoxemia.

There are 3 major components in the pathogenesis of chronic PAH: endothelial dysfunction and vasoconstriction, vascular remodeling, and in situ thrombosis, each of which is a target for treatment (Fig. 2) [3,4]. The fourth, which occurs in severe forms or late PAH (including IPAH, scleroderma, Eisenmenger's), is the development of plexiform lesions that irreversibly obliterate the pulmonary arterioles.

Impaired endothelial function is the earliest abnormality and results in vasoconstriction due to decreased endothelial-derived nitric oxide, decreased prostacyclin, and an increase in the vasoconstrictor endothelin (ET). Abnormal endothelial function also results in in situ thrombi within the pulmonary arterioles and secondary branches due to increased thrombosis and diminished thrombolysis. Aggravating factors in both acute and chronic settings include hypoxia, acidosis (ie, in the setting of infection), and increased cardiac output (stroke volume), as occurs with pregnancy, anemia, and hyperthyroidism.

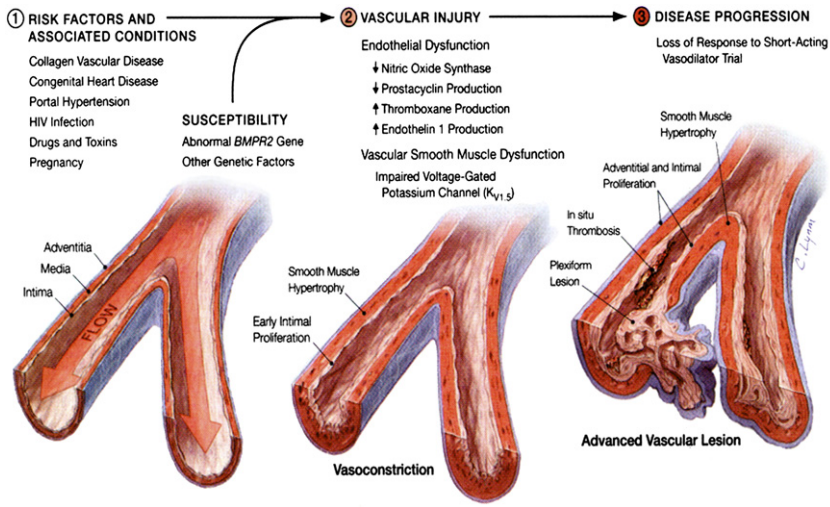

Fig. 2. Pathogenesis of pulmonary arterial hypertension. (*From* Gaine S. Pulmonary hypertension. JAMA 2000;284(24):3160–8; with permission.)

PH from any cause can result in increasing right ventricular afterload and contributes to right ventricular failure [4]. The clinical significance of PH is highly dependent on the rate of progression of the inciting disease, which influences the ability of the RV to compensate. For example, Eisenmenger's reaction in congenital heart disease has a relatively good long-term prognosis because of longstanding RV hypertrophy, while IPAH and PAH associated with scleroderma can progress to death within months to a few years.

Diagnosis, clinical characteristics, and clinical assessment

The diagnosis of PH involves detection of elevated pulmonary pressures and characterization of severity, associated findings, and hemodynamic parameters [2]. It is essential that PH is adequately characterized at the time of diagnosis, whether it is chronic or acute, since appropriate and specific treatment depends on the results. This requires measurement of pressures, mixed venous oxygen saturations, cardiac output, and assessment of right ventricular function. A stepwise approach to the diagnosis of PH has been outlined by the American College of Chest Physicians (ACCP) [5] and may be modified in the ICU as in Figs. 3 and 4.

The major determinant of symptoms in PAH is right ventricular function at rest and during exercise. Patients present with fatigue and shortness of breath due to impaired oxygen transport and reduced cardiac output, syncope from systemic hypotension resulting from systemic vasodilation and underfilling of the RV and LV, angina associated with right ventricular ischemia, and right sided failure symptoms such as lower extremity edema, hepatic congestion, and ascites. When the jugular venous pressure (JVP) exceeds 10 to

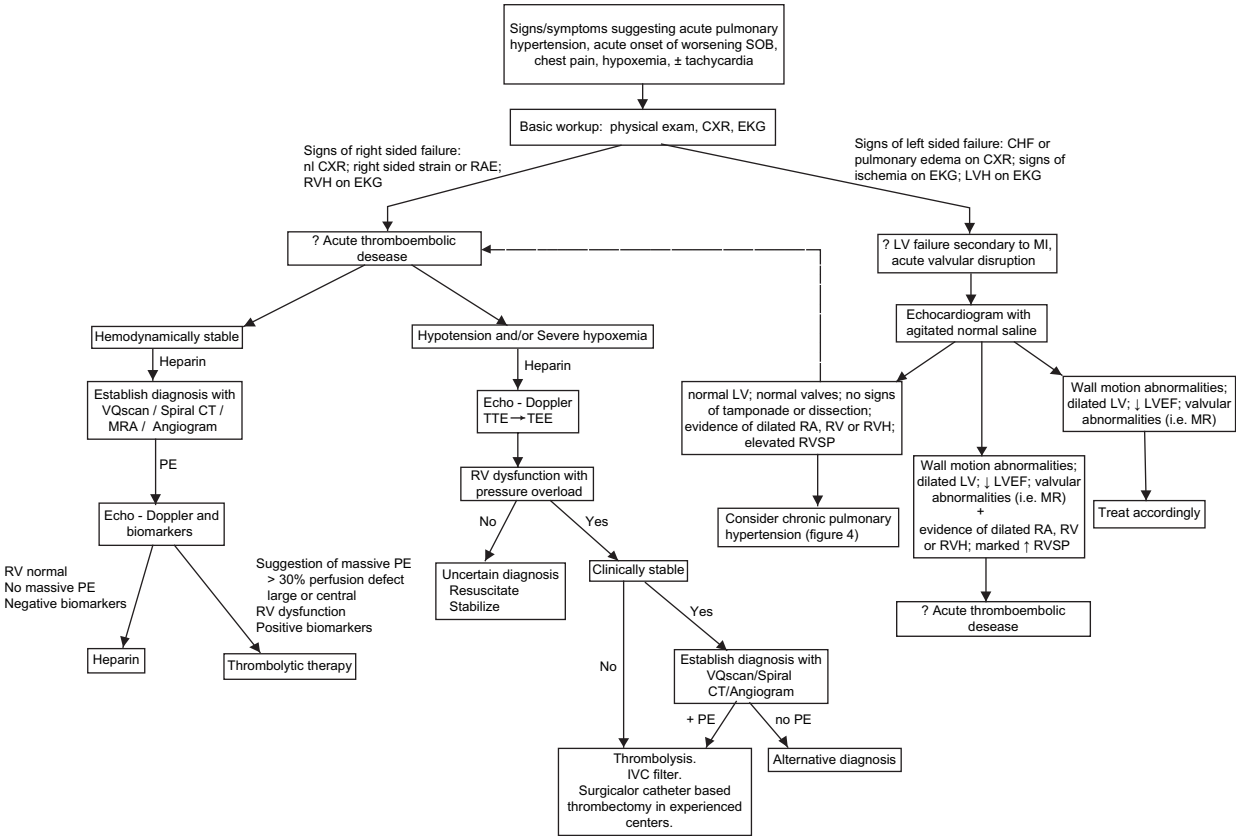

Fig. 3. Diagnostic algorithm for acute onset pulmonary hypertension. (*Adapted from* Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of the hemodynamically significant pulmonary embolism. Chest 2002;121:877–905; with permission.)

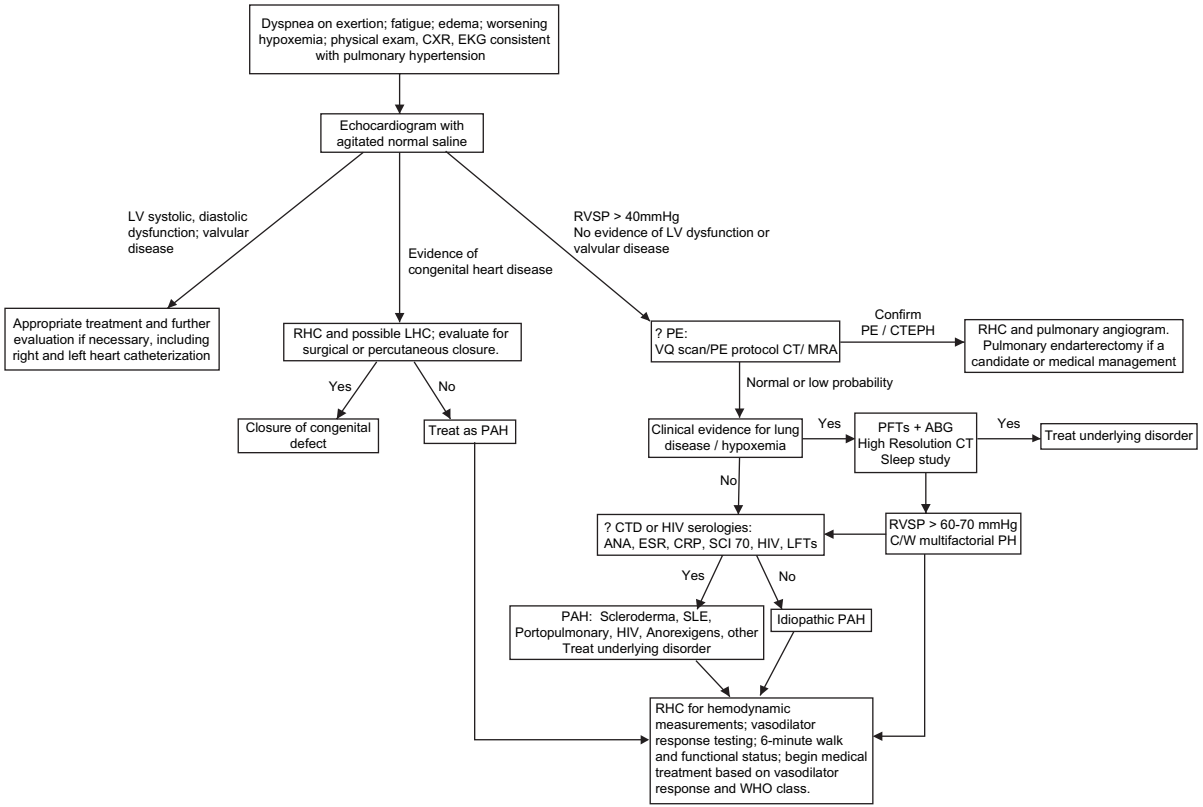

Fig. 4. Diagnostic algorithm for chronic pulmonary hypertension.

15 mm Hg, patients may have early satiety, anorexia, and gut edema, which can be associated with constipation, abdominal pain, and malabsorption. The combination of low cardiac output and high venous pressure can lead to mesenteric ischemia, pancreatitis, and ischemic nephropathy.

The severity of clinical symptoms is classified using the WHO terminology, classes I to IV, which is similar to the New York Heart Association (NYHA) classification for heart failure (Box 2).

In the ICU, patients with PH often present with severe hypoxemia, hypotension, and right-sided heart failure. The differential diagnosis in acutely decompensated PAH is described in Boxes 3 and 4.

Sudden severe precapillary PH is most commonly a result of a massive or submassive PE defined as occlusion of at least 30% of the pulmonary vascular bed in previously healthy persons, but can be less in persons with previous cardiopulmonary disease and particularly the elderly. Mild to moderate degrees of PH may be seen with acute hypoxemia, chronic obstructive pulmonary disease (COPD), pneumonia, pneumothorax, acute thromboemboli, or a left-sided event such as an acute myocardial infarction (MI) or valvular dysfunction causing pulmonary edema. Sudden severe PH can be seen when an acute insult (hypoxemia, pulmonary embolism) occurs in the setting of moderate degrees of PH associated with CHF. History and physical exam together with simple studies such as routine labs, chest x-ray (CXR), EKG, and arterial blood gases (ABG) help to clarify many of the possible etiologies.

Electrocardiogram

The ECG findings in PH lack both the sensitivity and specificity to distinguish among the various causes of PH, but the ECG should be obtained in

Box 2. WHO pulmonary hypertension functional assessment classification

Class I: Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Slight limitation of physical activity; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Marked limitation of physical activity; comfortable at rest, but less-than-ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope; signs of right-sided heart failure may be present.

Class IV: Inability to carry out any physical activity without symptoms; dyspnea and/or fatigue may even be present at rest; discomfort is increased by any physical activity; signs of right-sided heart failure are usually present.

Box 3. Causes of rapid deterioration in PAH

1. Natural history of the disease
2. Catheter occlusion or pump malfunction (prostacyclin)
3. Pneumonia
4. Indwelling catheter infection
5. RV ischemia, stunning, infarction
6. Pulmonary embolism
7. In situ pulmonary thrombus
8. Gastrointestinal (GI) bleeding
9. Anemia
10. Ischemic bowel
11. Pancreatitis
12. Acute renal failure
13. Hypothyroidism
14. Hyperthyroidism
15. Arrhythmias (atrial fibrillation/flutter)
16. Subdural hematoma (confusion/central nervous system (CNS) symptoms)
17. Hyponatremia
18. Hypokalemia
19. Dehydration (rare)

patients with dyspnea to assess for right ventricular hypertrophy (RVH) and its effects and ischemic disease, which can overlap. Care must be taken in interpretation of certain ECG findings. The $S_1Q_3T_3$ pattern (S wave in lead I, Q wave and inverted T wave in lead III), for example, reflects RVH and

Box 4. Causes of acute worsening of hypoxemia in PAH

1. RV failure and decrease cardiac output
2. Pump or catheter malfunction in patients who are on continuous therapy (ie, prostacyclin analogues)
3. In situ thrombosis
4. Pulmonary embolism (unlikely for patients who are therapeutic on warfarin and/or who are on prostacyclin analogues)
5. Pneumonia/atelectasis
6. Sepsis
7. Right to left shunt via a patent patent foramen ovale (PFO) or atrial septal defect (ASD)
8. Large pleural effusion
9. Pneumothorax

RV strain and is of no value in distinguishing PE from other causes of PH unless it appears suddenly. Left atrial abnormality or enlargement (LAE) may suggest pulmonary venous pressure elevation such as would occur in LVH, but an LAE pattern is not specific and may reflect right atrial (RA) enlargement. The typical ST-T findings in the right-sided precordial leads and inferior leads in RVH with RV strain mimic those seen in inferior MI and "anterior ischemia," and must be interpreted in the context of other available information. Automatic computerized interpretations are frequently misleading in PH [6]. An example is shown in Fig. 5.

Gas exchange and pulmonary function testing

Hypoxemia is common in PH, and usually occurs in the setting of increased minute ventilation and normal or low pCO_2. It is multifactorial in etiology, resulting from ventilation-perfusion inequality, loss of vascular bed volume, decreased cardiac output, and, in some cases, intracardiac shunting or associated interstitial lung disease. Neither the overall oxygen content nor the alveolar-arterial (A-a) oxygen gradient are useful in the diagnosis of PE [7], nor are they useful in distinguishing various causes of PH. An exception occurs when 100% oxygen does not change the arterial oxygen tension, which suggests an intracardiac shunt. In IPAH and CTEPH, pulmonary function

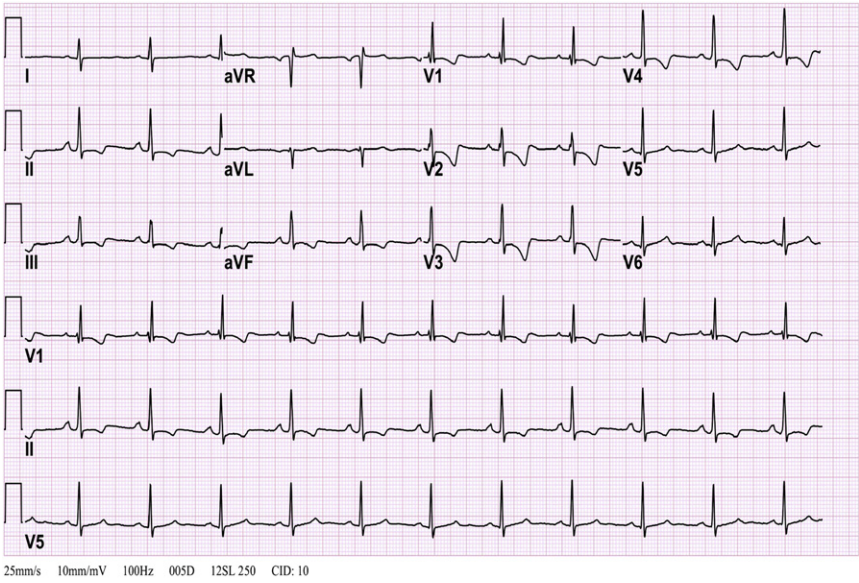

Fig. 5. Sample ECG from a patient with IPAH. This was interpreted as "ST and T wave abnormality, consider anterior ischemia, ST and T wave abnormality, consider inferior ischemia" by the computer and a cardiologist unaware of the clinical history. With the clinical history known, a more accurate interpretation would be right ventricular hypertrophy with RV strain pattern in the inferior and anterior leads (V1–V4), borderline right atrial enlargement.

tests show a restrictive pattern and a reduction in diffusion capacity (DLCO), both of which are usually mild unless the cardiac output is very low. Obstructive disease and more severe restrictive disease suggest comorbid parenchymal lung disease and should prompt a high-resolution CT scan. Severe reduction in DLCO suggests associated interstitial lung disease, a very low cardiac output, or both.

Echocardiographic evaluation of pulmonary hypertension

The transthoracic echocardiogram (TTE) can be done at the bedside in unstable patients and provides an estimate of chamber pressures and volumes and valve competence, and can be used to distinguish pulmonary venous hypertension from PAH (see diagnostic algorithm Figs. 3 and 4). RVSP is calculated based on the peak Doppler derived systolic tricuspid regurgitation (TR) velocity, and equals the sPA in the absence of RV outflow obstruction. RVSP higher than 40 mm Hg represents PH, but this measurement must be interpreted in the context of other information. RVSP higher than 80 to 90 mm Hg suggests chronic disease, since the acutely stressed right ventricle cannot generate very high pressures. Other echocardiographic features of PH include RV hypokinesis, dilation of RA and RV, tricuspid annular dilatation with TR, and abnormal systolic bowing of the intraventricular septum toward the LV causing a D-shaped LV (Fig. 6) [8].

Echo-Doppler is useful in the unstable patient with evidence of RV dysfunction. One should keep in mind, however, that elevated right-sided pressures alone without RA/RV dilation, RV failure, or abnormal systolic bowing of the interventricular septum (IVS) may not be sufficient to explain

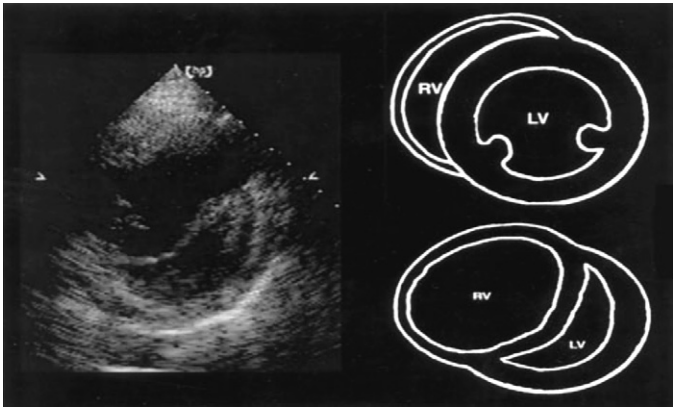

Fig. 6. Taken from a patient with hypotensive response to nifedipine. Left, short axis view shows diminished LV size and left-to-right septal bowing. Right above, normal; right below, diagram of echocardiogram on left. (*From* Ricciardi MJ, Bossone E, Bach DS, et al. Echocardiographic predictors of an adverse response to nifedipine trial in primary pulmonary hypertension: diminished left ventricular size and leftward ventricular septal bowing. Chest 1999;116(5):1221; with permission.)

hemodynamic instability. In the acutely unstable patient, TTE and/or transesophageal echocardiography (TEE) is useful for assessing LV and mitral and aortic valvular function, and to eliminate pericardial tamponade, aortic dissection, and myocardial infarction. Agitated saline should be routinely used and supplemented by cough and Valsalva's maneuver to detect intracardiac shunts such as atrial septal defect (ASD) and patent foramen ovale. The TTE may be useful in suspected PE with PH including visualization of clots in transit and by assessment of RV function, determination of prognosis, and to decide the treatment paradigm. McConnell's sign can be used to differentiate RV hypokinesis secondary to PE from other causes. It refers to the sparing of contractility in the RV apex with hypokinesis of the right ventricular base. McConnell's sign is 77% sensitive and 94% specific for PE [9].

Evaluation for pulmonary thromboembolic disease

The combination of elevated jugular venous pressure, clear lungs, hypoxemia, and cool extremities with a narrow pulse pressure is highly suggestive of acute right heart failure and the differential diagnosis in this setting includes massive PE, cardiac tamponade, right ventricular infarction, pericardial constriction, and decompensated PAH. In patients not known to have PH who present with severe hypoxemia and/or evidence of isolated right heart failure, PE should be the working diagnosis. Echo-Doppler is appropriate in some patients (see Fig. 3) while others will require computer tomographic angiography (CTA), ventilation perfusion scanning, or conventional angiography to confirm or exclude the diagnosis. In extremely unstable patients with RV failure and no underlying cardiopulmonary disease, empiric thrombolytic therapy may be considered without confirmation of the diagnosis.

Multiple strategies exist for the exclusion of PE as a potential diagnosis. Findings that are considered to exclude the diagnosis include a normal invasive pulmonary angiography, normal ventilation/perfusion scanning (V/Q), a negative D-Dimer combined with a low clinical probability of venous thromboembolic disease (VTE), and negative serial compression ultrasonography [10]. Multidetector-row CT angiography has rapidly penetrated clinical practice to become the most frequently employed modality for diagnosis of VTE in many centers, although fewer prospective data on its predictive value are available. In patients with nonacute presentation who are suspected of having PAH, central and or peripheral CTEPH must first be excluded by a V/Q scan and if necessary confirmed with a PE protocol CT or pulmonary angiogram.

Pulmonary embolism protocol computed tomography

Prospective studies evaluating the accuracy of spiral CTA in the diagnosis of PE [11,12] suggest anticoagulation can safely be withheld in clinically stable patients with low to moderate clinical probability and a negative CTA. A major advantage of CT is its ability to evaluate pulmonary

parenchyma and mediastinal structures, whereby diagnoses other than PE are made in a large proportion of patients scanned [11]. In the event of PE, as with the echo-Doppler, the finding of an enlarged right ventricle and septal bowing on CT imply an increased risk of morbidity and mortality and potential value of therapies beyond anticoagulation.

In the recently completed Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) study, multidetector row CT angiography had a sensitivity of 90% and a specificity of 95% for the diagnosis of PE, when combined with accompanying CT venography. Results that were discordant with clinical probability (ie, negative CT scan in a patient with high clinical probability or positive CT scan in a patient with low clinical probability) had significantly lower predictive values [12]. Critically ill patients were excluded from PIOPED II, however, and data regarding the use of CTA in this population are limited. A study of multidetector row CT in ICU patients revealed that 25% of CTA examinations were considered nondiagnostic on technical grounds, most commonly due to poor contrast bolus or artifact from motion or hardware [13].

Findings on CTA in CTEPH include increased size of the main pulmonary artery and branches, sharp vessel cutoffs, intraluminal thrombi or fibrotic material in the main PA and major and secondary branches, subpleural densities, bronchial artery collateral flow (arteriovenous malformations), and mosaic attenuation of pulmonary parenchyma. Negative results on CTA do not exclude CTEPH as reliably as V/Q and the latter is therefore recommended as the initial study in stable patients being evaluated for PH. CT angiography may be used for anatomic characterization in patients with intermediate or high probability V/Q scans.

Ventilation/perfusion scanning

Ventilation/perfusion scintigraphy (V/Q scan) has long been the initial diagnostic study of choice for suspected PE, but is being eclipsed by CTA, despite lack of data on reproducibility in the clinical setting as opposed to expert academic centers. In the PIOPED study [14], high probability V/Q scans with concordant clinical probability had a positive predictive value of 96% and normal scans had a negative predictive value of 96%. The principal drawback of V/Q scanning is the frequent low and intermediate probability results, which occurred in 73% of patients in the PIOPED study, and must be considered nondiagnostic. Critically ill patients, many of whom have underlying cardiopulmonary disease, are even less likely than the population at large to have a normal V/Q scan, making its utility in eliminating PE as a diagnostic possibility low. High probability results have positive predictive value in critically ill patients similar to that in other populations, and strongly suggest the diagnosis of PE, especially if clinical suspicion is also high [15]. High probability V/Q scans can be seen with tumors, vasculitis, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis [15].

Pulmonary angiography

Right heart catheterization and pulmonary angiography (PA) has largely been replaced in clinical practice by CTA because of its difficulty, expense, and the added risks associated with use of an invasive diagnostic procedure. Invasive angiography allows for localization of the embolism and measurement of hemodynamic parameters, but its primary advantage is that it allows for simultaneous therapeutic intervention. Inferior vena cava (IVC) filters can be placed and thrombi can be fragmented or extracted via catheter-based techniques. Since most patients with PE are hemodynamically stable and are not candidates for therapy beyond anticoagulation, noninvasive diagnosis is adequate. In the critically ill, the ability to make a definitive diagnosis quickly, and provide potential for therapeutic intervention, makes pulmonary angiography an attractive first-line modality. It is also useful when noninvasive testing is not definitive and empiric treatment is not justified.

PA and right heart catheterization are necessary in CTEPH patients who are unstable or at least WHO class II. Clinical, hemodynamic, and anatomic data are used to determine candidacy for surgical intervention with a pulmonary thromboendarterectomy. It may be preferable to defer angiography and hemodynamic assessment to experienced centers.

Biomarkers in pulmonary hypertension

The D-dimer assay can be helpful in excluding VTE in hemodynamically stable patients, especially if the pretest probability of VTE is low, but its role in the acutely ill or unstable patient is limited by the need to make a definitive diagnosis rapidly [10] and the high prevalence of comorbidities that can cause false-positive results.

Elevations in cardiac troponin I and troponin T occur in PE and can be useful in risk stratification. The degree of troponin elevation correlates with right ventricular dysfunction, mortality, and complicated hospital course [16]. Patients with a normal troponin have a low risk of in-hospital death, and can be safely treated with anticoagulation alone [17]. The presence of detectable troponin T is also associated with a poorer prognosis in PAH [18]. Detectable levels do not necessarily imply an acute event in PAH and CTEPH patients who may have chronic elevations.

Brain natriuretic peptide (BNP) and N-terminal brain natriuretic peptide (NT-BNP) are released in response to myocardial wall stress, and have been useful for differentiating pulmonary and cardiac causes of dyspnea. However, both are elevated in left or right ventricular pressure overload, including PE, CTEPH, and the various forms of PAH. Levels of BNP expected in WHO class IV or hypotension associated with PH range from 500 to 3000 pg/mL. BNP may be falsely low in obesity and elevated in acute or chronic

renal failure of even mild to moderate degree. A normal BNP indicates a favorable prognosis in PE [19] and IPAH [20].

Hemodynamics in pulmonary hypertension

The normal range of directly measured and derived parameters obtained on a right heart catheterization is summarized in Box 5. In healthy adults,

Box 5. Normal hemodynamic parameters

Hemodynamic Parameter	Normal Value
Right atrial pressure (RA)	≤ 6 mm Hg
Right ventricular pressure	Systolic 15–25 mm Hg Diastolic 0–8 mm Hg
Pulmonary artery pressure (PA, electrical mean PA = sPA + 2dPA/3)	sPA 15–30 mm Hg dPA 8–15 mm Hg mPA 6–19 mm Hg
Pulmonary artery occlusive pressure (mean PAOP) or PCW	≤12 mm Hg
Mean arterial pressure = (SBP + 2DBP)/3	70–100 mm Hg
Cardiac output (CO)	4–8 L/min
Fick = Oxygen consumption/ [Hgb(g/dL) × 13.6 × (SaO_2 – SvO_2)]	
Mixed venous O_2 (SvO_2) – as measured in RA, RV, or PA if no shunt;	65%–75% (without anemia)
In presence of shunt, SvO_2 = [3 × (O_2 sat in SVC) + (O_2 sat in IVC)]/4	
Cardiac index (CI) = CO/BSA	2.6–4.2 L/min/m^2
Systemic vascular resistance (SVR) = [(mean arterial pressure – mean RA)/CO]	800–1200 dynes × sec/cm^5
Pulmonary vascular resistance (PVR) = [(mPA – mean PAOP)/ CO] × 80. RU or Wood units are the absolute value not multiplied by 80.	40–120 dynes × sec/cm^5 0.5–1.2 RU or Wood units
Pulmonary vascular resistance index (PVRI) = PVR/CI	≤ 2.8 (ages 6 to 10) ≤ 3.2 (ages 32 to 45) ≤ 4.6 (ages 60 to 83)

the normal mean pulmonary artery pressure (mPA) range is 9 to 19 mm Hg. An mPA of 20 to 24 is characterized as mild PH; 25 to 35 mm Hg mild to moderate; mPA 35 to 45 mm Hg moderate; and mPA greater than 45 mm Hg is severe PH [21,22]. In PAH the PAOP or PCW is equal to or less than 15 mm Hg, whereas in pulmonary venous hypertension PAOP is greater than 15 mm Hg. Obtaining an accurate PAOP can be difficult in PH patients due to high-velocity TR jets, and enlarged and thickened vessels and elevated pressures that prevent the balloon from occluding the vessel. Special flotation catheters are available through which a stiffening wire can be carefully advanced to stabilize the catheter in place. These catheters must be used with caution to avoid perforation of the RA, RV, or pulmonary artery. When the PAOP or PCW is elevated in the setting of PH, a left heart catheterization is necessary to determine the accuracy of the PCW and contribution of left ventricular filling pressure to the mPA, dPA, and PVR. As per the Venn diagram in Fig. 1, multifactorial PH should always be a consideration when interpreting the hemodynamic data and deciding treatment strategies. For example, in scleroderma, each of the following can occur together: systemic hypertension and LV diastolic dysfunction; scleroderma heart disease; interstitial lung disease; and intrinsic pulmonary arterial disease. The presence of an elevated LV diastolic pressure and PAOP does not exclude a contribution of pulmonary arteriole vasculopathy, which could be a therapeutic target. The latter can be suspected when the mean PA to PAOP gradient is greater than 10 mm Hg, and the dPA to PAOP gradient is greater than 5 to 10 mm Hg.

Cardiac output (CO) can and should be determined by both the thermodilution and Fick methods. In the presence of significant tricuspid regurgitation (TR), the thermodilution technique may underestimate CO, whereas in the presence of a left to right intracardiac shunt it overestimates the systemic CO. In the absence of left to right or bidirectional intracardiac shunts, both techniques are useful together. Particularly since the oxygen consumption is estimated, patients are usually on supplemental oxygen, and may be anemic. A single measure or continuous monitoring of the mixed venous oxygen saturation (mVO_2) is useful for estimating cardiac output and prognosis. An mVO_2 less than 60% is associated with a poor prognosis in PAH. The implications of the mVO_2 need to be considered in light of the hemoglobin, since it will decrease proportionately.

A mean right atrial pressure (mRA) $\geq$ 8 and RV end diastolic pressure $\geq$ 12 are consistent with RV failure. The mRA correlates with the RV filling pressure unless there is more than mild tricuspid insufficiency characterized by RA v-wave $>$ a-wave. Severe degrees of RV failure (RA usually $>$10 to 12 mm Hg and as high as 25 mm Hg with giant "V" waves) results in a marked increase in RV diastolic pressure (mid-diastolic 10 to 15 mm Hg, end-diastolic 15 to 20 mm Hg), which can compress the LV causing an increased LV filling pressure and reduced LV filling volume. The dynamic interaction between the RV and LV can be associated with an increase in PCW in

precapillary PH. The underfilling of the left ventricle can result in a marked reduction in LV stroke volume and cardiac output, which will be demonstrated in the section on echo-Doppler. Markedly increased right ventricular pressures together with decreased left ventricular stroke volume and systemic pressure can compromise the right coronary artery flow resulting in right ventricular ischemia and further contributing to the right-sided failure.

Vasodilator response during hemodynamic measurements

PH specialists use the hemodynamic response to vasodilators to help decide treatment and prognosis. Vasodilator reserve infers a better prognosis [23] and treatment response to calcium channel blocker (CCB) therapy. Vasodilators that can be used include inhaled nitric oxide (iNO), intravenous (IV) epoprostenol, and IV adenosine. There is no utility to IV nitroglycerin. We prefer iNO because of its rapid onset of action and short half-life, ease of administration, and no effect on systemic pressures. Testing should be done by physicians experienced with the agents and the pitfalls with the interpretation. A positive response includes a reduction in mean PA $\geq$ 10 mm Hg to achieve a mean PA $\leq$ 40 mm Hg with an increased or unchanged cardiac output [23]. About 10% to 20% of PAH patients have a positive response, which could warrant consideration of CCB therapy. CCB therapy is never given in unstable patients, or those with right heart failure.

Treatment of acute and chronic thromboembolic disease

Acute pulmonary embolism

Fig. 3 is an algorithm for the evaluation and management of patients with symptoms and signs consistent with acute PE. In the absence of a contraindication, anticoagulation with unfractionated heparin (UFH) should be started in patients with suspected major PE. Recent meta-analyses comparing low molecular weight heparin (LMWH) to UFH in patients with nonmassive PE have demonstrated trends toward decreased recurrence and decreased bleeding with LMWH [24,25], but there are no data in massive PE (defined as hemodynamic instability and severe hypoxemia). Once the diagnosis has been confirmed, oral anticoagulation with warfarin should be continued for at least 6 months if the event was related to a reversible risk factor, and up to 5 years or longer if not [26,27].

Additional therapies may be warranted in certain patient populations. Mortality in PE increases with right ventricular dysfunction on echo-Doppler [28] or CT [29], systemic hypotension, shock, and cardiac arrest [30]. Surgical embolectomy and catheter-based interventions are options in acute PE with systemic hypotension, shock, or cardiac arrest, although the use of such modalities is not well supported by large randomized clinical trials in any population. In experienced hands, aggressive protocols for intervention

in patients with severe RV dysfunction due to PE have resulted in mortality rates below what would be expected based on historical data [31]. There are no trials comparing the effectiveness of thrombolytic therapy with surgical or catheter-based approaches. In patients with significant hypoxemia, hypotension, and other high-risk indices, thrombolytic therapy is used unless contraindicated. Surgical embolectomy and catheter-based thrombus extraction are appropriate in experienced centers in patients with hypotension who require cardiac surgery for an alternate indication and those with contraindication to thrombolytics, although the contraindications for the two approaches overlap.

Appropriate treatment of patients with RV dysfunction and preserved systemic blood pressure is controversial. Such patients face mortality rates approximately twice as high as those with uncomplicated PE [28], and some authorities advocate aggressive intervention, but improved outcomes with this approach have yet to be clearly demonstrated. In the Management Strategies and Prognosis of Pulmonary Embolism-3 (MAPPET-3) study, normotensive patients with RV dysfunction who were given IV thrombolytic therapy had decreased need for escalation of therapy, including endotracheal intubation, pressor support, and use of open-label thrombolytics, but there was no difference in mortality [32]. A recent meta-analysis of thrombolytics in PE showed no benefit overall, but there was a decrease in death or recurrent PE, which was confined to studies that enrolled patients with hemodynamic instability [33]. Larger trials are needed to definitively elucidate the role of thrombolysis and embolectomy (surgical or catheter-based) in PE. Until such studies are done, practice patterns will continue to differ by experience and intuitive bias.

IVC filters are warranted in patients who cannot be anticoagulated, have failed anticoagulation, or are thought to have insufficient cardiopulmonary reserve to tolerate further thromboemboli including those with chronic thromboembolic PH. In patients who can tolerate oral anticoagulation there is little advantage to a filter. The short-term reduction in pulmonary emboli that can be achieved via IVC filter placement is no longer evident 2 years after placement, presumably because of propagation of thrombus through the filter and formation of collateral vessels, and is balanced by a long-term increase in deep vein thrombosis [34].

Hypotension in acute PE is usually a reflection of RV failure and its treatment is similar to that in RV failure due to PAH. The use of fluids and catecholamines in RV failure is discussed later in this article.

Chronic thromboembolic pulmonary hypertension (CTEPH)

CTEPH is thought to follow incomplete resolution of one or more acute massive or submassive PE. The concept that recurrent small pulmonary emboli result in severe PH is not supported by clinical or pathologic findings.

Following occlusion of primary and secondary pulmonary artery branches, both loss of volume in the pulmonary vasculature and a progressive secondary vasculopathy [35] that is histologically indistinguishable from other forms of PH contribute to elevated pulmonary vascular resistance. Hemodynamic parameters found in significant CTEPH are similar to those found in PAH, but symptoms can occur with lower degrees of PH, particularly when associated with anemia, COPD, or CHF.

Patients with CTEPH require lifelong anticoagulation with warfarin, regardless of the presence or absence of acute PE by history. Anticoagulation does not affect the chronic emboli/thrombi that are replaced with fibrous tissue, nor prevent the progression of the pulmonary vasculopathy, but may reduce in situ thrombi and recurrent thromboembolus. Because these patients cannot tolerate further acute emboli, an inferior vena cava filter is indicated.

A pulmonary thromboendarterectomy (PEA) is indicated in CTEPH in patients who are WHO class III or greater and have a PVR of at least 3 Wood units [36]. While the risk of PEA can be as high as 25% and depends on the experience of the surgical team and patient risk factors, more than 90% of survivors benefit from surgery. At the University of California in San Diego, where the procedure was developed and refined, the mortality in the recent past is 4.4% [36]. Experience, however, is that a percentage of survivors may have persistent PH or gradual worsening of PH that requires treatments similar to PAH. There are, as yet, no clear guidelines on selection of patients for surgery. The location of the emboli influences the technical feasibility of the operation with more distal thrombus being less accessible. The degree of distal vessel vascular remodeling has important prognostic implications for patients undergoing surgery with later stage disease being associated with increased perioperative mortality and decreased postoperative hemodynamic improvement. Patients found to have CTEPH should be referred to an experienced center for determination of candidacy.

Medical therapy with IV epoprostenol has been used as a bridge to PEA in patients with CTEPH and severe peripheral pulmonary vasculopathy [37]. Improving hemodynamics by treatment of the pulmonary vasculopathy in non-occluded vessels may improve surgical outcomes, given that higher preoperative PVR confers a worse prognosis. Treatment of CTEPH patients who are not surgical candidates or who have failed PEA includes inhaled iloprost [38], sildenafil [39], and bosentan [40]. Improvements in clinical outcomes and 6-minute walk distance, and hemodynamic outcomes including PVR have been noted with each of these agents. Continuous infusion of sub-Q treprostinil was associated with an improved survival in CTEPH compared to historic controls [41]. Intravenous prostacyclins, treprostinil, and epoprostenol can be effective in WHO class III and IV CTEPH.

Treatment of pulmonary arterial hypertension

Drug treatment options for PAH or pre-capillary pulmonary hypertension are complex, vary considerably, and each has a particular role. It is important to understand the indications and complications of each. For patients with known PAH who deteriorate or with newly diagnosed WHO class III or IV PAH requiring hospitalization, referral to an experienced PAH center should be made as early as possible.

Rapid deterioration in PAH is associated with marked fatigue and dyspnea, increasing edema and ascites (anasarca), renal failure, malnutrition and malabsorption, hypoxemia, hypotension, and CNS symptoms including confusion. Box 4 summarizes the most common causes. Management of acute deterioration must be urgently targeted toward the underlying mechanisms.

Hypotension

Hypotension in WHO class IV PAH is rarely related to low intravascular volume with the exception of acute GI bleeding, overdiuresis, vomiting, and diarrhea. The risk of both upper and lower GI bleeding is increased in PH with RV failure and hypotension due to decreased gastric emptying; hypoperfused ischemic and congested bowel; warfarin; and prostacyclin, a potent platelet antagonist that causes thrombocytopenia (not immune mediated and usually 40-75 K platelet count) in 10% of cases.

More commonly, hypotension is due to worsening RV failure. If a drug delivery pump failure or Hickman catheter occlusion is found, the drug should be restarted through alternative access (including peripheral) as soon as possible. Considerations for hypotension include systemic vasodilation from CCBs (which should be avoided), sildenafil, ACEi or ARBs, and the negative inotropic effect of beta blockers and diltiazem. An excessive dose of IV prostacyclin (epoprostenol, treprostinil) may cause hypotension, which would often be accompanied by a headache, macular rash, or diarrhea. If suspected, the infusion rate can be reduced by 25% after a 1-minute interruption to test for overdose. If there is no change, that may be repeated in 5 minutes. If blood pressure is adversely affected, the previous dose should be resumed.

A quick infectious workup should be completed and broad-spectrum antibiotics should be started if infection is suspected. Central line infection occurs in 2% to 3% of patients each year in those receiving chronic IV prostacyclin therapy and is often subclinical.

It is difficult to determine volume status in PH given the RV dysfunction, low stroke volume and decreased arterial pulse pressure. An elevated jugular venous pressure (JVP) ($>$12–15 cm) is inconsistent with significant volume depletion, but intravascular volume can be low in patients with edema and ascites. Rapid fluid administration should be limited to those patients who are clearly volume depleted until invasive or echo-Doppler assessment of volume can be made. Fluid administration in the setting of right ventricular

pressure overload, as evidenced by septal bowing and a compressed left ventricle on echo (Fig. 7), will result in further dilatation and decrease in RV function and decreasing LV stroke volume. When volume status is not clear, it is reasonable to rapidly infuse 200 mL of saline over 10 minutes to assess the effect on systemic pressure.

Hypotension in patients with severe PAH *must be rapidly reversed* to avoid spiraling decrease in RV function and cardiac output. Super-systemic RV and PA pressures combined with systemic hypotension can result in critically low oxygen transport; severe hypoxemia (due to low flow and right to left shunt via a patent foramen ovale [PFO] or ASD); decrease in coronary blood flow, and RV ischemia, stunning, and infarction followed by electrical-mechanical dissociation or ventricular fibrillation. In patients not able to maintain a mean arterial pressure of at least 60 to 70 mm Hg, agents with $\alpha 1$ receptor activity (phenylephrine, norepinephrine, high dose dopamine [Table 1]) are preferred. The $\alpha 1$ receptor activity increases systemic arterial pressure and coronary perfusion pressure, systemic resistance and LV afterload, and reduces RV compression of the LV and LV outflow tract, which improves LV stroke volume and cardiac output. When systemic pressure is adequate, inotropic drugs such as dobutamine and milrinone can be added to improve cardiac output. Once systemic pressure is reasonable, IV epoprostenol can be used to increase cardiac output and reduce pulmonary pressures. On occasion, in de novo patients with PAH presenting with hypotension, iNO (not approved by the Food and Drug Administration [FDA] for this indication), a selective pulmonary vasodilator, will reduce the pulmonary artery pressure, improve cardiac output, and reverse hypotension, which gives time for long-term treatment options. Survival is rare in patients

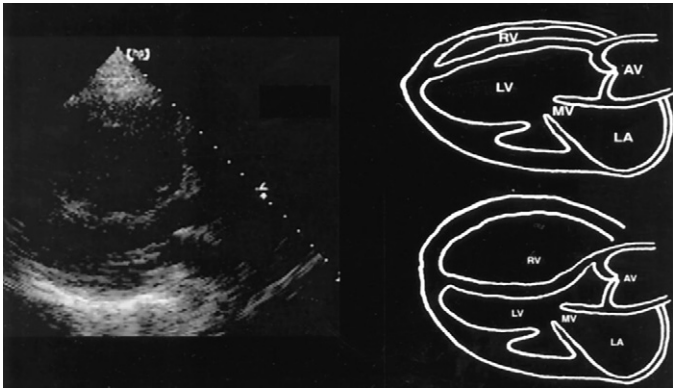

Fig. 7. Left is a parasternal long axis view taken from a patient with nifedipine hypotension. Demonstrates the decreased LV size and septal bowing occluding the LV outflow tract. Right above is normal; right below is a diagram of the echocardiogram on the left. (*From* Ricciardi MJ, Bossone E, Bach DS, et al. Echocardiographic predictors of an adverse response to nifedipine trial in primary pulmonary hypertension: diminished left ventricular size and leftward ventricular septal bowing. Chest 1999;116(5):1221; with permission.)

Table 1
Vasopressor and inotropic agents used in hypotension/shock

Agent	Receptor activity and dose (IV)	Effect	Onset and duration of action	Pitfalls
Dopamine	D1 = D2 ≫ β ≫ α Dopamine receptors: 0.5–2 μg/kg/min Beta receptors: 5–10 μg/kg/min Mixed alpha and beta: 10–20 μg/kg/min Predominantly alpha: >20 μg/kg/min	Effects on dopaminergic receptors produce renal and mesenteric vasodilation. β1 receptor activity has inotropic and chronotropic effects; β2 vasodilatory effects. Overall effect on α1 and α2 receptors causes peripheral vasoconstriction.	Onset within 5 min. Duration < 10 min after discontinuation	Initial titration may result in further hypotension. Increases ventricular ectopy and arrhythmias especially at high doses; hypertension at high doses; peripheral ischemia in presence of peripheral vascular disease.
Phenylephrine Neosynephrin	α1 > α2 ⋙⋙ β Start 100–180 μg/min, once BP is stable decrease dose to 40–60 μg/min for maintenance.	Potent vasoconstrictor secondary to α1 receptor activity	Immediate onset of action. Duration 15–20 min after discontinuation.	Hypertension; headaches restlessness; reflex bradycardia; peripheral ischemia in presence of peripheral vascular disease.
Norepinephrine Levophed	α1 = α2; β1 ≫ β2 Start with 0.05–0.1 μg/kg/min, adjust dose to blood pressure response to a maximum of 1.5 μg/kg/min.	Main action is on the β1 and α receptors, thus has inotropic, and chronotropic effects and causes peripheral vasoconstriction.	Onset is in 1–2 min; duration is 1–2 min after discontinuation.	Dose-related hypertension; reflex bradycardia; arrhythmias.
Dobutamine	β1 > β2 ⋙ α Start with 2.5 μg/kg/min, increasing gradually in 2.5-μg/kg/min increments to 20 μg/kg/min, adjusting dosage to response	Major action is inotropic effect via dopaminergic receptors and β1. The clinical effect is a potent β1 agonist with mild vasodilatory properties. Effective in combination with vasoconstrictor phenylephrine	Onset very rapid (< 2 min), peak within 10 min; duration <10 min	Arrhythmias, ventricular and atrial. May worsen hypotension given without vasoconstrictors.

with long-standing PAH on treatment who develop cardiogenic shock without a clear alternative explanation.

Hypoxemia

A similar search for a superimposed insult should be undertaken when a PAH patient becomes acutely hypoxemic, with the differential diagnosis in Box 5. When each has been excluded, the cause is deteriorating RV function and morbidly low cardiac output. Very often it is a combination of factors. Pulmonary emboli are rare in patients on warfarin and epoprostenol. Supplemental oxygen should be provided to maintain arterial saturation above 92% if possible. To maintain adequate oxygen transport (the product of arterial oxygen content [Hgb $\times$ 1.34 $\times$ sAO_2%] $\times$ cardiac output), blood transfusions should be considered. Blood products may be life saving, but could increase the antigen burden so as to preclude lung or heart-lung transplant.

Continuous positive pressure ventilation may improve oxygenation temporarily. Intubation and ventilator support may be needed for adequate oxygenation, particularly in the setting of pneumonia.

Arrhythmias

Sinus tachycardia in chronic PH is unusual and generally a manifestation of infection, hypovolemia, hypoxemia, or low output. Atrial fibrillation and flutter are the most common types of dysrhythmia and can result in rapid clinical worsening. The loss of atrial contraction and increasing rate result in decreasing LV filling pressure and volume, and decreasing RV and LV stroke volume, CO, and hypotension. Treatment of tachyarrhythmia follows the advanced cardiac life support (ACLS) algorithm with DC cardioversion of unstable patients (hypotension, hypoxemia). IV diltiazem and adenosine should be avoided in PH with markedly impaired RV function and hypotension. Rate slowing can be achieved with IV digoxin, carefully administered short-acting IV beta blockers, and IV amiodarone. For maintenance of sinus rhythm, amiodarone and type 1C agents including propafenone and flecainide can be used with caution. Disopyramide should be avoided.

Ventricular arrhythmias occur primarily in end-stage disease and their treatment, according to ACLS algorithms, is minimally effective in improving outcomes. Cardiopulmonary resuscitation (CPR) status should be discussed with PH patients and families, preferably before they become critically ill, so they can make an informed end-of-life decision. CPR is uniformly ineffective in PAH when associated with end-stage disease and severe right heart failure [42].

Adjunctive therapy in PAH

Nonspecific adjunctive therapy in PAH includes warfarin, supplemental oxygen, diuretics, digoxin, nutrition to ideal weight, salt restriction, and

regular exercise. Warfarin has been shown to improve survival in IPAH (prior to the prostacyclin era), possibly by preventing in-situ thrombi [43]. While there are no supporting data, it is also considered appropriate for PAH from associated conditions (eg, scleroderma, Eisenmenger's) [2]. Target international normalized ratio (INR) is usually 2 to 3, but is reduced to 1.5 to 2.5 when used with prostacyclins. Unlike in thromboembolic PH, there is no need to transition to warfarin with heparin or LMWH.

Patients should be assessed for the need of supplemental O_2 to maintain arterial oxygen saturation higher than 90% at rest, during sleep, and during activity. Diuretics are used to prevent RV volume overload, and the discomfort and complications of edema, ascites, and malabsorption associated with bowel edema. Electrolytes and renal function should be observed closely. Spironolactone can be used as an adjunctive and potassium-sparing diuretic and thiazides can be used sparingly to augment loop diuretics. Digoxin increases baroreceptor sensitivity, and may increase cardiac output, but there are no controlled studies. Predose blood levels should not exceed 1 ng/mL.

Because of their complexity and the need for frequent, intensive, and skilled physician and nurse monitoring, initiation of PAH-specific therapies should generally be deferred to experienced physicians and centers with dedicated programs and appropriate nursing support. Fig. 8 shows the portion of the treatment algorithm developed at the third World Symposium on Pulmonary Arterial Hypertension [44], applicable to acutely ill patients. The algorithm is based on drug safety, efficacy, ease of use, and need for rapid effectiveness. The degree and duration of benefit from each available treatment option is not predictable, and is dependent upon many factors including the duration of the disease/symptoms, WHO class, RV function, severity of PH, and etiology (eg, scleroderma worst prognosis). Combination therapies are required in most WHO class III and IV patients. The goal is to improve the patient to at least WHO class II without evidence for right heart failure. Patients are generally begun on a single agent and reevaluated every 3 months with clinical and functional assessment that includes presence of RH failure, BNP level, distance achieved on a 6-minute hall walk, oxygen requirements, and periodic repeat right heart catheterization. If patients have not improved to WHO class II with improvement in the other parameters, a second agent and/or third agent is added. If they deteriorate from WHO class III to IV, a prostacyclin analogue is added, which is usually parenteral.

CCB treatment is rarely effective and generally should be avoided, in particular empiric unmonitored use. A retrospective analysis of survival on long-term CCB therapy showed that only 54% of patients with response to acute vasodilator therapy continued to have long-term response (>1 year) [23]. The use of CCBs can result in systemic hypotension and rapid progression to death in minutes to hours.

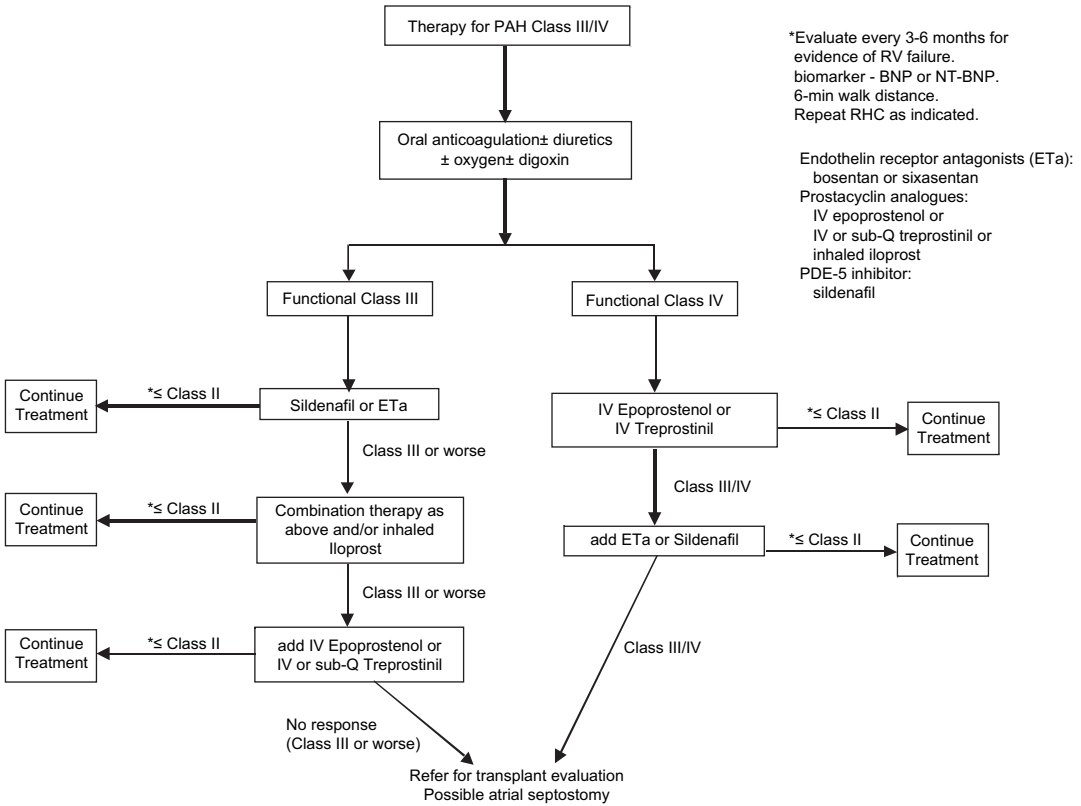

Fig. 8. Treatment algorithm for pulmonary arterial hypertension WHO classes III and IV.

Specific treatment for pulmonary hypertension

Table 2 summarizes each of the drug therapies for PAH. The material has been extracted from FDA-approved drug information inserts, references, and is supplemented by experience.

Endothelin antagonists

Endothelin antagonists (ETa) are the first oral drug class found specifically effective in PAH. Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen capable of inducing smooth muscle cell hypertrophy and is increased in patients with IPAH. There are two types of endothelin receptors—ET-A (involved in vasoconstriction and smooth muscle proliferation) and ET-B (vasodilation and involved in clearance of endothelin). Bosentan, a nonspecific ETa, and sitaxsentan (6000 times more specific for ET-A) are the two endothelin receptor antagonists that have been studied extensively. Bosentan (Tracleer) is FDA approved for PAH WHO classes III and IV. Following approval by third-party insurance, it is distributed via special pharmacies. In IPAH and scleroderma-related disorders, it improves symptoms, hemodynamics, and exercise capacity [45]. The major risk is hepatic toxicity, and liver function tests (LFTs) must be monitored monthly (see Table 2). About 10% of patients require discontinuation because of ALT/AST rise by more than threefold upper lab limits, and a small percentage for unexplained anemia. Double birth-control precautions are recommended. Other considerations include the interaction with drugs using the P-450 system, and the effects on spermatogenesis and teratogenesis. Sitaxsentan (Thelin) has been evaluated in WHO functional class II-IV patients with IPAH, PAH secondary to connective tissue diseases and congenital heart disease. It improves exercise capacity and functional class [46] and is associated with less hepatotoxicity than bosentan (3% versus 11%) [46], but still requires regular monitoring for hepatoxicity. Sitaxsentan can reduce the required dose of warfarin and increase bleeding risk if the INR is not monitored appropriately (see Table 2). A third endothelin antagonist, ambrisentan, which is intermediate regarding selectivity, is in phase III clinical trials.

Phosphodiesterase-5 inhibitor

Sildenafil (Revatio), a potent inhibitor of phosphodiesterase-5 (PDE-5), used for erectile dysfunction, is an effective treatment option for PAH. Nitric oxide (NO), the endothelial-derived relaxing factor, has vasodilatory effects that are by mediated by activation of guanylate cyclase and increased cGMP production. PDE-5 inhibition increases intracellular cGMP and prolongs its vasodilatory effects. When sildenafil is used in combination with iNO, it has been shown to augment and prolong the hemodynamic effects

Table 2
Pulmonary arterial hypertension specific drug therapy

Drug class	Dosing	Pharmacology	Effect	Adverse effect	Other benefits/pitfalls
Prostacyclin Analogue: Epoprostenol (intravenous) Flolan	Start 2 ng/kg/ min; titrate 1–2 ng/kg/min daily for 3–4 days. Wait at least 15 min between dose changes. Dose adjust q 1–2 weeks as tolerated until improved. Long-term dosing averages 45 ng/kg/min; range 10–>100 ng/kg/min. Adjust dose with weight loss and symptoms.	Half life <4–6 min. Reaches steady state in 15 min. Clinical improvement may be seen within hours.	Potent vasodilator of the systemic and pulmonary vasculature; antiplatelet; Major effect is long-term improved RV function and cardiac output and vascular remodeling. Benefit in days, but major effects at 3–6 mos.	Headache; flushing; jaw pain; diarrhea; nausea; body aches; hypotension; dizziness rash; anemia; thrombocytopenia; hypersplenism, hyper- and hypothyroid, goiter	Unstable at room temperature, needs to be kept at 2–8°C at all times; mixed by the patients in sterile fashion; requires central venous access for long term; interruption may cause rebound worsening of PH and death; infusion line infections not uncommon. May be infused via peripheral IV. Can use standard high-precision infusion pump in the hospital setting. Monitor regularly for thrombocytopenia (40–80K) that occurs in 10% of long-term users and is an indication to stop warfarin

(*continued on next page*)

Table 2 (*continued*)

Drug class	Dosing	Pharmacology	Effect	Adverse effect	Other benefits/pitfalls
Treprostinil (intravenous; subcutaneous). Remodulin	Sub Q and IV: start 1.25 ng/kg/min and increase by 1.25 ng/kg/min/wk × 4 wks then by 2.5 ng/kg/min/wk as tolerated. Dose range 15–100 ng/kg/min. Experienced centers will titrate faster.	Half life 3 h. Almost 100% bioavailable. Reaches steady state in 10 h.	Similar to epoprostenol.	Sub-Q: pain, induration or erythema at infusion site; otherwise as with epoprostenol for IV with possibly less side effects.	Stable at room temperature; comes premixed; catheter can be replaced or pump switched without serious complications given the long half-life; used sub Q need to change the infusion site every 2–30 days to prevent infusion site reaction. Dosing IV and sub Q are the same. Dosing experience less than epoprostenol, In unstable patients would prefer epoprostenol.
Iloprost (inhaled) Ventavis	Start 2.5 μg/inh × 6–8/day. Increase to 5 μg/inh in 1–2 wks as tolerated. Daily doses >45 μg has not been studied in randomized control studies.	Half-life 20–30 min. Acts within 30 min. Not detectable in plasma 30 min–1 h after inhalation	Similar to others but less potent	Jaw pain; headache; mild cough; flushing; dizziness; hypotension.	Inconvenient given frequency and duration of inhalations. Can be used safely with sildenafil and endothelin antagonists. When combined with sildenafil may need less frequent dosing. No clinical trial data with ventilators or during anesthesia

Endothelin Antagonists: Bosentan (oral) Tracleer	Initiate at 62.5 mg twice a day × 4 wks then increase to 125 mg twice a day.	Half-life is 5 h. Max plasma concentration is attained in 3–5 h.	Causes vasodilation in the systemic and pulmonary vasculature. First effect at 2–4 wks maximal effect 3–6 mo.	Liver toxicity (10%); headache; flushing; hypotension; edema; anemia; decreases efficacy of oral contraceptives	Teratogenic. Liver toxicity is enhanced when used with glyburide. Metabolized by and inducer of CYP2C9 and CYP3A4 and caution with drugs affecting this system (ketaconazole). Contraindicated with cyclosporine and glyburide.
Sitaxsentan (oral) Thelin	100 mg daily	Half-life is 10 h and steady state reached in about 6 d.	Causes vasodilation in the systemic and pulmonary vasculature with remodeling. Initial effect seen at 2–4 wks and continues to improve 3–6 mos.	Liver toxicity 3%; peripheral edema; nausea; nasal congestion; headache; dizziness	Primarily metabolized by and inhibitor of CYP2C9, which interferes with warfarin metabolism and elevates INR. Teratogenic.
PDE-5 inhibitors: Sildenafil (oral) Revatio	20 mg, 3 times a day, with 4–6 h between doses.	Half-life is 4 h. Peak levels in 60 min after ingestion.	Systemic and pulmonary vasodilation and remodeling likely. Onset may be in hours to days with maximal effects in 3–6 mos.	Visual changes; dyspepsia; flushing; headache; hypotension.	Metabolized by CYP 450 system. Contraindicated with nitrates.

and prevent rebound vasoconstriction when iNO is discontinued [47]. Sildenafil has been evaluated extensively in a large randomized placebo-controlled trial in PAH WHO classes II to IV. At both 12-week and 1-year follow-up there was an improvement in functional class and exercise tolerance, and a very good safety profile [48]. Hemodynamic benefits are similar to those found with the endothelin antagonists. Clinical experience suggests it is safe and effective in combination with prostacyclin and ETa, each of which is being evaluated in clinical trials. Sildenafil is approved for PAH regardless of WHO class.

Prostacyclin analogues

IV epoprostenol (Flolan) is the first available drug specific for PAH and remains the most appropriate first-line agent in the critically ill. Epoprostenol improves symptoms, hemodynamics, and long-term survival in PAH classes III and IV [48,49], and is FDA approved for use in WHO classes III to IV. It has a sustained benefit on survival; 62.8% at 3 years compared to expected 35.4% survival based on historical controls [49].

Because it is a complicated drug with a very short half-life requiring continuous IV delivery via an indwelling catheter (see Table 2), patients initiated on epoprostenol and their significant others require a great deal of education and support to manage the drug and its delivery system. Complications of therapy include failure of the infusion pump; dislodgement, occlusion, or fracture of the indwelling catheter; and catheter infections ranging from local abscess and cellulitis to bacteremia and sepsis, which can be mono- and poly-microbial. Any bacterial pathogen including diptheroids can seed the catheter and result in bacteremia.

Treprostinil (Remodulin), a newer prostacyclin analogue with a half-life of 3 to 4 hours, can be given by continuous subcutaneous or IV infusion. IV epoprostenol, IV treprostinil, and subcutaneous treprostinil have similar hemodynamic effects [50]. Because of less long-term experience, IV treprostinil is best used in patients who are stable. The largest treprostinil trial included WHO class II to IV patients (IPAH, scleroderma, and congenital heart disease) and showed improved exercise capacity with 6-minute walk distance [51]. There is a long-term survival benefit in PAH and CTEPH, when compared to historic controls [41]. Both sub-Q and IV treprostinil are easier to administer than epoprostenol because of its longer half-life and stability at room temperature (see Table 2). Sub-Q administration is safe and effective, and avoids the risks of the indwelling catheter. However, it is associated with injection site pain, which is tolerated by most patients. With appropriate correction of dosing, transitions between epoprostenol and IV and sub-Q treprostinil can be done safely and quickly in the hospital setting.

Iloprost (Ventavis), a prostacyclin analogue, is an effective treatment for PAH that is delivered by inhalation six to eight times a day. Because of the

limited dosing delivery that can be achieved by inhalation, it is potentially less effective than parental prostacyclin. It has been shown to improve hemodynamics, exercise capacity, quality of life, and survival (see Table 2) [38,49,52]. It can be used as an alternative to parental prostacyclins in patients who refuse or do not have the ability to tolerate the complexity of those agents. It is generally used in combination with oral agents in patients who remain symptomatic (>WHO class II) or have had inadequate improvement in 6-minute hall walk or invasive hemodynamic parameters, particularly cardiac output.

Inhaled NO

Although not FDA approved for children and adults with PAH, iNO is a treatment option for the hemodynamically unstable patient in the ICU and postoperatively. It has the advantage of increasing pulmonary perfusion only in ventilated areas, which can improve gas exchange and decrease PVR without increasing intrapulmonary shunting, as could occur with epoprostenol (presumably by vasodilating unventilated lung segments). Inhaled NO is rapidly inactivated in the alveolar capillaries preventing effects on the systemic vasculature. Patients stabilized with iNO may be converted to IV epoprostenol therapy for longer-term use. Sildenafil prolongs the effect of NO by preventing breakdown of its second messenger, cGMP, and may mitigate the rebound effect seen with discontinuation of iNO.

Surgical options for PAH

The mortality in PAH remains high despite advances in therapy, particularly for those WHO class III and IV who do not improve within the first 3 to 6 months. The average life expectancy of 2 years in IPAH has been extended to beyond 5 years with epoprostenol [53]. Death is usually a result of progressive right ventricular failure. As discussed, the markedly dilated RV progressively compresses the LV resulting in hypotension and low cardiac output and worsening RV function. Based on better survival in PAH with a PFO or ASD, catheter-based balloon and blade atrial septostomy have been used to create right to left shunting at the atrial level. By reducing the RV systolic and diastolic load and increasing flow to the underfilled left ventricle, the induced shunt can increase systemic pressure and cardiac output. While high risk, atrial septostomy can improve functional capacity at the expense of profound hypoxemia if the hemoglobin is adequate. In the United States it is generally reserved as a bridge to lung or heart lung transplantation. Lung and heart-lung transplantation are options for relatively young PAH patients who remain WHO class III and IV, and do not achieve adequate quality of life and hemodynamic improvement after 3 to 6 months on prostacyclin and combination therapies [53]. The 1-year survival

following lung transplantation is about 80% to 90%, but posttransplant survival time averages about 5 years. Patients in extremis are not candidates for transplantation. Patients whose life expectancy is less than 1 to 2 years should be referred to a lung transplant center, preferably one with experience in PH.

References

[1] Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43(12 Suppl S):5S–12S.
[2] Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004;43(12 Suppl S):40S–7S.
[3] Gaines S. Pulmonary hypertension. JAMA 2000;284:3160–8.
[4] Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol 2004;43(12 Suppl S):13S–24S.
[5] McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004; 126(Suppl 1):14S–34S.
[6] Bossone E, Butera G, Bodini BD, et al. The interpretation of the electrocardiogram in patients with pulmonary hypertension: the need for clinical correlation. Ital Heart J 2003; 4(12):850–4.
[7] Stein PD, Goldhaber SZ, Henry JW, et al. Arterial blood gas analysis in the assessment of suspected pulmonary embolism. Chest 1996;109:78–81.
[8] Bossone E, Duong-Wagner T, Paciocco G, et al. Echocardiographic features of primary pulmonary hypertension. J Am Soc Echocardiogr 1999;12(8):655–62.
[9] McConnell MV, Solomon SD, Rayan ME, et al. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. Am J Cardiol 1996;78(4):469–73.
[10] Kruip MJ, Leclercq MG, van der Heul C, et al. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138(12):941–51.
[11] van Strijen MJ, de Monye W, Schiereck J, et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. Ann Intern Med 2003;138(4):307–14.
[12] Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006;354(22):2317–27.
[13] Kelly AM, Patel S, Carlos RC, et al. Multidetector row CT pulmonary angiography and indirect venography for the diagnosis of venous thromboembolic disease in intensive care unit patients. Acad Radiol 2006;13(4):486–95.
[14] The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: result of the prospective investigators of pulmonary embolism diagnosis (PIOPED). JAMA 1990;263:2753–9.
[15] Henry JW, Stein PD, Gottschalk A, et al. Scintigraphic lung scans and clinical assessment in critically ill patients with suspected acute pulmonary embolism. Chest 1996;109(2):462–6.
[16] Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106(10): 1263–8.
[17] Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation 2003;108(18):2191–4.
[18] Torbicki A, Kurzyna M, Kuca P, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. Circulation 2003;108:844–8.

[19] Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107(20):2545–7.
[20] Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102(8):865–70.
[21] Chemla D, Castelain V, Herve P, et al. Hemodynamic evaluation of pulmonary hypertension. Eur Respir J 2002;20:1314–31.
[22] McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:78–92.
[23] Sitbon O, Humbert M, Jaïs X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105–11.
[24] Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med 2004;140:175–83.
[25] Mismetti P, Quenet S, Levine M, et al. Enoxaparin in the treatment of deep vein thrombosis with or without pulmonary embolism: an individual patient data meta-analysis. Chest 2005; 128(4):2203–10.
[26] Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348(15): 1425–34.
[27] Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349(7):631–9.
[28] Kucher N, Rossi E, De Rosa M, et al. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. Arch Intern Med 2005;165:1777–81.
[29] Quiroz R, Kucher N, Schoepf UJ, et al. Right ventricular enlargement on chest computed tomography: prognostic role in acute pulmonary embolism. Circulation 2004;109: 2401–4.
[30] Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30:1165–71.
[31] Aklog L, Williams CS, Byrne JG, et al. Acute pulmonary embolectomy: a contemporary approach. Circulation 2002;105:1416–9.
[32] Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347: 1143–50.
[33] Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004;110:744–9.
[34] Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998;338:409–15.
[35] Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993;103:685–92.
[36] Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003;76:1457–62.
[37] Bresser P, Fedullo PF, Auger WR, et al. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. Eur Respir J 2004;23:595–600.
[38] Olschewski H, Simonneau G, Galie N, et al. Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347(5):322–9.
[39] Ghofrani HA, Schermuly RT, Rose F, et al. Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2003; 167:1139–41.

[40] Hughes RJ, Jais X, Bonderman D, et al. The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study. Eur Respir J 2006;28: 138–43.
[41] Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. Chest 2006;129:1636–43.
[42] Sandroni C, Maggiore SM, Proietti R, et al. Cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2003;167:664–5.
[43] Fuster V, Steele PM, Edwards WD, et al. Primary pulmonary hypertension: natural history and importance of thrombosis. Circulation 1984;70:580–7.
[44] Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:35–62.
[45] Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.
[46] Barst RJ, Langleben D, Badesch D, et al. STRIDE-2 Study Group. Treatment of pulmonary arterial hypertension with selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006;47:2049–56.
[47] Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148–57.
[48] Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296–302.
[49] McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477–82.
[50] McLaughlin VV, Gaine SP, Barst RJ, et al. Efficacy and safety of trepostinil, a prostacyclin analogue for primary pulmonary hypertension. J Cardiovasc Pharmacol 2003;41:293–9.
[51] Simonneau G, Barst RJ, Galie N, et al. Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165(6):800–4.
[52] Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerolozed iloprost, a prostacyclin analogue. N Engl J Med 2000;342: 1866–70.
[53] Pielsticker E, Martinez F, Rubenfire M. Lung and heart-lung transplant practice patterns in pulmonary hypertension centers. J Heart Lung Transplant 2001;20:1297–304.